

# Nickel-Catalyzed C(sp<sup>3</sup>)-H Functionalization of Benzyl Nitriles: Direct Michael Addition to Terminal Vinyl Ketones

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**ABSTRACT:** An efficient nickel(0)-catalyzed addition of benzyl nitriles to terminal vinyl ketones via C(sp<sup>3</sup>)-H functionalization has been developed. The reaction provides a novel and efficient protocol for the synthesis of  $\alpha$ -functionalized benzyl nitriles with a wide range of structural diversity under mild reaction conditions while obviating the use of a strong base. The work might be potentially useful toward the development of an enantioselective variant using chiral nitrogen ligands.

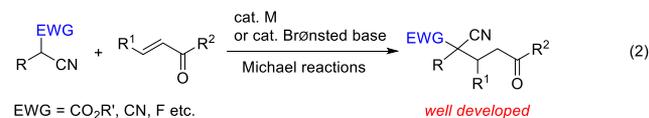
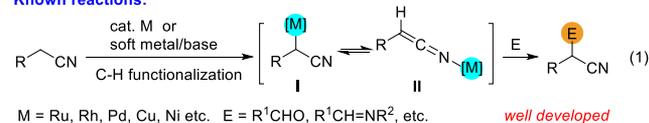


Transition-metal-catalyzed C(sp<sup>3</sup>)-H bond activation or functionalization reactions have attracted much interest in recent years because they provide the atom-economic routes for the construction of carbon-carbon or carbon-heteroatom bonds.<sup>1</sup> Among the various reactions, metal-catalyzed<sup>2</sup> and cooperative soft-metal Lewis acid- or base-catalyzed<sup>3</sup>  $\alpha$ -functionalizations of organonitriles represent some of the most efficient approaches for the synthesis of diversely substituted nitriles, which not only serve as common structural motifs in pharmaceuticals and agrochemicals but also work as important building blocks in organic chemistry.<sup>4</sup> Upon the coordination of the cyano group with the transition metal, the  $\alpha$ -C-H acidity of the nitrile substrate could be enhanced, resulting in either the  $\alpha$ -metalated nitrile I or the N-bound complex II, which undergoes further reactions with electrophiles such as aldehydes or imines to furnish the functionalized products (Scheme 1, eq 1). Although the  $\alpha$ -deprotonated nitriles could

also be generated by a base, a strong base such as LDA<sup>5</sup> or proazaphosphatranes<sup>6</sup> is usually required due to the low acidity of  $\alpha$ -protons in nitriles (for PhCH<sub>2</sub>CN, pK<sub>a</sub> = 21.9 in DMSO),<sup>7</sup> which may cause undesirable side products. Michael-type reactions of nitriles with  $\alpha,\beta$ -unsaturated carbonyl compounds could also be achieved through metal-catalyzed<sup>8</sup> or Brønsted base (organocatalysis)-catalyzed<sup>9</sup> C-H functionalization reactions (Scheme 1, eq 2). However, in both methods the scope of the nitriles is usually restricted to those bearing an additional geminal electron-withdrawing (EWG) group with higher  $\alpha$ -C-H acidity to be able to engage in the reaction processes, such as  $\alpha$ -cyano esters,  $\alpha$ -cyanoacetic acids,  $\alpha$ -sulfonyl nitriles, malononitriles,  $\alpha$ -fluorobenzyl nitriles,  $\alpha,\alpha$ -dithioacetone nitriles, etc. (Scheme 1, eq 2). Reports on the use of benzyl nitriles without an additional EWG group at the benzylic position are significantly scarce, especially when terminal vinyl ketones are employed as the Michael acceptors. Possibly, terminal vinyl ketones tend to oligomerize in the presence of the transition metal catalysts or under strong basic conditions.<sup>10</sup> It was reported that benzyl nitriles bearing a strong electron-withdrawing group (-NO<sub>2</sub>) at the phenyl ring were able to participate in organocatalytic Michael additions to  $\alpha,\beta$ -unsaturated aldehydes.<sup>11</sup> To our knowledge, there is no report for the metal-catalyzed Michael reaction of terminal vinyl ketones with normal benzyl nitriles. Herein we report the first example of a Ni(0)-catalyzed Michael-type reaction of benzyl nitriles without an additional EWG group at the benzylic position with terminal vinyl ketones under the mild

