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Synthesis of Polysubstituted Fused Pyrroles by Gold-Catalyzed Cycloisomerization/1,2-Sulfonyl Migration of Yndiamides

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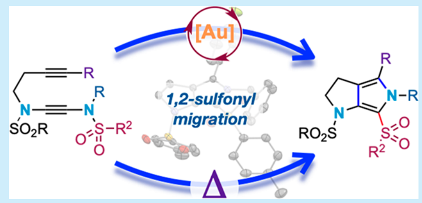
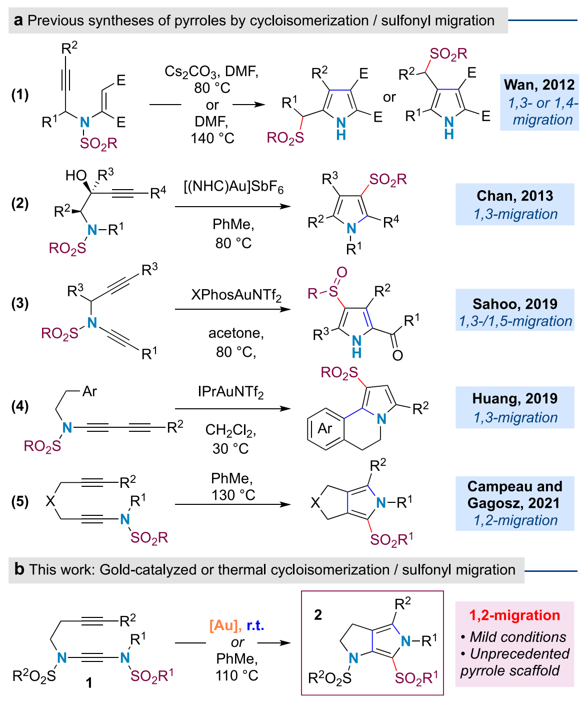
ABSTRACT: Yndiamides (bis-N-substituted alkynes) are valuable precursors to azacycles. Here we report a cycloisomerization/1,2-sulfonyl migration of alkynyl-yndiamides to form tetrahydropyrrolopyrroles, unprecedented heterocyclic scaffolds that are relevant to medicinal chemistry. This functional group tolerant transformation can be achieved using Au(I) catalysis that proceeds at ambient temperature, and a thermally promoted process. The utility of the products is demonstrated by a range of reactions to functionalize the fused pyrrole core.



Cycloisomerization is a powerful method for the synthesis of nitrogen heterocycles.[1] Pyrroles are no exception, for example, being accessible from unsaturated sulfonamides via cyclizations that are accompanied by N-to-C migration of the sulfonyl group.[2] Wan and co-workers described the first example of this strategy,[3] in which alkynyl ene-sulfonamides underwent cyclization under thermal conditions accompanied by 1,3- or 1,4-sulfonyl migration (Scheme 1, eq 1); soon after, a gold-catalyzed dehydrative cyclization of alkynyl sulfonamides was reported by the Chan group that also involved a 1,3-sulfonyl shift (eq 2).[4] The use of gold catalysis to promote cycloisomerizations of ynamides has emerged as a rich source of medicinally relevant heterocycles,[5,6] and accordingly, pyrroles have been prepared by cycloisomerizations of alkynyl ynamides (Sahoo et al., eq 3)[7] and diynamides (Huang et al., eq 4),[8] accompanied by 1,3/1,5- and 1,3-sulfonyl migrations, respectively. Contemporaneously with our studies, Gagosz et al. developed the first 1,2-sulfonyl rearrangement of ynamides, which under thermal conditions affords fused pyrroles (eq 5).[9]

