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Synthesis of Spirocyclic Isoindolones Using an Alkynyl *aza*-Prins/Oxidative *halo*-Nazarov Cyclization Sequence

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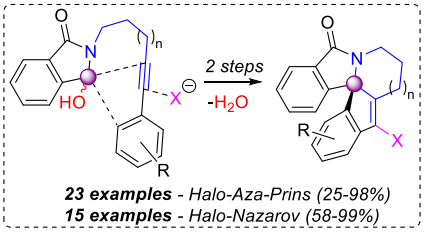
ABSTRACT: In this report, we describe an alkynyl *halo-aza*-Prins cyclization of 3-hydroxyisoindolones to prepare *aza*-Prins products. These Prins adducts undergo oxidation at the 3-isoindolone position after activation of the amide by triflic anhydride and 2-chloropyridine to form a pentadienyl cation capable of undergoing a *halo*-Nazarov cyclization. Using this methodology, angular-fused N-heterocyclic small molecules with two new rings, two new carbon−carbon bonds, a vinyl halide, and an *aza*-tertiary stereocenter can be obtained in good yields.



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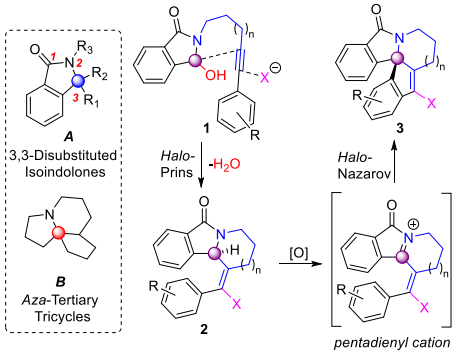
The N-heterocyclic systems **A** and **B** (Scheme 1, Box) are substructures found in an array of bioactive molecules.[1−6] In particular, 3,3-disubstituted[4−10] or 3-spirofused isoindolones[11] (**A**, Scheme 1) have been identified as valuable substructures to access for drug design. Scaffolds consisting of a tricyclic *aza*-tertiary core (**B**, Scheme 1) are also ubiquitous among bioactive alkaloids and typically require several steps to assemble.[1−3] Alkaloids containing both of these motifs have never been synthesized or studied before, which means that the newly accessed chemical space has the potential for some interesting bioactivity.

We report a new strategy for the synthesis of spirofused isoindolones **3** (Scheme 1). Our recent studies focusing on the alkynyl Prins reaction and *halo*-Nazarov cyclization guided the synthetic design.[12−14] First, we leverage a new variant of the alkynyl *halo-aza*-Prins reaction[15−18] to prepare key intermediate **2**. This cyclization is the first example of an alkynyl *halo*-Prins reaction with 3-hydroxyisoindolones **1** for the formation of **2**. Then, the isoindolone core is oxidized using an unusual amide activation strategy in order to access a pentadienyl cation intermediate capable of undergoing a *halo*-Nazarov cyclization. Overall, our approach enables the synthesis of unique spirocyclic N-heterocycles from a sequential, double-functionalization of 3-hydroxyisoindolones **1**, generating two new rings, two C−C bonds, and a vinyl halide in two steps. In this report, we outline the scope and limitations of the methodology.

Initially, we focused on developing an alkynyl *halo-aza*-Prins cyclization capable of generating compounds like **2** (Scheme 1). Treatment of **1a** with an excess of triflic acid (TfOH) and two equivalents of tetrabutylammonium iodide (TBAI) gives a 70% yield of **4a** (Entry 1, Table 1).[19] The use of triflic acid, however, gives inconsistent yields and reactions are not scalable. Using triflimide leads to similar results (Entry 2, Table 1).

Seeing the poor reproducibility, we decided to move away from Brønsted acidic conditions and try more mild Lewis acidic reagents.[20] Using four equivalents of chlorotrimethylsilane

Scheme 1. Scaffolds of Interest (Box); Synthesis of Spirocyclic Isoindolones 3 from Hydroxyisoindolones 1



(TMSCl) gives *chloro*-Prins product **6a** in 98% yield (Entry 3, Table 1). Bromotrimethylsilane (TMSBr) gives the *bromo*-Prins product **5a** in 94% yield (Entry 4, Table 1). The addition of two equivalents of TMSI in two portions at −50 °C leads to good yields of *iodo*-Prins product **4a** (Entry 5, Table 1).

