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A Catalytic Asymmetric Isatin-Involved Povarov Reaction: Diastereo- and Enantioselective Construction of Spiro[indolin-3,2′-quinoline] Scaffold

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ABSTRACT

The first catalytic asymmetric isatin-involved Povarov reaction has been established. This method provides an unprecedented approach to access the enantioenriched spiro[indolin-3,2′-quinoline] scaffold with concomitant creation of two quaternary stereogenic centers in high yields and excellent stereoselectivities (all >99:1 *dr*'s, up to 97% *ee*).

The Povarov reaction[1] has exhibited its great significance in organic synthesis, which represents an inverse electron-demand aza-Diels–Alder reaction (IEDDA reaction) between 2-azadienes and electronically rich olefins. In particular, the catalytic asymmetric Povarov reaction is a powerful protocol to obtain enantioselective tetrahydroquinoline skeletons, which exist in a variety of natural products and synthetic compounds with relevant pharmaceutical properties.[2] As a result, the catalytic enantioselective Povarov reactions of aldehyde-derived 2-azadienes with electron-rich olefins have been extensively investigated and well-developed in the past decades (eq 1).[3] However, in sharp contrast, *ketone-derived 2-azadienes have not yet been employed as* reaction *components* to participate in the catalytic enantioselective Povarov reactions (eq 2). Only a few nonenantioselective Povarov reactions of ketimines with olefins were sporadically documented,[4] presumably due to the low reactivity inherent in both ketones and its

(1) For early reports: (a) Sauer, J.; Wiest, H. *Angew. Chem.* **1962**, *74*, 353. For reviews: (b) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656. (c) Waldmann, H. *Synthesis* **1994**, 535. (d) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (e) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (f) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (g) Kobayashi, S.; Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002.

(2) For reviews: (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031. (b) Sridharan, V.; Suryavanshi, P.; Menéndez, J. C. *Chem. Rev.* **2011**, *111*, 7157. For selected examples: (c) Paris, D.; Cottin, M.; Demonchaux, P.; Augert, G.; Dupassieux, P.; Lenoir, P.; Peck, M. J.; Jasserand, D. *J. Med. Chem.* **1995**, *38*, 669. (d) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S.-C.; Hamel, E.; Hackl, T.; Lee, K.-H. *J. Med. Chem.* **1998**, *41*, 1155.

(3) For metal-catalyzed transformations: (a) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357. (b) Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* **2001**, *3*, 1973. (c) Xie, M.-S.; Chen, X.-H.; Zhu, Y.; Gao, B.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3799. (d) Xie, M.; Liu, X.; Zhu, Y.; Zhao, X.; Xia, Y.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2011**, *17*, 13800. For organocatalyzed transformations: (e) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (f) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598. (g) Wang, C.; Han, Z.-Y.; Luo, H.-W.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 2266. (h) Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. *Chem. Commun.* **2010**, *46*, 327. (i) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986. (j) Dagousset, G.; Zhu, J.; Masson, G. *J. Am. Chem. Soc.* **2011**, *133*, 14804. (k) Dagousset, G.; Retailleau, P.; Masson, G.; Zhu, J. *Chem.—Eur. J.* **2012**, *18*, 5869. (l) He, L.; Bekkaye, M.; Retailleau, P.; Masson, G. *Org. Lett.* **2012**, *14*, 3158. (m) Shi, F.; Xing, G.-J.; Tao, Z.-L.; Luo, S.-W.; Tu, S.-J.; Gong, L.-Z. *J. Org. Chem.* **2012**, *77*, 6970. (n) Lin, J.-H.; Zong, G.; Du, R.-B.; Xiao, J.-C.; Liu, S. *Chem. Commun.* **2012**, *48*, 7738.

(4) (a) Kouznetsov, V. V.; Forero, J. S. B.; Torres, D. F. A. *Tetrahedron Lett.* **2008**, *49*, 5855. (b) Kouznetsov, V. V.; Arenas, D. R. M.; Arvelo, F.; Forero, J. S. B.; Sojo, F.; Muñoz, A. *Lett. Drug Des. Discovery* **2010**, *7*, 632.

