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Preparation and Rearrangement of *N*-Vinyl Nitrones: Synthesis of Spiroisoxazolines and Fluorene-Tethered Isoxazoles

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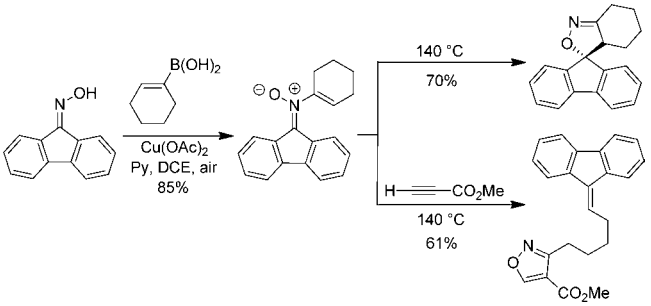
ABSTRACT



***N*-Vinyl nitrones derived from fluorenone have been prepared via a copper-mediated coupling between fluorenone oxime and vinyl boronic acids. These compounds undergo subsequent rearrangement and addition reactions that are distinct from the traditional [3 + 2] cycloaddition reactivity of nitrones. Thermal rearrangements of fluorenone *N*-vinyl nitrones give spiroisoxazolines, while treatment with alkynes provides fluorene-tethered isoxazoles. The scope and limitations of the preparation of fluorenone *N*-vinyl nitrones and their subsequent rearrangement and addition reactions are discussed.**

Despite the proven utility of nitrones in chemical synthesis, *N*-vinyl nitrones are unusual compounds that have rarely been targeted as synthetic intermediates because of the challenges associated with their preparation by traditional methods.[1,2] Recently, Denmark and Montgomery reported that *N*-vinyl nitrones could be synthesized from nitroalkenes and aldehydes in four steps as illustrated in Scheme 1.[3] Coinciding reactivity studies included an intramolecular [4 + 2]-cycloaddition (Scheme 1) and suggested that these uncommon heterodienes may be generally useful as precursors to isoxazolopyridine ring systems. While studying the use of copper-mediated C−O bond forming coupling reactions for the preparation of *N*-enoxyphthalimides, we observed that *N*-vinyl nitrones can be prepared in a single step from fluorenone oxime and vinyl boronic acids under copper-mediated coupling conditions (Scheme 1).[4,5] The

(1) For reviews on the preparation of nitrones and their applications in organic synthesis, see: (a) Merino, P. Nitrones and Cyclic Analogues. In *Science of Synthesis, Knowledge Updates 2010/4*; Bode, J. W., Carreira, E. M., Ishihara, K., Li, J. J., Marek, I., Oestreich, M., Schaumann, E., Yus, M., Eds.; Thieme: New York, 2011; pp 325−404. (b) Chiacchio, U.; Padwa, A.; Romeo, G. *Curr. Org. Chem.* **2009**, *13*, 422. (c) Grigor'ev, I. A. Nitrones: Novel Strategies in Synthesis. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, 2nd ed.; Feuer, H., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2008; pp 129−434. (d) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235. (e) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473.

(2) For examples of *N*-vinyl nitrones as side products and proposed intermediates, see: (a) Singh, P.; Berlinguet, L. *Can. J. Chem.* **1964**, *42*, 1901. (b) Pennings, M. L. M.; Reinhoudt, D. N.; Harkema, S.; Van Hummel, G. J. *J. Am. Chem. Soc.* **1980**, *102*, 7570. (c) Pennings, M. L. M.; Reinhoudt, D. N. *J. Org. Chem.* **1982**, *47*, 1816. (d) Grigg, R.; Perrior, T. R.; Sexton, G. J.; Surendrakumar, S.; Suzuki, T. *J. Chem. Soc., Chem. Commun.* **1993**, 372. (e) Heaney, F.; Kelly, B. M.; Bourke, S.; Rooney, O.; Cunningham, D.; McArdle, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 143. (f) Badawi, H. M.; Ali, S. A. *THEOCHEM* **2002**, *589*, 393. (g) Yeom, H.-S.; So, E.; Shin, S. *Chem.—Eur. J.* **2011**, *17*, 1764.