Yndiamides [**1** (Scheme 1b)] are a relatively new addition to the ynamide family that feature a nitrogen substituent at both alkyne termini.[10] Building on our interest in transition metal-catalyzed ynamide cycloisomerization[11] and recent exploration of gold-catalyzed oxidative functionalizations of yndiamides,[12] we were keen to explore their reactivity in gold-catalyzed processes in which cyclization might be achieved. Alkynyl yndiamides **1** seemed well-suited for this, given the potential for activation of either triple bond.[6,13] Here we described the successful realization of this gold-catalyzed cycloisomerization, which unexpectedly resulted in a rare 1,2-migration of the sulfonyl group to give fused tetrahydropyrrolopyrroles **2**; unlike most previous sulfonyl migrations, the reaction proceeds under very mild conditions (ambient temperature) due to the unique activating properties of the yndiamide. The cyclization can also be achieved under thermal conditions, where it displays a complementary substrate scope. While benzannu-

Scheme 1. (a) Pyrrole Syntheses Involving 1,2-, 1,3-, or 1,4-Sulfonyl Migrations and (b) 1,2-Sulfonyl Migration of Yndiamides 1 in the Synthesis of the Unprecedented Tetrahydropyrrolopyrrole Scaffold 2



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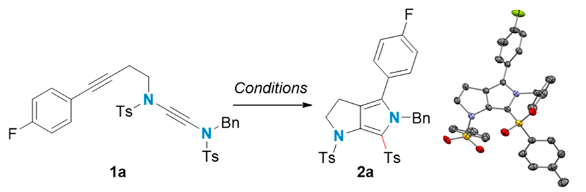
lated analogues of **2** (i.e., pyrrole[3,4-*b*]indoles) are known,[14] **2** itself represents a novel heterocyclic scaffold; given the importance of pyrroles in medicinal chemistry, and the value of methods that expand heterocycle chemical space,[16] access to this new framework could be of significant utility.

Investigations began with alkynyl yndiamide **1a** (Table 1), which was readily prepared from the corresponding benzyl 1,1-dibromoensulfonamide.[10,17] Exposure of **1a** to various gold(I) catalysts (10 mol %) at room temperature led to the formation of fused pyrrole **2a** (entries 1−5), with $Ph_3PAuNTf_2$ giving an optimal isolated yield of 72% after reaction for 3 h (entry 5).[17] The identity of **2a** was readily confirmed by single-crystal X-ray diffraction studies,[15] including the unexpected 1,2-migration of the sulfonyl group. Notably, the use of preformed $Ph_3PAuNTf_2$[18] offered a significant benefit over its *in situ* formation from PPh_3AuCl and $AgNTf_2$, which control experiments revealed is likely due to competing silver-promoted decomposition of the yndiamide.[17] A solvent screen identified 1,2-dichloroethane (DCE) as optimal, with other polar aprotic solvents such as chloroform and dichloromethane generating **2a** in lower yields (entries 6 and 7, respectively) and ethyl acetate and acetone resulting in extensive decomposition of **1a** (entries 8 and 9, respectively). No reaction was observed using a Brønsted acid catalyst ($HNTf_2$, entry 10) or in the absence of a catalyst (entry 11).

Table 1. Optimization of Cycloisomerization Conditions[a]



entry	additive/catalyst[b]	solvent	temp	time (h)	yield (%)[c]
1	Me_2AuCl	DCE	rt	18	19
2	$IPrAuNTf_2$	DCE	rt	18	55
3	Me_2SAuCl and $AgNTf_2$	DCE	rt	18	50
4	PPh_3AuCl and $AgNTf_2$	DCE	rt	3	50
5	PPh_3AuNTf_2	DCE	rt	3	75 (72)
6	$Ph_3PAuNTf_2$	$CHCl_3$	rt	3	67
7	$Ph_3PAuNTf_2$	CH_2Cl_2	rt	3	60
8	$Ph_3PAuNTf_2$	EtOAc	rt	3	12
9	$Ph_3PAuNTf_2$	acetone	rt	3	<5
10	$HNTf_2$	DCE	rt	3	6
11	–	DCE	rt	18	nr
12	–	DCE	80 °C	18	38
13	–	PhMe	110 °C	18	41
14	0.1 equiv of BHT	PhMe	110 °C	18	74
15	1.0 equiv of BHT	PhMe	110 °C	18	78 (76)
16	3.0 equiv of BHT	PhMe	110 °C	18	76

[a]Reactions carried out on a 0.033 mmol scale under Ar using an anhydrous solvent. The structure of **2a** was determined by single-crystal X-ray diffraction.[15] Abbreviations: BHT, butylated hydroxytoluene; DCE, 1,2-dichloroethane; IPr, 1,3-bis(2,6-diisopropylphenyl)-2-imidazolidinylidene. [b]All additives/catalysts loads are 10 mol %. [c]Yields determined by quantitative ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Yields in parentheses are isolated yields. nr indicates no reaction.