## Scheme 1. Metal- or Brønsted Base-Catalyzed C-H Functionalization of Nitriles

### Known reactions:



### This work:



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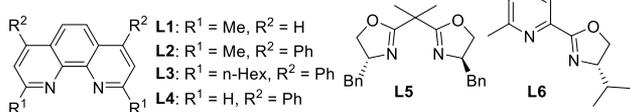
reaction conditions. This new method offers an expanded substrate scope with respect to both nitriles and  $\alpha,\beta$ -unsaturated ketones.

Initially, we chose the benzyl nitrile **1a** bearing an *ortho*-alkynyl substituent as the model substrate for optimizing the reaction conditions with 1-phenylprop-2-en-1-one **2a**. It is known that vinyl ketones undergo oligomerization in the presence of a low-valent nickel catalyst,<sup>12</sup> and such a side reaction might compete with the main reaction pathway. We reasoned that the judicious choice of the reaction conditions might solve the problem. After the evaluation of the reaction parameters, such as nickel catalysts, ligands, additives, solvents, and substrate concentration (see the [Supporting Information](#) for details), we were pleased to find that the desired Michael reaction of **1a** with **2a** occurred at 80 °C when using Ni(cod)<sub>2</sub> as the catalyst, a 1,10-phenanthroline-type ligand (**L3**) as the ligand, and 4 mol % PhNHTs as the additive. The expected product **3a** was formed in a 76% yield (Table 1, entry 1).

**Table 1. Optimization of the Reaction Conditions<sup>a</sup>**



Entry	Deviation from standard conditions	yield (%) <sup>b</sup>
1	none	76
2	no PhNHTs	56
3	BnNHTs instead of PhNHTs	70
4	PhNHMs instead of PhNHTs	74
5	TsNHBoc or TsNH <sub>2</sub> instead of PhNHTs	66–69
6	10 mol% PhNH <sub>2</sub> was used instead of PhNHTs	64
7	20 mol% H <sub>2</sub> O or EtOH was used instead of PhNHTs	65–73
8	10 mol% PhNHTs was used	76
9	PPh <sub>3</sub> instead of <b>L3</b>	26
10	dppf instead of <b>L3</b>	7
11	<b>L1</b> instead of <b>L3</b>	66
12	<b>L2</b> instead of <b>L3</b>	70
13	<b>L4</b> instead of <b>L3</b>	31
14	<b>L5</b> instead of <b>L3</b>	46 <sup>c</sup>
15	<b>L6</b> instead of <b>L3</b>	55 <sup>d</sup>
16	2,2':6',2''-terpyridine instead of <b>L3</b>	48
17	Ni(acac) <sub>2</sub> instead of Ni(cod) <sub>2</sub>	61
18	dioxane instead of toluene	71
19	DMF or CH <sub>3</sub> CN instead of toluene	41–45
20	no nickel catalyst	0
21	no ligand	32