A different set of conditions is optimal for enyne substrates. TMSBr leads mainly to decomposition and only 38% Prins product formation for **5n** (Entry 6, Table 1). $BiBr_3$ gives better results with only 1.2 equiv required to give full conversion to *bromo*-Prins product **5n** in 70% yield (Entry 7, Table 1).[21]

Chloro-, *bromo*-, and *iodo*-Prins products can all be synthesized in good yield (Scheme 2, **4**−**6a**, **4**−**6j**). Electron-

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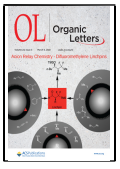

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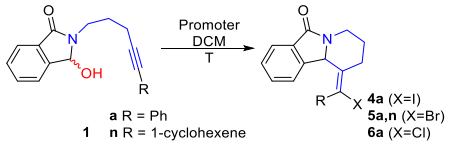
Table 1. Alkynyl *halo-aza*-Prins Optimization



entry	promoter (equiv)	T (°C)	prod. (% yield)
1[a]	TfOH (1.4)	−20 to rt	**4a** (70)
2[a]	Tf_2NH (2.0)	−20 to rt	**4a** (71)
3	TMSCl (4.0)	−20 to rt	**6a** (98)
4	TMSBr (4.0)	−40 to rt	**5a** (94)
5[b]	TMSI (2.0)	−50	**4a** (87)
6[c]	TMSBr (4.0)	−40 to rt	**5n** (38)
7[c]	$BiBr_3$ (1.2)	−40 to rt	**5n** (70)

[a]2.0 equiv of TBAI, 5 Å molecular sieves (500 mg/mmol **1**). [b]TMSI added in two portions, 30 min between additions. [c]Enyne **1n** was used.

deficient arenynes react slowly to provide Prins products like **5f**. Electron-rich arenynes react faster, showing full conversion to the Prins product within a few hours (**5b−e**,**g−i**). While both six- and seven-membered rings form smoothly (**4−6a**; **5b−i** and **4−6j**), five-membered rings are problematic (compare **4a** and **4j** with **4k**). Cyclization is sluggish, and mixtures of products are obtained. It is possible that the shorter tether length makes it difficult to achieve optimal geometry for cyclization.

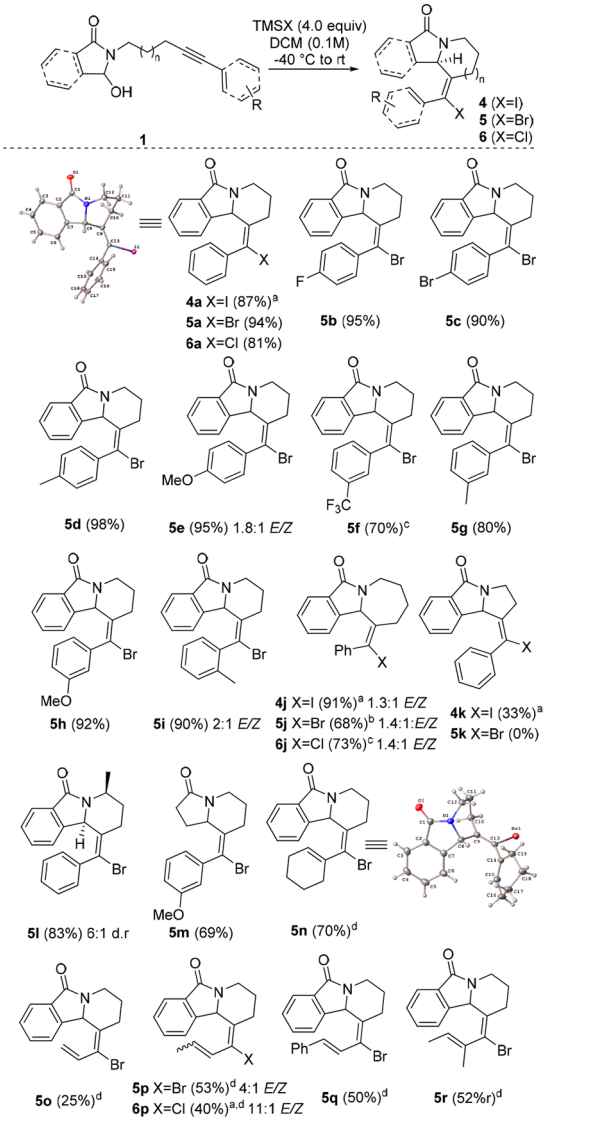
In general, the *E* isomer is formed exclusively in cyclizations that form six-membered rings, whereas selectivity is poor for the formation of seven-membered rings (close to 1:1 ratio; see **4j−6j**). Exceptions to this trend are substrates **5e** and **5i**, which give approximately a 2:1 mixture of *E*/*Z* isomers. Taken together, the data suggests that *E*/*Z* selectivity in the Prins reaction can be impacted by either sterics (hindrance at the site of C−X bond formation or the conformation of the ring system) or electronics.[22] It is not clear whether the observed selectivities are kinetic or thermodynamic in origin.