As cycloisomerizations formally require no external reagents, we questioned whether the same transformation could also be effected in the absence of a catalyst under thermal conditions.[9a] In the event, heating **1a** at 80 and 110 °C resulted in the formation of **2a** in moderate yield but with significant decomposition (entries 12 and 13, respectively). Pleasingly, addition of the radical inhibitor butylated hydroxytoluene (BHT) significantly improved yields (entries 14−16), with 1.0 equiv of BHT proving optimal (76% isolated yield, entry 15). While a substoichiometric quantity of BHT was equally effective for the synthesis of **2a** (0.1 equiv, 74%, entry 14), this loading gave inconsistent results for other substrates. We therefore elected to investigate the reaction scope using 1.0 equiv of BHT.

With optimized conditions for both gold-catalyzed (conditions A, Scheme 2) and thermal (conditions B) cycloisomerizations in hand, the scope of the transformation was evaluated. Both methods successfully afforded a wide range of pentasubstituted pyrroles, with several displaying contrasting behavior between the two conditions. We found that both reactions performed well on a 1 mmol scale with no detriment to yield **2a** [72% (0.43 g) and 76% (0.46 g) for [Au] and thermal conditions, respectively]. Aryl-substituted alkynes (**2a**−**2e**) were well tolerated under both gold catalysis (27−71%) and thermal conditions (63−95%), although the efficiency of the gold-catalyzed process decreased for electron-rich aromatics. In contrast, subjecting alkyl alkynyl yndiamide **1f** to gold catalysis gave methyl-substituted pyrrolopyrrole **2f** in 67% yield, whereas no reaction was observed under thermal conditions. Alkenyl groups were tolerated under gold catalysis (**2g** and **2h**), although the latter required an extended reaction time. However, whereas **2h** could also be formed via thermal cycloisomerization, **1g** decomposed when heated. Intriguingly, neither **1g** nor **1h** underwent (4+2) cycloaddition under heating, as might have been expected given the reactivity of analogous ynamides,[19] highlighting an aspect of divergence between ynamide and yndiamide chemistry. A terminal alkyne did not react under gold promotion, possibly as a result of formation of a σ-complex between the terminal alkyne and the Au(I) catalyst,[20] but did undergo the thermal cycloisomerization, albeit accompanied by extensive decomposition (**2i**, 22%).

We next investigated variation of the nonmigrating group on the pyrrole nitrogen atom (R^3). Replacing the *N*-benzyl group with an *n*-butyl chain was reasonably well-tolerated under thermal conditions (**2j**−**2l**, 28−71%), but significant decomposition was observed under gold catalysis (e.g., **2l**, 39%). Varying the electronic character of the *N*-benzyl group was similarly well-tolerated under conditions B (**2m** and **2n**, 66−72%), whereas the PMB protecting group in **1n** was problematic under gold catalysis, leading to a low yield; bromide-substituted **1m** afforded only trace product.

The scope of the yndiamide EWG groups was next probed. Changing the sulfonyl protecting group on the internal nitrogen atom to a methanesulfonyl group maintained high yields under both Au catalysis and heating (both 72%, **2o**). Variation of the migrating sulfonyl group revealed that aryl sulfonamides underwent cycloisomerization under both thermal and gold-catalyzed conditions in moderate to good yields (**2p**−**2r**, 45−81%), albeit more electron-deficient sulfonamides were less efficient under the latter. An alkyl sulfonamide was successful only using gold catalysis (**2s**, 25%), possibly due to competing deprotonation under thermal