(3) Denmark, S. E.; Montgomery, J. I. *J. Org. Chem.* **2006**, *71*, 6211.

(4) For reviews and seminal publications on copper-mediated C−O and C−N bond forming reactions using boronic acid reagents, see: (a) Rao, K. S.; Wu, T.-S. *Tetrahedron* **2012**, *68*, 7735. (b) Qiao, J. X.; Lam, P. Y. S. Recent Advances in the Chan-Lam Coupling Reaction. In *Boronic Acids*, 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011; pp 315−361. (c) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829. (d) Partyka, D. V. *Chem. Rev.* **2011**, *111*, 1529. (e) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *9*, 1233. (f) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077.

(5) Patil, A. S.; Mo, D.-L.; Wang, H.-Y.; Mueller, D. S.; Anderson, L. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 7799.

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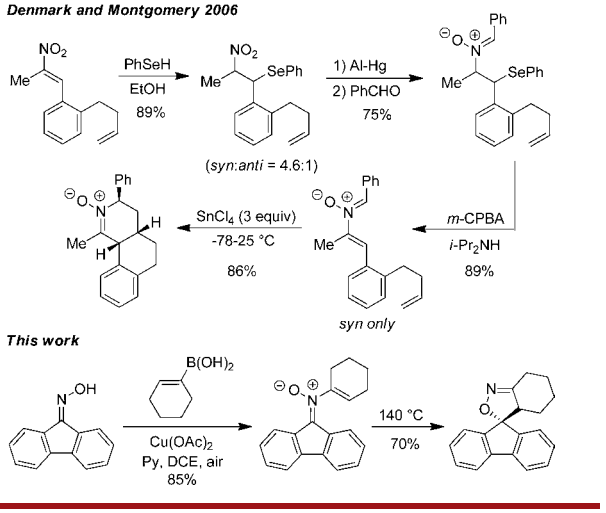
reactivity of these fluorenone-*N*-vinyl nitrones is distinct from traditional nitrones because the electrophilic fluorenyl carbon does not participate in cycloaddition processes. This surprising characteristic can be exploited to afford spiroisoxazolines and fluorenone-tethered isoxazoles—products normally inaccessible directly from nitrones—that exhibit privileged structural motifs present in bioactive pharmaceuticals, dyes, and organic materials.[6−8] Herein we describe the optimization and scope of the facile preparation of fluorenone-*N*-vinyl nitrones from fluorenone oxime and vinyl boronic acids as well as the unique synthetic utility of these new compounds.

The synthesis of *N*-vinyl nitrones from fluorenone oxime and vinyl boronic acids occurred serendipitously. *N*-Vinyl nitrone **3a** was observed when a mixture of fluorenone oxime **1** and 3-hexenyl boronic acid **2a** was treated with $Cu(OAc)_2$ (Table 1, entry 1). This compound was initially obtained in moderate yield and identified by a distinctive ^{1}H NMR resonance at 8.87 ppm which is indicative of the aryl resonance H_a.[9] When a mixture of **1** and cyclohexenyl boronic acid **2b** was subjected to similar conditions, an analogous product **3b** was observed and the structural assignment was corroborated by independent synthesis via oxidation and elimination of selenide-substituted imine **4** (Table 1, entry 10 and eq 1).[10] The *N*-vinyl nitrone structures of **3a** and **3b** were eventually further confirmed by X-ray crystallography of analogous **3g** (see below). Observation of these *N*-vinyl nitrone products was surprising since we had previously used a similar transformation to prepare *N*-enoxyphthalimides and had expected to obtain the analogous oxime ether.[5]