Alkyne **1l**, with a methyl substituent at the carbon next to the nitrogen, cyclizes to afford **5l** with moderate diastereoselectivity (6:1 dr). Succinimide-derived hemiaminal **1m** also cyclized efficiently to give **5m** in 69% yield. Using $BiBr_3$ as the promoter gives modest yields for terminal enynes like **5o** (25%). The increase of the substitution on the alkene leads to improved yields, giving **5p** in 53% and **6p** in 40% yields (for the *bromo* and *chloro* cases, respectively) and **5q** in 50% yield. Enynes with trisubstituted alkenes also give good yields (52% for **5r** and 70% for **5n**).

With these substrates in hand, we moved on to finding conditions to activate the 3-position of isoindolones **5−7a** and promote the desired *halo*-Nazarov cyclization. Previous methods for 3-isoindolone oxidation use toxic reagents like 2,2′-bipyridinium chlorochromate[6] and palladium acetate.[23] Less toxic reagents have also been used like KHMDS,[9] Eosin Y/selectfluor with blue LEDs,[8] and PIDA.[11] We discovered, somewhat serendipitously, that conditions developed for electrophilic activation of amides (triflic anhydride and a pyridine base derivative)[24−30] can also be used to oxidatively activate C3 of isoindolones **4−6**.

Treatment of isoindolone **4a** with 2.0 equiv of triflic anhydride and 1.1 equiv of 4-(dimethylamino) pyridine (DMAP) gives 39% yield of 3-hydroxyisoindolone **10a** after a basic aqueous workup at −40 °C (Entry 1, Table 2). The addition of 1.2 equiv of di-*tert*-butyl-methylpyridine (DTBMP) to a solution of **4a**

Scheme 2. Scope of Alkynyl *halo-aza*-Prins Cyclization of 3-Hydroxyisoindolones 1[a]



[a](a) 2.0 equiv of TMSI, kept at −50 °C; (b) warmed from 0 °C to room temperature; (c) heated from 0 to 40 °C for 4 days; (d) BiX_3 used (1.2 equiv for X = Br; 2.0 equiv for X = Cl), warmed from −40 to 0 °C.

followed by warming from −78 °C to room temperature gives a 44% yield of the *iodo*-Nazarov product **7a** (Entry 2, Table 2). The change of bases to 2-bromopyridine gives a slight increase in yield to 54% of **7a** (Entry 3), whereas 2-chloropyridine and 2-fluoropyridine give 73% (Entry 4) and 67% (Entry 5) yields, respectively. Unexpectedly, for *bromo*-Prins product **5a**, warming from −78 °C to room temperature gives only a 38% yield of *bromo*-Nazarov product **8a** (Entry 6). The addition of triflic anhydride at 0 °C followed by warming the reaction mixture to room temperature fixes this issue and gives 74% of **8a** (Entry 7).