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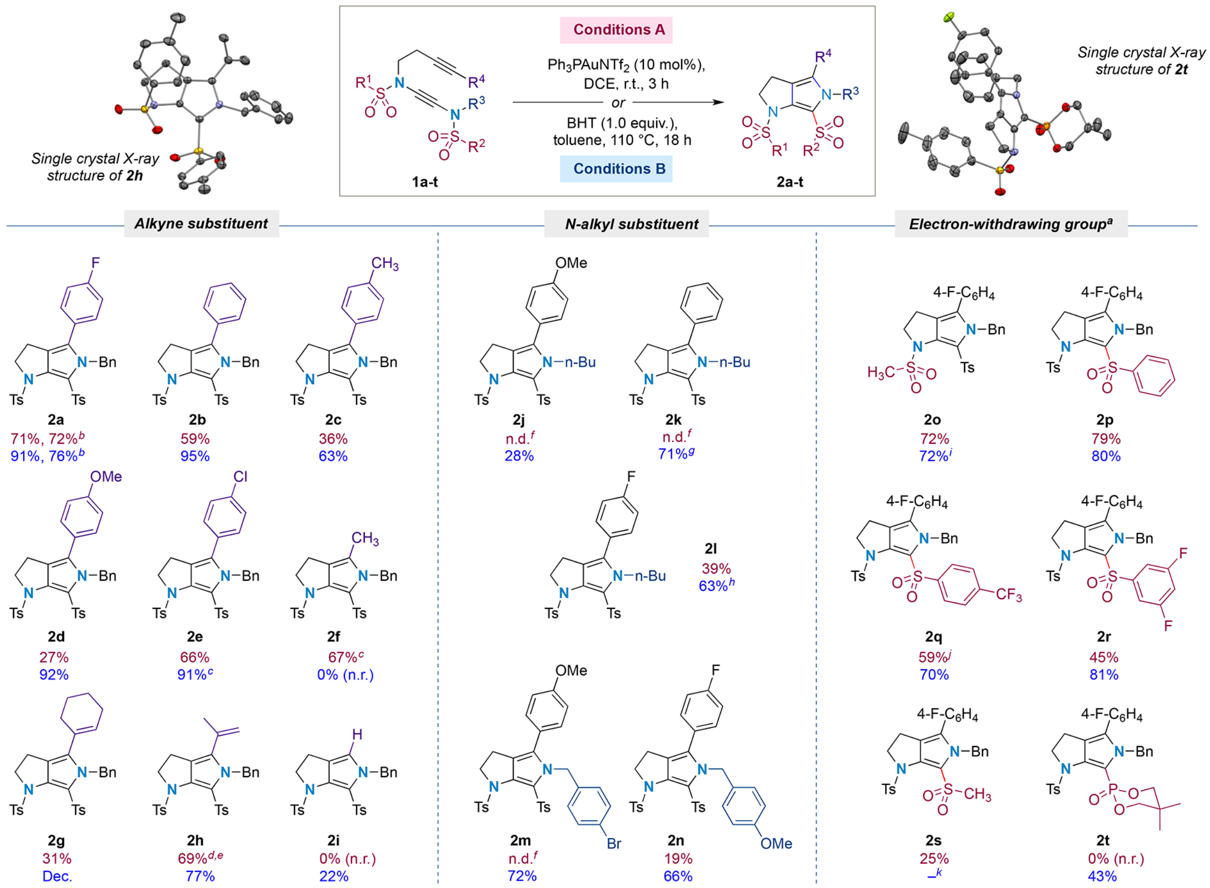
Scheme 2. Scope of Gold-Promoted (conditions A, red yields) and Thermal (conditions B, blue yields) Yndiamide Cycloisomerization[a]



[a]Reactions carried out on a 0.1 mmol scale, under Ar in an anhydrous solvent; yields are isolated yields. n.r. indicates no reaction [b]On a 1.0 mmol scale. [c]On a 0.05 mmol scale. [d]Reaction time of 42 h. [e]The structures of **2h** and **2t** were determined by single-crystal X-ray diffraction.[15] [f]Yield not determined (n.d.) due to significant decomposition. [g]With 3.0 equiv of BHT. [h]With 0.1 equiv of BHT. [i]On a 0.06 mmol scale. [j]Reaction time of 24 h. [k]Reaction not conducted.