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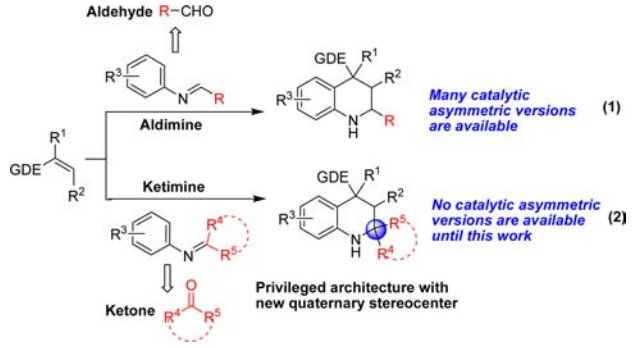
2-azadiene derivatives. Therefore, the development of ketone-involved Povarov reactions, especially the catalytic asymmetric transformations, has become an urgent need in the organic community.



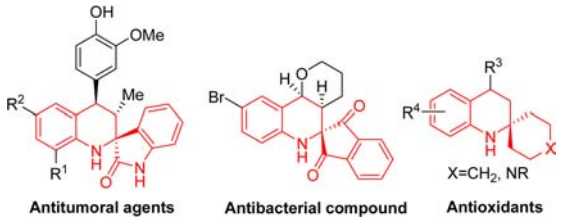


Figure 1. Bioactive spiro-tetrahydroquinolines.

More importantly, the asymmetric Povarov reaction with ketones, in particular with unsymmetrical cyclic ketones, would directly furnish enantioenriched spiro-tetrahydroquinolines with a new quaternary stereogenic center (eq 2), which defines the characteristic structural core of a large family of heterocycles with pronounced and diverse bioactivities (Figure 1).[4b,5] Of particular concern is that isatins, a type of unsymmetrical cyclic ketones with high activity, have emerged as privileged building blocks in the synthesis of spiro-fused heterocycles with potential bioactivities.[6] In this context, the asymmetric Povarov reaction of isatin-derived 2-azadiene with electron-rich olefins would allow for the construction of an optically pure spiro[indolin-3,2′-quinoline] scaffold, which constitutes the core structural element of antitumoral molecules[4b] (in Figure 1) and hence holds great synthetic importance.

We recently described a number of chiral phosphoric acid[7] catalyzed multicomponent reactions for the synthesis of enantioenriched heterocycles with biological relevance.[3m,8] Inspired by the above success and the fact that there has not been a report on an enantioselective ketone-involved Povarov reaction for the synthesis of important spiro-[indolin-3,2′-quinoline] scaffolds, we considered utilizing isatin in the asymmetric Povarov reaction, wherein the isatin-derived ketimine should be activated by the chiral phosphoric acid. In this work, we present the first enantioselective ketone-involved Povarov reaction, which directly assembles isatins, anilines, and styrenes into biologically important spiro[indolin-3,2′-quinolines] with two quaternary stereogenic centers in high yields and excellent stereoselectivities (all >99:1 *dr*'s, up to 97% *ee*).

Our study commenced with a three-component reaction of 1-benzylisatin **1a**, 4-methoxyaniline **2a**, and α-methyl *o*-hydroxystyrene **3a** in the presence of 10 mol % of chiral phosphoric acids **5** in toluene at 50 °C (Table 1). All the chiral phosphoric acids **5** enabled the reaction to proceed smoothly to afford a single diastereomer of spiro[indolin-3,2′-quinoline] **4aaa** in high yields but with various levels of enantioselectivity (entries 1−6). The results revealed that 2,4,6-triisopropylphenyl-substituted phosphoric acid (Trip-PA) **5f** was far more superior to other analogues with regard to enantioselectivity (entry 6 vs 1−5). The subsequent screening of the solvents at 25 °C disclosed that toluene was the most suitable reaction media, affording the desired product in 92% yield and 81% *ee* (entry 7 vs 8−10). Lowering the reaction temperature from 25 to −20 °C led to a substantial increase in the enantioselectivity with maintained reactivity (entries 7, 11−12), but lowering the temperature further to −30 °C resulted in a moderate yield albeit with an excellent enantiomeric excess (entry 13). Finally, increasing the stoichiometry of **3a** rendered the reaction to proceed at −20 °C in a quantitative yield of 99% with a maintained enantioselectivity of 94% *ee* (entry 14 vs 12).