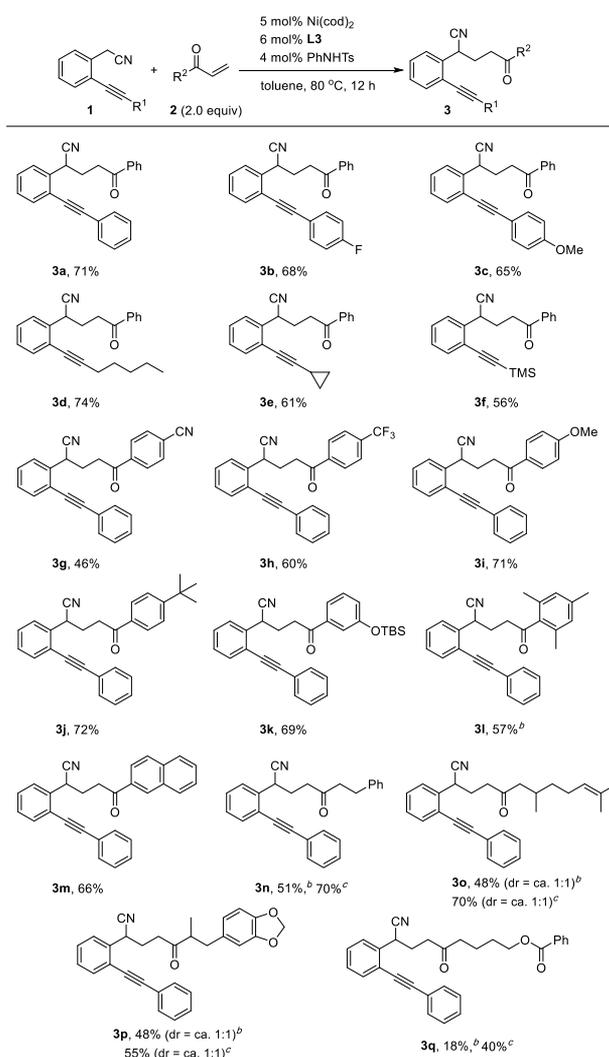
<sup>a</sup>Reaction conditions are as follows: **1a** (0.2 mmol), **2a** (0.4 mmol), Ni(cod)<sub>2</sub> (0.01 mmol), ligand (0.012 mmol), additive (0.008 mmol), solvent (2 mL), 80 °C, 12 h. <sup>b</sup>Determined by <sup>1</sup>H NMR using 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup>The ee value is –4.0%. <sup>d</sup>The ee value is 10.9%.

Without PhNHTs, a lower yield of 56% was obtained (Table 1, entry 2). Other *N*-tosyl or *N*-mesylamines, PhNH<sub>2</sub>, and even H<sub>2</sub>O and EtOH were also effective for reaction, leading to **3a** in 64–74% yields (Table 1, entries 3–7, respectively). We found that the steric and electronic properties of the ligands on the nickel catalyst have a significant influence on the reaction course, and less basic phosphine ligands such as PPh<sub>3</sub> and dppf

provided **3a** in only 7–26% yields (Table 1, entries 9 and 10, respectively). 1,10-Phenanthroline-type ligands bearing a substituent at the C-2 or C-9 position, such as neocuproine (**L1**) and 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline (**L2**), gave **3a** in 66–70% yields, while the use of **L4** without a substituent at the C-2 position afforded **3a** in a low yield (Table 1, entries 11–13, respectively). Possibly, the stability of the nickel-containing intermediates could be enhanced by more encumbered ligands of **L1**–**L3**. Employing oxazoline- or pyridine–oxazoline-type ligands or terpyridine led to **3a** in 46–55% yields (Table 1, entries 14–16, respectively). The reaction could also proceed efficiently in dioxane, while DMF or CH<sub>3</sub>CN were less effective (Table 1, entries 18 and 19, respectively). No desired product was observed in the absence of Ni(cod)<sub>2</sub>. However, **3a** could also be formed without a ligand, albeit with a low yield of 32% (Table 1, entries 20 and 21). Reactions catalyzed by pincer-type Ni(II) complexes that involve the addition of alkyl nitriles such as acetonitrile to aldehydes or aldimines have been developed by Ozerov,<sup>3d</sup> Shibasaki,<sup>13</sup> and Guan et al.;<sup>14</sup> however, the use of a Ni(0) catalyst for the activation of nitriles is quite rare.