Once the identity of **3a** was established as an *N*-vinyl nitrone, the coupling reaction was optimized to identify the most efficient mixture of reagents. As illustrated in Table 1, $Cu(OAc)_2$ was shown to be the most effective copper salt for the coupling of **2a** with **1** when compared to other Cu(I) and Cu(II) reagents (entries 5−8). The use of 2 equiv of $Cu(OAc)_2$ also enhanced the yield for the formation of **3a** (entry 5). In contrast, the coupling of cyclohexenyl boronic acid **2b** with **1** was generally a more efficient transformation and could be achieved with stoichiometric quantities of $Cu(OAc)_2$ as well as lower concentrations of vinyl boronic acid and pyridine (entry 10). The choice of desiccant had little effect on the preparation of either **3a** or **3b**, but the use of a chlorinated solvent and an aerobic atmosphere was required for the desired transformation. The copper-mediated nitrone synthesis could be proceeding via a direct C−N bond forming pathway or an initial C−O bond forming step followed by a rearrangement.[11] These mechanistic details of this transformation are currently under investigation.

Scheme 1. Preparation and Reactivity of *N*-Vinyl Nitrones



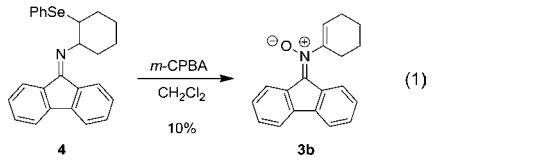
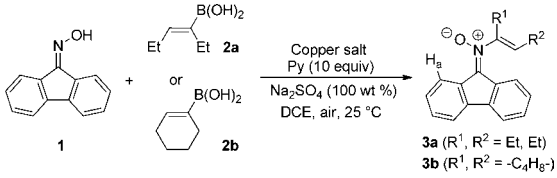


Table 1. Optimization of Cu-Mediated *N*-Vinyl Nitrone Synthesis



entry	R^1/R^2	Cu salt	equiv of Cu	t (h)	yield (%)[a]
1	Et/Et	$Cu(OAc)_2$	1	24	45
2	Et/Et	$Cu(OAc)_2$	1	48	54
3	Et/Et	$Cu(OAc)_2$	0.3	24	20
4	Et/Et	$Cu(OAc)_2$	0.1	24	5
5	Et/Et	$Cu(OAc)_2$	2	24	63
6	Et/Et	CuI	2	24	6
7	Et/Et	$Cu(OTf)_2$	2	24	NR
8	Et/Et	CuTC	2	24	10
9	$-C_4H_8-$	$Cu(OAc)_2$	2	24	85
10	$-C_4H_8-$	$Cu(OAc)_2$	2	24	86[b]
11	$-C_4H_8-$	$Cu(OAc)_2$	0.3	24	60

[a] Determined by ^{1}H NMR spectroscopy using 3 equiv of **2a** or **2b** and CH_2Br_2 as a reference. [b] 5 equiv of py and 2 equiv of **2b** were used. TC = 2-thiophenecarboxylate.

(6) For examples of the preparation of spiroisoxazolines and discussion of their pharmaceutical properties, see: (a) Bardhan, S.; Schmitt, D. C.; Porco, J. A. *Org. Lett.* **2006**, *8*, 927. (b) Ogamino, T.; Obata, R.; Nishiyama, S. *Tetrahedron Lett.* **2006**, *47*, 727. (c) Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni, P. *J. Org. Chem.* **2005**, *70*, 8395. (d) Hirotani, S.; Kaji, S. *Tetrahedron* **1999**, *55*, 4255. (e) Najim, N.; Bathich, Y.; Zain, M. M.; Hamzah, A. S.; Shaameri, Z. *Molecules* **2010**, *15*, 9340. (f) Benltifa, M.; Hayes, J. M.; Vidal, S.; Gueyrard, D.; Goekjian, P. G.; Praly, J.-P.; Kizilis, G.; Tiraidis, C.; Alexacou, K.-M.; Chrysina, E. D. *Biol. Med. Chem.* **2009**, *17*, 7368.