The exclusion of the pyridine base additive gives 59% recovery of the starting material **5a** and about 12% product formation after stirring for 24 h (Entry 8, Table 2). This experiment shows that pyridine is necessary for optimal results. The omission of the triflic anhydride from the reaction mixture leads to 100% recovery of starting material **5a** (Entry 9, Table 2). To explore

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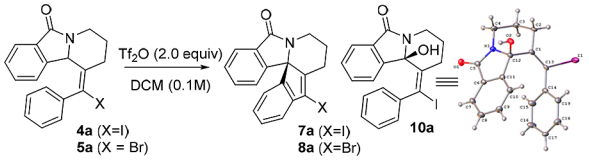
Table 2. Optimization of 3-Isoindolone Oxidation/*halo*-Nazarov Cyclization



entry	additive (equiv)	T (°C)	prod. (% yield)
1[a]	DMAP (1.1)	−78 to −40	**10a** (39), **4a** (32)
2[a]	DTBMP (1.2)	−78 to rt	**7a** (44)
3[a]	2-Br-pyr (1.5)	−78 to rt	**7a** (54)
4[a]	2-Cl-pyr (1.5)	−78 to rt	**7a** (73)
5[a]	2-F-pyr (1.5)	−78 to rt	**7a** (67)
6[b]	2-Cl-pyr (1.5)	−78 to rt	**8a** (38)
7[b]	2-Cl-pyr (1.67)	0 to rt	**8a** (74)
8[b]	none	0 to rt	**8a** (12), **5a** (59)
9[b,c]	2-Cl-pyr (1.67)	0 to rt	**5a** (100)
10[b−d]	2-Cl-pyr (1.67)	0 to rt	**5a** (100)

[a]*iodo*-Prins product **4a** used. [b]*bromo*-Prins product **5a** used. [c]No Tf_2O added. [d]Argon/oxygen atmosphere.

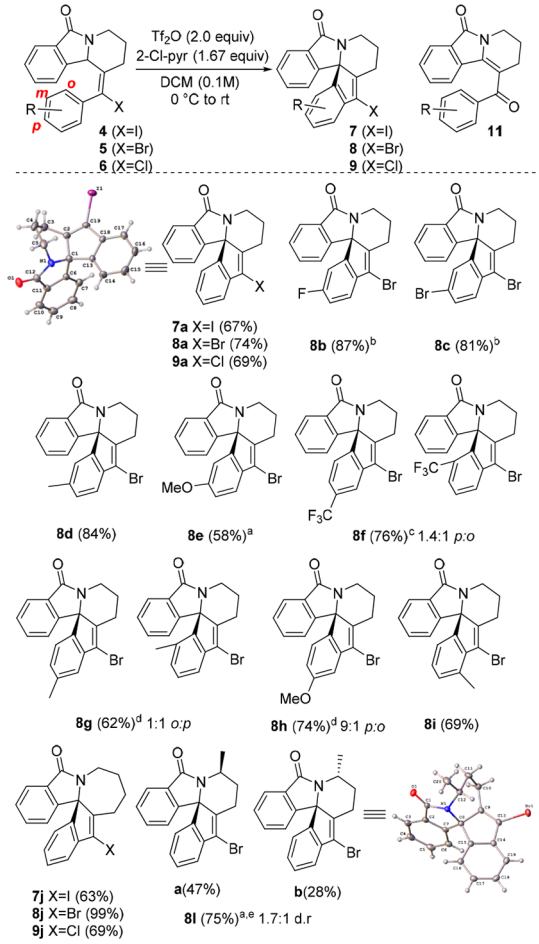
the possibility of oxygen taking part in the oxidation of **5a**, the reaction was attempted under an argon/oxygen atmosphere with no triflic anhydride (Entry 10, Table 2).[31] This experiment resulted in the full recovery of the starting material. When the optimized conditions from Entry 7 were used, the scope of this 3-isoindolone oxidation/*halo*-Nazarov cyclization was explored (Scheme 3).