With the optimal conditions in hand, we then carried out the investigation on the substrate scope of isatins **1** (Table 2). At first, isatins bearing different types of *N*-substituents were utilized as substrates (entries 1−5), which demonstrated that this approach was applicable to various isatins with *N*-benzyl, alkyl, or phenyl substituents, affording spiro[indolin-3,2′-quinolines] in excellent diastereoselectivities (all >99:1 *dr*s) and with a high level of enantiomeric excesses (up to 97% *ee*). Generally speaking, isatins with *N*-benzyl groups were superior to those with *N*-alkyl or *N*-phenyl groups in terms of yield and enantioselectivity (entries 1−3 vs 4−5). As for *N*-benzyl substituted isatins, changing the substituents on the benzyl group had some delicate effect on the enantioselectivity (entries 1−3). Notably, the perfluorinated *N*-benzylisatin **1c** exhibited the highest capability of affording the corresponding product in 99% yield and 97% *ee* (entry 3). Basically, the reactivity of *N*-alkyl and *N*-phenyl substituted isatins was lower than that of *N*-benzylisatins; therefore the reaction temperature was increased to 50 °C to render a cleaner reaction (entries 4−5). Moreover, the use of CCl_4 as

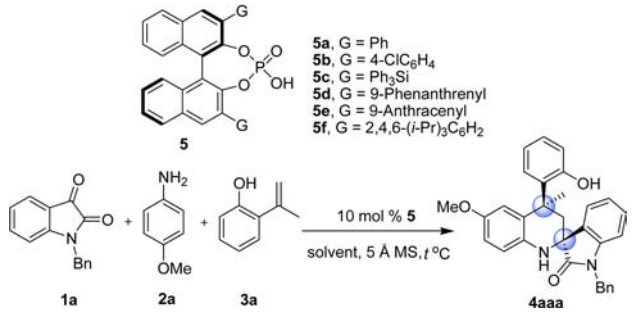
(5) (a) Dorey, G.; Lockhart, B.; Lestage, P.; Casara, P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 935. (b) Ramesh, E.; Manian, R. D. R. S.; Raghunathan, R.; Sainath, S.; Raghunathan, M. *Bioorg. Med. Chem.* **2009**, *17*, 660. (c) Kouznetsov, V. V.; Leonor, Y.; Acevedo, A. M. *Lett. Drug Des. Discovery* **2010**, *7*, 710. (d) Brown, D. W.; Mahon, M. F.; Ninan, A.; Sainsbury, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, *16*, 2329.

(6) For a recent review: Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104.

(7) For early examples: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. For reviews: (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Terada, M. *Chem. Commun.* **2008**, 4097. (f) Terada, M. *Synthesis* **2010**, 1929.

(8) (a) Shi, F.; Luo, S.-W.; Tao, Z.-L.; He, L.; Yu, J.; Tu, S.-J.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 4680. (b) Shi, F.; Tao, Z.-L.; Luo, S.-W.; Tu, S.-J.; Gong, L.-Z. *Chem.—Eur. J.* **2012**, *18*, 6885. (c) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156. (d) Shi, F.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 11423.

Table 1. Optimization of Reaction Conditions[a]



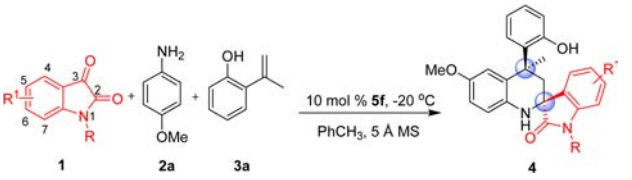
entry	5	solvent	t (°C)	yield (%)[b]	ee (%)[c]
1	**5a**	$PhCH_3$	50	81	36
2	**5b**	$PhCH_3$	50	97	14
3	**5c**	$PhCH_3$	50	99	10
4	**5d**	$PhCH_3$	50	99	43
5	**5e**	$PhCH_3$	50	99	44
6	**5f**	$PhCH_3$	50	99	76
7	**5f**	$PhCH_3$	25	92	81
8	**5f**	CH_2Cl_2	25	12	73
9	**5f**	$CHCl_3$	25	19	69
10	**5f**	CCl_4	25	99	78
11	**5f**	$PhCH_3$	0	99	88
12[d]	**5f**	$PhCH_3$	−20	90	93
13[d]	**5f**	$PhCH_3$	−30	58	95
14[d,e]	**5f**	$PhCH_3$	−20	99	94

[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in solvent (1 mL) with 5 Å MS (150 mg) for 48 h, and the ratio of **1a**/**2a**/**3a** was 1.2/1/2.4. [b] Isolated yield and a single diastereomer was observed unless indicated otherwise. [c] Determined by HPLC. [d] The reaction time was 84 h. [e] The ratio of **1a**/**2a**/**3a** was 1.2/1/3.6.