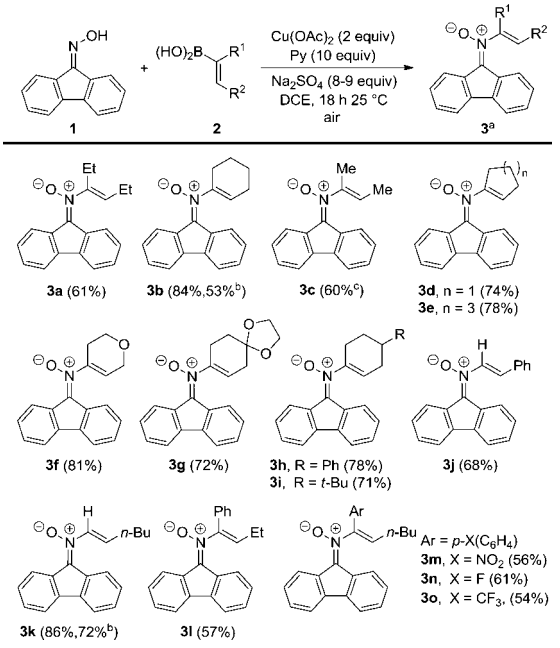
(7) For examples of the use of fluorene derivatives in pharmaceuticals, dyes, and materials, see: (a) Makanga, M.; Krudsood, S. *Malar. J.* **2009**, *8*, S5. (b) Kuo, M. R.; Morbidoni, H. R.; Alland, D.; Sneedon, S. F.; Gourlie, B. B.; Staveski, M. M.; Loenard, M.; Gregory, J. S.; Janjigian, A. D.; Yee, C.; Musser, J. M.; Kreiswirth, B.; Iwamoto, H.; Perozzo, R.; Jacobs, W. R.; Sacchettini, J. C.; Fidock, D. A. *J. Biol. Chem.* **2003**, *278*, 20851. (c) Andrade, C. D.; Yanez, C. O.; Rodriguez, L.; Belfield, K. D. *J. Org. Chem.* **2010**, *75*, 3975. (d) Kurdyukova, I. V.; Ishchenko, A. A. *Russ. Chem. Rev.* **2012**, *81*, 258. (e) Xin, Y.; Wen G.-A.; Zeng, W.-J.; Zhao, L; Zhu, X.-R.; Fan, Q.-L.; Feng, J.-C.; Wang, L.-H.; Wei, W.; Peng, B.; Cao, Y.; Huang, W.; Huang, W. *Macromolecules* **2005**, *38*, 6755. (f) Leclerc, M. *J. Polym. Sci., Part A: Polym. Chem* **2001**, *39*, 2867.

To explore the scope of the method for tolerance of the boronic acid partner, the most general conditions identified in Table 1 were applied to a variety of vinyl boronic acids (entry 5). As shown in Scheme 2, *trans*-monosubstituted, *Z*-disubstituted, and cyclic boronic acids all efficiently form *N*-vinyl nitrones **3** as single *E*-alkene isomers when treated with fluorenone oxime. While *Z*-disubstituted alkenyl boronic acids give moderate yields, the best results were obtained using cyclic boronic acids and *trans*-monosubstituted vinyl boronic acids. Homocoupling products of the boronic acids were identified as the common byproduct of these transformations, and tetrasubstituted vinyl boronic acids were unreactive. Single crystals of **3g** were grown from $EtOH/CH_2Cl_2$, and X-ray diffraction analysis confirmed the structure of the nitrone. The range of fluorenone-derived *N*-vinyl nitrones obtained from the copper-mediated coupling reactions allowed us to further explore the reactivity of these new unusual compounds.

First, isolated *N*-vinyl nitrones **3** were heated to explore the possibility of a thermal rearrangement. In each case, a new product was observed to form cleanly at 140 °C and exhibited a diagnostic ^{13}C NMR resonance at 90 ppm which suggested that a polarized sp^3 quaternary center was present in the molecule.[12] The identity of this product was established by X-ray diffraction analysis of **5m** to be a spiroisoxazoline. The scope of this rearrangement is broad with both disubstituted- and cyclic vinyl nitrones tolerated as substrates (Table 2). Monosubstituted vinyl nitrones, however, decomposed. To the best of our knowledge, this structural rearrangement is unprecedented, and we are currently exploring the mechanism of this transformation.[13] Since spiroisoxazolines have been identified as antitubercular agents and fluorenone derivatives have been identified as antimalerial drugs, we anticipate that the combined influence of these biologically active functional groups may lead to expanded pharmaceutical applications.[6,7]