Next, the substrate scope of these nickel-catalyzed reactions of nitriles with vinyl ketones was examined (Scheme 2). To our delight, a wide range of *o*-alkynylbenzyl nitriles and vinylketones could be accommodated in this reaction. The scope of *o*-alkynylbenzyl nitriles was first investigated using **2a** as the reaction partner. Alkynes bearing *p*-F or *p*-OMe groups at the terminal aryl rings were well-tolerated, leading to the corresponding ketones **3b**–**3c** in 65–68% yields. Alkyl-substituted alkynes such as those bearing an *n*-pentyl or cyclopropyl substituent reacted with **2a** smoothly to give **3d** and **3e**, respectively, in good yields. A TMS-substituted alkyne was also suited (**3f**). Next, the scope of the vinyl ketones was examined. Aryl vinyl ketones bearing either electron-withdrawing (*p*-CN and *p*-CF<sub>3</sub>) or electron-donating (*p*-OMe and *p*-<sup>t</sup>Bu) substituents on the aryl rings transformed efficiently to the corresponding products **3g**–**3j**. Generally, the more electron-rich vinyl ketones afforded the products in higher yields, possibly due to the diminished side reactions. A *m*-OTBS-substituted aryl vinyl ketone was also suitable (**3k**). Substrates with a sterically demanding group such as mesityl and 2-naphthyl groups also worked well, leading to the corresponding products **3l** and **3m** in 57–66% yield. Besides, various alkyl-substituted vinyl ketones also smoothly underwent the addition of nitriles, and the phenyl, alkenyl, 1,3-benzodioxole, and ester groups on the alkyl side chains were well-tolerated (**3n**–**3q**, respectively). It was noted that using 1.0 equiv of NaHCO<sub>3</sub> instead of PhNHTs in the presence of 10 mol % Ni(cod)<sub>2</sub> and 12 mol % **L3** gave higher yields of these products. No desired products were observed when styrene or phenyl acetylene was employed instead of **2a**. It was also noted that products purified through column chromatography on silica gel contained a trace amount of impurity in some cases. These products were further purified using recycling preparative HPLC. Alternatively, the ketone products **3** could be easily reduced to the corresponding alcohols by NaBH<sub>4</sub>, and the alcohols were then purified with a high purity by column chromatography (see the [Supporting Information](#) for details).

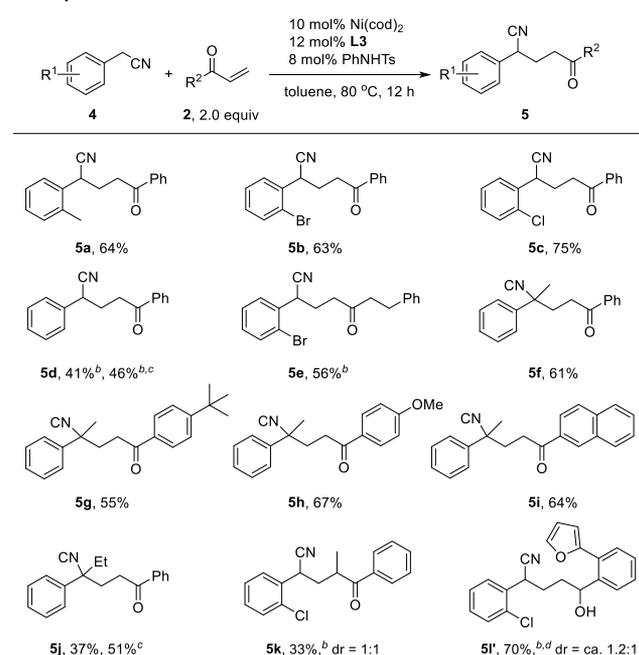
The above results encouraged us to evaluate the reactivities of benzyl nitriles without an alkynyl group (Scheme 3). To our delight, a series of benzyl nitriles smoothly converted to the corresponding products. The use of *ortho*-substituted benzyl