solvent greatly improved the yield but with a slightly decreased enantioselectivity (entries 4−5, in parentheses). Then, the influence of various substituents at different positions of the phenyl moiety of isatins on the reaction was investigated. As shown in entries 6−16, this protocol is amenable to a wide range of electronically different substituents at the C5, C6, or C7 position of isatins, delivering structurally diverse spiro[indolin-3,2′-quinolines] in high yields (60−99%) and good stereoselectivities (all >99:1 *dr*'s, 81−97% *ee*'s). The position of the substituent seemingly exerts some influence on the enantioselectivity and reactivity. For instance, the C5-substituted isatin exemplified by **1f** showed lower reactivity and enantioselectivity than C6- or C7-substituted analogues; thus the reaction was conducted at 50 °C (entry 6). The C6- or C7-substituted isatins regardless of the electronic feature of the substituents were able to deliver high yields and excellent enantioselectivities (92−97% *ee*s), and no remarkable difference in the stereoselectivity was observed between the C6- and C7-substituted isatins (entries 7−14 and 16). Moreover, C5,C6-disubstituted isatin **1o** also smoothly participated in the reaction with 93% *ee* and 87% yield (entry 15).

Next, the substrate scope with respect to anilines **2** was explored by the reaction with isatin **1a** or **1h** and α-methyl

Table 2. Substrate Scope of Isatins[a]



entry	4	R^1/R (**1**)	yield (%)[b]	dr (%)[c]	ee (%)[d]
1	**4aaa**	H/Bn (**1a**)	99	>99:1	94
2	**4baa**	H/*p*-*t*Bu$C_6H_4CH_2$ (**1b**)	90	>99:1	93
3	**4caa**	H/$C_6F_5CH_2$ (**1c**)	99	>99:1	97
4	**4daa**	H/*i*Pr (**1d**)	41[e] (79[f])	>99:1[e] (>99:1[f])	88[e] (84[f])
5	**4eaa**	H/Ph (**1e**)	31[e] (56[g])	>99:1[e] (>99:1[g])	90[e] (82[g])
6[e]	**4faa**	5-Cl/Bn (**1f**)	65	>99:1	81
7	**4gaa**	6-F/Bn (**1g**)	76	>99:1	96
8	**4haa**	6-Cl/Bn (**1h**)	95	>99:1	97
9	**4iaa**	6-Br/Bn (**1i**)	99	>99:1	93
10	**4jaa**	6-CH_3/Bn (**1j**)	99	>99:1	96
11	**4kaa**	7-F/Bn (**1k**)	99	>99:1	92
12	**4laa**	7-Br/Bn (**1l**)	99	>99:1	93
13	**4maa**	7-CF_3/Bn (**1m**)	89	>99:1	94
14	**4naa**	7-CH_3/Bn (**1n**)	60	>99:1	94
15	**4oaa**	5,6-F_2/Bn (**1o**)	87	>99:1	93
16	**4paa**	7-Br/*p*-*t*Bu$C_6H_4CH_2$ (**1p**)	63	>99:1	95

[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in toluene (1 mL) with 5 Å MS (150 mg) at −20 °C for 84 h, and the ratio of **1**/**2a**/**3a** was 1.2/1/3.6. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC. [e] Performed at 50 °C. [f] In the presence of 15 mol % **5f** with 4 Å MS at 50 °C in CCl_4. [g] Performed at 50 °C in CCl_4 with 4 Å MS.

o-hydroxystyrene **3a** (Table 3, entries 1−6). The results disclosed that the anilines substituted with electron-donating groups served as appropriate substrates, providing the corresponding products in good yields (70−99%) and excellent stereoselectivities (all >99:1 *dr*'s, 91−97% *ee*'s, entries 1−5). In addition, the anilines with electron-withdrawing groups such as **2d** could also be employed to react with excellent diastereoselectivity and reasonable enantioselectivity (>99:1 *dr*, 78% *ee*, entry 6). The generality for α-alkyl *o*-hydroxystyrenes **3** was also examined by the reaction with isatin **1h** and 4-methoxyaniline **2a**. Several α-alkyl *o*-hydroxystyrenes bearing different substituents on their benzene rings or with different α-alkyl groups were accommodated in the reaction, leading to the generation of desired products in high yields (86−99%) and good stereoselectivities (all >99:1 *dr*s, 89−97% *ee*s, entries 1 and 7−9). Significantly, the use of α-alkyl *o*-hydroxystyrenes as dienophiles to react with isatin-derived ketimine provides an easy access to optically pure spiro[indolin-3,2′-quinolines] with two quaternary stereogenic centers, one of which is an all-carbon quaternary chiral center.