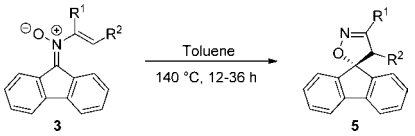
Next, *N*-vinyl nitrones **3** were treated with electron-deficient alkynes to test for [3 + 2] cycloaddition reactivity (Table 3). To our surprise, when **3b** was heated in the presence of methyl propiolate, a [3 + 2] cycloaddition product was not observed. Instead, fluorene-tethered isoxazole **6** was isolated in 60% yield. This product suggests that the *N*-vinyl substituent and the bulky fluorenone nitrone scaffold favor an alternative cyclization and elimination process while hindering the expected [3 + 2]

Scheme 2. Scope of Cu-Mediated *N*-Vinyl Nitrone Synthesis



[a] Isolated yields are reported using 3 equiv of **2**. [b] Isolated yield reported using 1.5 equiv of **2**. [c] 2 equiv of **2c** were used.

Table 2. Scope of Spiroisoxazole Formation



entry	R^1	R^2	product	yield %[a]
1	Et	Et	**5a**	81
2			**5b**	70
3	Me	Me	**5c**	69
4			**5e**	76
5			**5f**	75
6			**5g**	49
7	Ph	Et	**5l**	78
8	*p*-$NO_2(C_6H_4)$	*n*-Bu	**5m**	61
9	*p*-$F(C_6H_4)$	*n*-Bu	**5n**	62
10	*p*-$CF_3(C_6H_4)$	*n*-Bu	**5o**	68

[a] Isolated yields are reported.

(8) For examples of the preparation of isoxazoles and their use in pharmaceuticals and materials, see: (a) Margaretha, P. Isoxazoles, In *Science of Synthesis, Knowledge Updates 2010/1*; Furstner, A., Li, J. J., Moloney, M. G., Ramsden, C. A., Schaumann, E., Eds.; Thieme: New York, 2011; pp 109−131. (b) Lilienkampf, A.; Pieroni, M.; Franzblau, S. G.; Bishai, W. R.; Kozikowski, A. P. *Curr. Top. Med. Chem.* **2012**, *12*, 729. (c) Silva, A. M. S.; Tome, A. C.; Pinho e Melo, T. M. V. D.; Elguero, J. Five-membered Heterocycles: 1,2-Azoles. Part 2. Isoxazoles and Isothiazoles, In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J., Vaquero, J. J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, 2011; pp 727−808.

(9) Grubbs, E. J.; Milligan, R. J.; Goodrow, M. H. *J. Org. Chem.* **1971**, *36*, 1780.

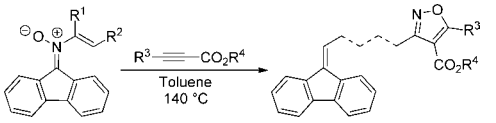
(10) Compound **4** was prepared from 1-nitrocyclohexene and fluorenone. Details are provided in the Supporting Information.