Electron neutral substrates react smoothly to give *halo*-Nazarov products **7**−**9a** in good yields. Interestingly, *bromo*-Nazarov **8a** works better than *chloro*-Nazarov **9a**, which works better than the *iodo*-case **7a**. *para*-Substituted, electron-rich substrates react well to give products **8b**−**e**. The more electron-rich substrates **8b,c** and **8e** need to be heated to 70 and 40 °C, respectively, for optimal yields. When these reactions proceeded at room temperature, ketones like **11** were formed. We were happy to see that Prins substrate **5f** cyclizes to give **8f** as a 1.4:1 mixture of the *para*/*ortho* (with respect to the CF_3 group) trapped product, albeit after heating to 80 °C overnight (running the reaction at room temperature also favors ketone **11f** formation). *meta*-Substituted, electron-rich substrates such as **5g** and **5h** require more Tf_2O (3.0 equiv) to fully undergo the desired oxidation.

Following oxidation, substrate **5g** cyclizes to give a 1:1 mixture of the *para*/*ortho* (with respect to the methyl group) trapped product, while **8h** forms as a 9:1 mixture of the *para*/*ortho* trapped product. *ortho*-Substituted substrates such as **5i** cyclize efficiently to give **8i** in 69% yield. Seven-membered ring containing substrates like **4**−**6j** cyclize quickly to give ring systems like **7**−**9j** in good to excellent yields. Once again, we can see that the *bromo*-Nazarov works better than the *chloro*-Nazarov, which works better than the *iodo*-Nazarov. When one utilizes **5l** as a 6:1 mixture of diastereomers, it leads to a 1.7:1 separable mixture of diastereomers (see the Supporting Information for an explanation of diastereomeric ratio erosion).

Preliminary experiments showed that enyne-derived Prins adducts **5n**−**r** did not undergo smooth cyclization under the optimized conditions. Further studies into the oxidation/cyclization of this class of isoindolones are ongoing. In addition, the cyclization of **4k** gave complex mixtures, and none of the corresponding Nazarov product was formed. Succinimide-

Scheme 3. Scope of Spirocyclic Isoindolones Synthesized from Oxidation/*halo*-Nazarov Cyclization[a]



[a](a) Heated to 40 °C; (b) heated to 70 °C; (c) heated to 80 °C; (d) 3.0 equiv of Tf_2O and 2.5 equiv of 2-Cl-pyridine needed; (e) ketone **11l** isolated in 19% yield from this reaction.

derived Prins product **5m** did not undergo oxidation and led to the recovery of the starting material.

A mechanistic hypothesis for the oxidative *halo*-Nazarov cyclization is depicted in Scheme 4. Pyridine derivatives are known to react with highly electrophilic Tf_2O, leading to the formation of pyridinium triflate.[24] This pyridinium triflate can react with amide **5a** to give intermediate **A**. Amide **5a** could, in principle, react directly with Tf_2O, but experiments showed that the omission of 2-chloropyridine led to poor reactivity and recovery of the starting material.

Typically, the type **A** intermediate generated in the course of the amide activation either suffers a direct substitution at carbon or collapses to the corresponding keteneiminium/isonitrile intermediate.[24] Our findings suggest that, in isoindolones **4**−**6**, electrophilic amide activation renders the C3 proton of **A** acidic, leading to oxidative elimination facilitated by either 2-chloropyridine or the previously generated triflate anion. This pathway supersedes any kind of substitution reaction.

The expulsion of trifluoromethylsulfinate from **A** thus generates N-acyliminium intermediate/pentadienyl cation **B**/**B′**. Experimental results suggest that intermediate **B** forms at low temperatures and is long-lived. If the reactions are quenched prematurely, we isolate products of either type **10** or **11** from the corresponding amide precursors. Electron-neutral substrate **4a**,