conditions to form a sulfene, a pathway that is not possible for arylsulfonamides.[4] Attempts to investigate the migration of an electron-rich sulfonyl group [4-(MeO)$C_6H_4SO_2$] were unsuccessful, as the corresponding yndiamide was unstable. Pleasingly, a phosphonate-protected yndiamide also underwent successful thermal cycloisomerisation in moderate yield (**2t**, 43%). Whereas reports of sulfonyl migrations (including in ynamide cycloisomerization) have become more numerous in recent years,[2] equivalent migrations of phosphonate diesters are, to the best of our knowledge, without precedent.[21] Interestingly, equivalent ynamide substrates required extended reaction times and/or suffered from decomposition under gold catalysis and proved to be significantly less reactive under thermal conditions.[17]

The nature of the sulfonyl migration step was investigated via a crossover experiment with yndiamides **1d** and **1q** (Scheme 3a). No crossover products were observed under thermal conditions, suggesting that the sulfonyl migration is an intramolecular process, which is consistent with previously reported 1,*n*-sulfonyl/sulfinyl migrations with ynamides as starting materials.[4,7] Equally, no crossover was observed under gold catalysis.[17]

A possible mechanism for the thermal cycloisomerization is illustrated in Scheme 3b.[22] Under these conditions, a concerted (3+2) cycloaddition could give zwitterionic intermediate **A**, followed by an intramolecular 1,2-migration of the sulfonyl group. A rapid Stevens-type rearrangement may also be possible involving the transient formation of a sulfonyl radical **B**/**B′**[23] that is rapidly captured by the C2-pyrrolyl radical; both mechanisms would be consistent with the results of the crossover experiment. There are many proposals of both radical and polar pathways for sulfonyl migrations in the literature,[2] but as the reaction proceeds efficiently even in the presence of excess BHT (Table 1, entry 5), the polar migration process seems more likely.[9a] The role of the BHT additive itself is less clear; as it can be used in substoichiometric amounts, we hypothesize that it sequesters peroxy radicals that might otherwise initiate diyne degradation pathways.[9a,19,24]

For the Au-catalyzed reaction (Scheme 3c), we propose initial coordination of the yndiamide to a π-acidic Au(I) species, activating the triple bond toward attack by the alkyne (**C**).[25] For yndiamides, this process would be followed by formation of a keteniminium ion **D**, enhancing the electrophilicity of the π-bond and triggering nucleophilic attack to give vinyl cation **E**.[26] It is notable that intermediate **D** cannot be formed for ynamides (which lack the internal nitrogen atom), thus explaining their lower reactivity. Vinyl cation **E**[26,27] is then trapped by the external nitrogen atom of the yndiamide, to form the second ring (**F**). A 1,2-sulfonyl migration [which could also be viewed as a (1,5)-sigmatropic rearrangement],

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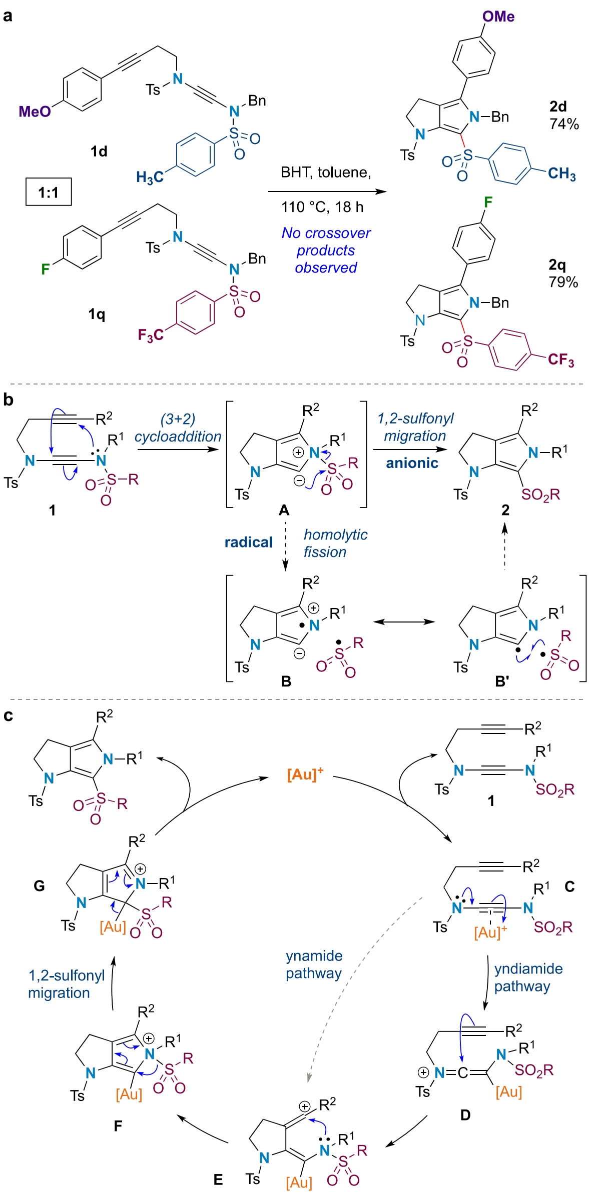
Scheme 3. Crossover Experiment and Mechanistic Proposals[a]