The absolute configuration of compound **4had** (>99% *ee* after recrystallization) was unambiguously determined to be

Table 3. Substrate Scope of Anilines and α-Alkyl *o*-Hydroxystyrenes[a]

entry	4	1	R^1 (2)	R^2/R^3 (3)	yield (%)[b]	dr (%)[c]	ee (%)[d]
1	**4haa**	**1h**	4-OMe (**2a**)	H/Me (**3a**)	95	>99:1	97
2	**4aba**	**1a**	4-OEt (**2b**)	H/Me (**3a**)	70	>99:1	94
3	**4hba**	**1h**	4-OEt (**2b**)	H/Me (**3a**)	99	>99:1	97
4	**4aca**	**1a**	4-OPh (**2c**)	H/Me (**3a**)	99	>99:1	91
5	**4hca**	**1h**	4-OPh (**2c**)	H/Me (**3a**)	99	>99:1	95
6[e]	**4ada**	**1a**	4-F (**2d**)	H/Me (**3a**)	44	>99:1	78
7	**4hab**	**1h**	4-OMe (**2a**)	Me/Me (**3b**)	99	>99:1	90
8	**4hac**	**1h**	4-OMe (**2a**)	OMe/Me (**3c**)	86	>99:1	90
9	**4had**	**1h**	4-OMe (**2a**)	H/Et (**3d**)	87	>99:1	89

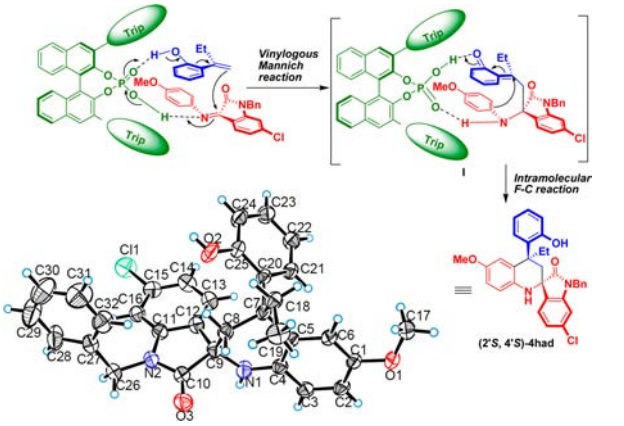
[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in toluene (1 mL) with 5 Å MS (150 mg) at −20 °C for 84 h, and the ratio of **1**/**2**/**3** was 1.2/1/3.6. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC. [e] Performed at 50 °C.

(2′*S*,4′*S*) by single-crystal X-ray diffraction analysis (in Scheme 1).[9] The configurations of other spiro[indolin-3,2′-quinolines] were assigned by analogy.

Based on our experimental results and recent related studies on the reaction mechanism,[3m] we proposed a plausible reaction pathway to explain the stereochemistry of the isatin-involved Povarov reaction (Scheme 1). As exemplified by the formation of **4had**, α-ethyl *o*-hydroxystyrene **3d** initially participated in the vinylogous Mannich reaction with the ketimine generated from isatin **1h** and aniline **2a** under

(9) CCDC 910489. See the Supporting Information for details.

Scheme 1. Proposed Reaction Mechanism



the catalysis of chiral phosphoric acid **5f** via a hydrogen-bonding interaction, generating a transient intermediate **I**, which subsequently underwent an intramolecular Friedel–Crafts reaction facilitated by the same phosphoric acid **5f**, to afford the enantioenriched spiro[indolin-3,2′-quinoline] (2′*S*,4′*S*)-**4had**.

In conclusion, we have realized the first enantioselective isatin-involved Povarov reaction, which is applicable to a variety of reaction components, delivering new spiro-[indolin-3,2′-quinolines] with concomitant creation of two quaternary stereogenic centers in high yields and excellent stereoselectivities (all >99:1 *dr*'s, up to 99% yield and 97% *ee*). This transformation has provided the first example of a ketone-involved asymmetric Povarov reaction and also has offered an efficient method to obtain enantioenriched spiro[indolin-3,2′-quinoline] scaffolds with medicinal relevance.

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Supporting Information Available. Experimental details, characterization of new compounds, and crystal data of **4had**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.