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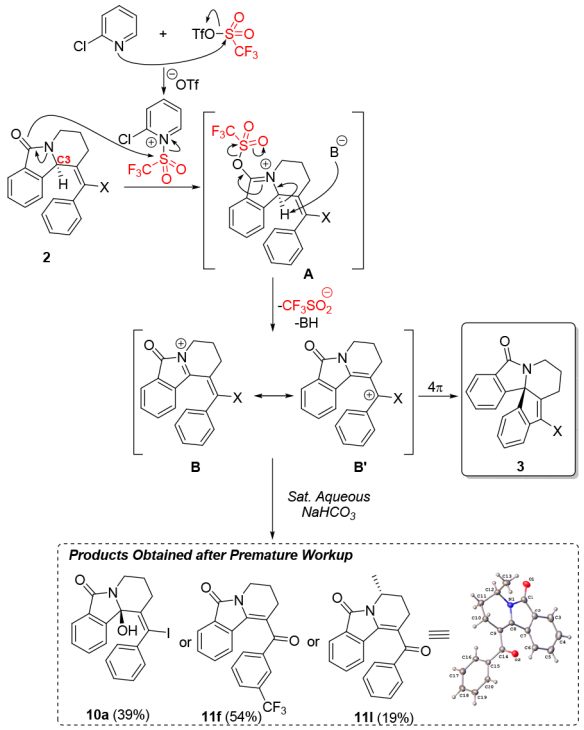
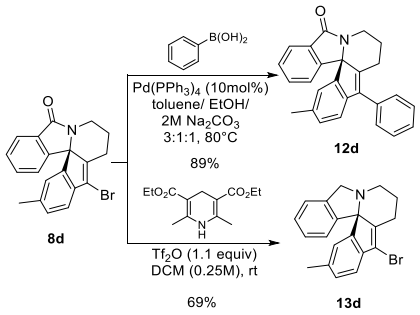
Scheme 4. Proposed Mechanism for 3-Isoindolone Oxidation/*halo*-Nazarov Cyclization



for example, results in the isolation of the 3-hydroxy trapped species **10a**, while electron-deficient substrate **5f** or sterically hindered substrate **5l** form ketones **11f** or **11l**, respectively (Scheme 4; see the Supporting Information for the mechanism). 4π-electrocyclization of intermediate **B**, however, requires warming to room temperature or significant heating in some cases. For instance, the electron-deficient substrate **5f** needs to stir at 80 °C to ensure full conversion to **8f**. In addition, substrates not activated at the *ortho*-position for aromatic substitution (**5b**, **5c**, and **5e**, Scheme 3) do not cyclize without heating.

Scheme 5. Further Diversification of Spirocyclic Isoindolone 8d



Scheme 5 shows two reactions that can further diversify spirocyclic isoindolones **3**, thus expanding the accessible chemical space and offering different options for synthesizing molecules with interesting bioactivity. The first example corresponds to a Suzuki cross-coupling reaction of **8d** with phenylboronic acid to give spirocycle **12d** in 89% yield.[14] The reduction of the amide to an amine can also be achieved using triflic anhydride and Hantzsch ester as a hydride source.[32] When **8d** is subjected to these conditions, the result is tertiary amine **13d** in 69% yield.

In summary, a two-step sequence has been developed for the synthesis of spirocyclic isoindolones **3** from arenyne and enyne 3-hydroxyisoindolone **1**. Specifically, an alkynyl *aza*-Prins cyclization delivers intermediate isoindolones **2**, and then, a novel C3 oxidation protocol generates an N-acyliminium ion intermediate capable of undergoing a *halo*-Nazarov cyclization. The method allows for the efficient installation of two new rings, two new carbon−carbon bonds, a vinyl halide, and an *aza*-quaternary stereocenter (which is found in a wide range of bioactive natural products). Ongoing work includes the exploration of different conditions for the efficient activation of enyne-derived Prins products as well as the development of an asymmetric variant of the reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00191.

General remarks; experimental details; *halo*-Prins and *halo*-Nazarov reactions; vinyl halide hydrolysis products; hydroxy-trapped oxidized Prins product; proposed mechanism for formation of ketone **11l**; ^{1}H NMR study of erosion of dr after oxidation of **5l**; greater than 1 mmol scale experiments; applications of synthesized *halo*-Nazarov spirocycles; X-ray crystal data; NMR spectra (PDF)

Accession Codes

CCDC 2057559−2057564 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Spectrometry Resource Laboratory, and are thankful for the NIH instrument grant (S10OD021486).

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