Scheme 2. Scope of the Substrates<sup>a</sup>

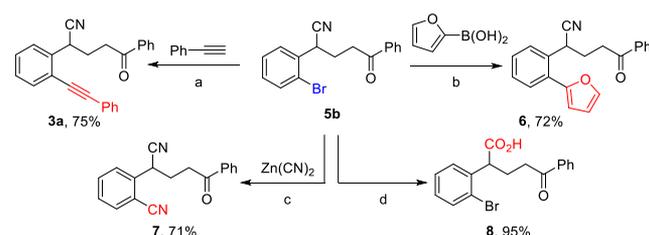
<sup>a</sup>Isolated yields. <sup>b</sup>Used 10 mol % Ni(cod)<sub>2</sub>, 12 mol % L3, and 8 mol % PhNHTs. <sup>c</sup>Used 10 mol % Ni(cod)<sub>2</sub>, 12 mol % L3, and 1.0 equiv of NaHCO<sub>3</sub>.

nitriles such as *o*-Me-, *o*-Br-, and *o*-Cl-substituted ones resulted in good yields of the desired products (5a–5c, respectively). Notably, a Br or Cl substituent was well-suited and could be further elaborated through metal-catalyzed coupling reactions. Benzyl nitrile bearing no substituent on the phenyl ring afforded the addition product 5d in a lower yield (41%) when using NaHCO<sub>3</sub> instead of PhNHTs. When an alkyl vinyl ketone was used as the Michael acceptor, a 56% yield of product 5e was observed. Reactions with secondary benzyl nitriles were also compatible (5f–5j). However, increasing the steric bulkiness of the benzylic substituent resulted in a lower product yield (5j), indicating that the reaction is sensitive to the steric bulk of the benzyl nitrile. However, an *ortho*-furanly-substituted vinyl ketone worked efficiently in this reaction (5l'). It was noted that in some cases the starting materials were not consumed completely. When the reactions for 5d and 5j were carried out for 24 h, the yields could be improved to 46–51%.

To illustrate the synthetical utility of this method, various transformations of product 5b was performed (Scheme 4). The palladium-catalyzed cross-coupling of 5b with furan-2-ylbor-

Scheme 3. Nickel-Catalyzed Michael Reactions of Common Benzyl Nitriles<sup>a</sup>

<sup>a</sup>Isolated yields. <sup>b</sup>Used 1.0 equiv of NaHCO<sub>3</sub> instead of PhNHTs. <sup>c</sup>Twenty-four hours. <sup>d</sup>After reduction with NaBH<sub>4</sub>.

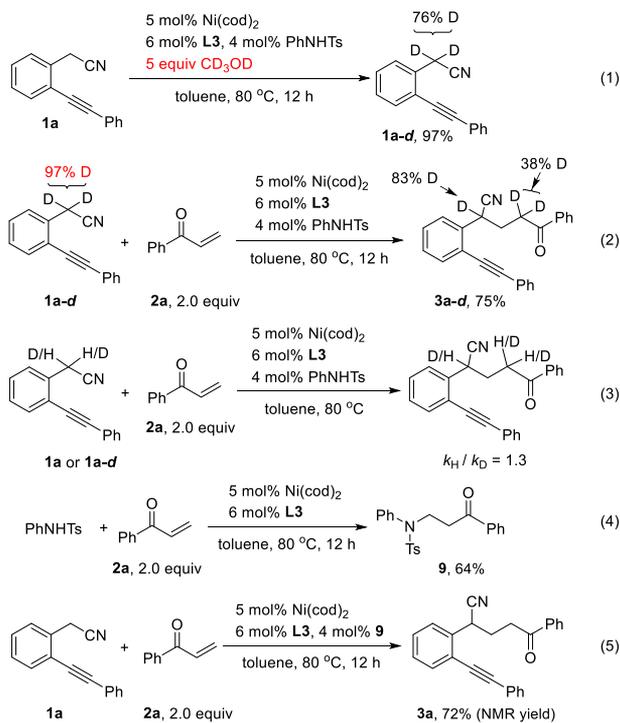
Scheme 4. Transformation of 5b<sup>a</sup>