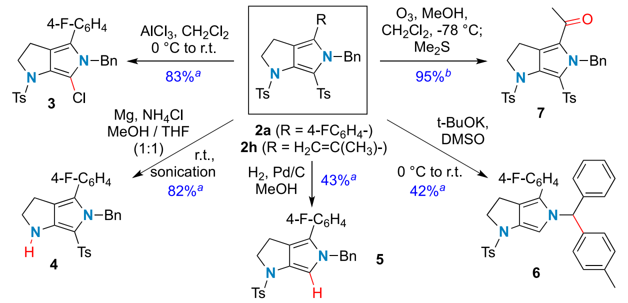


[a](a) Reaction carried out on a 0.033 mmol scale, yields determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. (b) Proposed mechanism for thermal cycloisomerization. (c) Proposed mechanism for Au-catalyzed cycloisomerization.

followed by aromatizing deauration of **G**, leads to the product and re-forms the cationic Au(I) species to complete the catalytic cycle.

The novel bicyclic structures formed in this cycloisomerization are appealing from the perspective of expanding heterocycle chemical space,[16] as the sulfonamide protecting groups present in the products (*N*-Ts and *C*-Ts) have the potential for removal under orthogonal conditions, allowing for selective postcycloisomerization diversification. For example (Scheme 4), treatment of **2a** with $AlCl_3$ resulted in efficient substitution of the *C*-Ts group with chlorine (**3**, 83%), while selective removal of the *N*-Ts protecting group could be achieved with magnesium to form **4** in good yield (82%). Hydrogenation of **2a** selectively removed the *C*-Ts group to form **5** in moderate yield (43%). Treatment of **2a** with *t*-BuOK in DMSO resulted in a desulfonative Smiles-type rearrangement to form **6**. Finally, ozonolysis of the alkene side chain in **2h** afforded acyl pyrrole **7** in excellent yield (95%). The ability to derivatize the core scaffold in this way enhances prospects for the use of these novel structures in, for example, pharmaceutical research.

Scheme 4. Further Transformations of 2a and 2h



[a]On a 0.05 mmol scale. [b]On a 0.025 mmol scale.

In conclusion, we have developed a novel cycloisomerization of yndiamides to form fused tetrahydropyrrolopyrroles. The reaction proceeds under mild conditions using cationic gold catalysts but can also be performed under thermal conditions with a complementary substrate scope. The use of gold catalysts to promote this transformation provides the benefit of avoiding stoichiometric amounts of the radical inhibitor and enhances the tolerance of thermally sensitive functional groups. The highly functionalized nitrogen heterocycles that result represent an unprecedented bicyclic scaffold, which will be of interest for medicinal chemistry and biological applications. The transformation underlines both the utility and the unique behavior of yndiamides in N-heterocycle synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02360.

Experimental procedures and characterization data for novel compounds (PDF)

Accession Codes

CCDC 2090822–2090824 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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