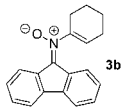
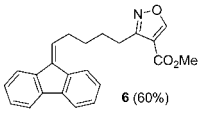
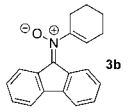
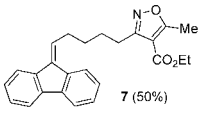
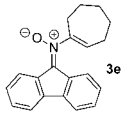
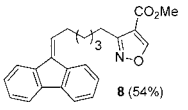
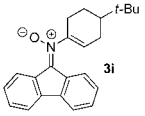
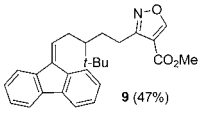
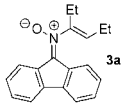
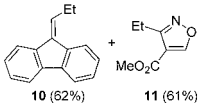
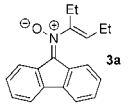
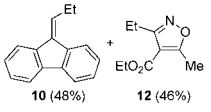
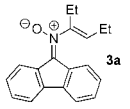
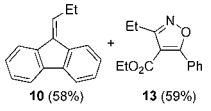
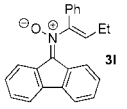
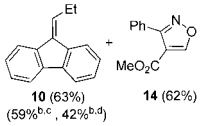
(11) For examples of a related copper-catalyzed rearrangement of a propargylic oxime, see: (a) Nakamura, I.; Kudo, Y.; Araki, T.; Zhang, D.; Kwon, E.; Terada, M. *Synthesis* **2012**, *44*, 1542. (b) Nakamura, I.; Iwata, T.; Zhang, D.; Terada, M. *Org. Lett.* **2012**, *14*, 206. (c) Nakamura, I.; Zhang, D.; Terada, M. *Tetrahedron Lett.* **2011**, *52*, 6470. (d) Nakamura, I.; Araki, T.; Zhang, D.; Kudo, Y.; Kwon, E.; Terada, M. *Org. Lett.* **2011**, *13*, 3616.

(12) Attenuated reactivity was observed at 120 °C, and no conversion of the *N*-vinyl nitrone to the spiroisoxazoline was observed below 100 °C.

(13) See Supporting Information for mechanistic discussion.

Table 3. Additions and Rearrangements of *N*-Vinyl Nitrones



entry	3	R^3/R^4	product (yield %)[a]
1		H/Me	 **6** (60%)
2		Me/Et	 **7** (50%)
3		H/Me	 **8** (54%)
4		H/Me	 **9** (47%)
5		H/Me	 **10** (62%) **11** (61%)
6		Me/Et	 **10** (48%) **12** (46%)
7		Ph/Et	 **10** (58%) **13** (59%)
8		H/Me	 **10** (63%) (59%[b,c], 42%[b,d]) **14** (62%)

[a] Isolated yield. [b] Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as a reference. [c] 120 °C. [d] 80 °C.

cycloaddition. This reactivity pattern appears to be common for fluorenone-derived vinyl nitrones with cycloalkenyl *N*-substituents when treated with either terminal or internal alkynes. Substrates with linear alkenyl *N*-substituents such as **3a** undergo an analogous transformation with either terminal or internal alkynes to afford alkyne addition and C−C bond cleavage products such as fluorene **10** and isoxazole **11**. Notably, nitrone **3l** was observed to undergo conversion to **10** and **14** at significantly lower temperatures than formation of isoxazoline **5l**.[12−14] This reactivity suggests that interaction between nitrone **3l** and methyl propiolate occurs via a lower energy pathway than the structural rearrangement of **3l** to give **5l**.

In summary, we have shown that fluorenone-derived *N*-vinyl nitrones can be prepared in a single-step by copper-mediated coupling of fluorenone oxime and vinyl boronic acids and that these compounds undergo thermal rearrangements to give spiroisoxazolines as well as a cyclization and elimination process with electron-deficient alkynes to give fluorene-tethered isoxazoles. The coupling represents a new facile route to *N*-vinyl nitrones, which have previously only been prepared by multistep procedures.[3] The reactivity of the fluorenone-based *N*-vinyl nitrones differs significantly from the intramolecular [4 + 2] cycloaddition chemistry observed for aldimine-based *N*-vinyl nitrones and provides access to new spirocyclic heterocycles and fluorene-tethered isoxazoles. Exploration of the scope of the copper coupling for the preparation of *N*-vinyl nitrones from other oximes and investigation of the mechanisms of the rearrangements are currently being pursued in our laboratory.

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Note Added after ASAP Publication. Table 2 contained errors in the version published ASAP October 9, 2012; the correct version reposted October 10, 2012.

Supporting Information Available. Experimental procedures, compound characterization data, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) Treatment of **5l** with methyl propiolate does not give a mixture of **10** and **14**. This control experiment suggests that the spiroisoxazoline is not an intermediate in this transformation.

The authors declare no competing financial interest.