<sup>a</sup>Conditions are as follows: (a) 5 mol % Pd(PPh<sub>3</sub>)<sub>4</sub>, 3 mol % CuI, Et<sub>3</sub>N, 80 °C, 13 h; (b) 3 mol % PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, toluene/EtOH/saturated K<sub>2</sub>CO<sub>3</sub>, 80 °C, 12 h; (c) 5 mol % NiCl<sub>2</sub>·6H<sub>2</sub>O, 6 mol % dppe, 20 mol % Zn, 1.0 equiv of DMAP, CH<sub>3</sub>CN, 80 °C, 5 h; and (d) NaOH (aq), EtOH, 80 °C, 6 h.

onic acid or phenylacetylene afforded 6 or 3a in a high yield, respectively. The cyanation product 7 was obtained in a 71% yield when using Zn(CN)<sub>2</sub> as the cyanide source in the presence of a nickel catalyst.<sup>15</sup> The treatment of 5b with NaOH in EtOH gave carboxylic acid 8 in a 95% yield.

To understand the reaction mechanism, we performed the following experiments (Scheme 5). In the presence of 5 equiv of CD<sub>3</sub>OD, significant deuterium incorporation was found at the benzylic position after treating 1a under the standard conditions (Scheme 5, eq 1). The result indicates that the α-C–H bond of benzyl nitrile could be activated under the nickel catalysis. The Michael reaction of deuterium-labeled 1a-d afforded the addition product with 38% deuterium incorporation at the α-position of the ketone moiety (Scheme 5, eq 2). A kinetic isotope effect (KIE) of *k*<sub>H</sub>/*k*<sub>D</sub> = 1.3 was observed by comparing the initial rates for the independent reactions using either substrate 1a or 1a-d, implying that the C–H bond cleavage is likely not involved in the rate-determining step (Scheme 5, eq 3). Interestingly, the conjugate addition of

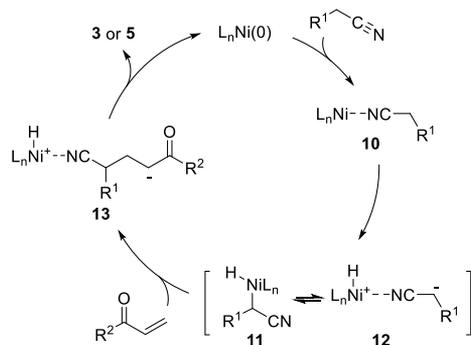
## Scheme 5. Mechanistic Studies



PhNHTs with a vinyl ketone occurs efficiently when using  $Ni(cod)_2/L3$  as the catalyst, leading to **9** in a 64% yield (Scheme 5, eq 4).<sup>16</sup> When the nickel-catalyzed reaction of **1a** with **2a** was carried out using **9** as the additive instead of PhNHTs, the desired **3a** was also formed in a good yield (Scheme 5, eq 5). The results indicated that the addition product **9** might also play a role in promoting the Michael reaction of benzyl nitriles. Possibly, PhNHTs or **9** acts as a coligand to stabilize the nickel intermediates and reduce the number of side reactions.<sup>17</sup>

A proposed reaction mechanism for this nickel-catalyzed Michael reaction of nitriles is shown in Scheme 6, which is

## Scheme 6. Possible Reaction Mechanism



analogous to those proposed for the Ru-catalyzed reaction.<sup>2b</sup> Initially, the coordination of the nitrile to a low-valent  $L_nNi(0)$  complex occurs, which can increase the basicity of the metal and the acidity of the  $\alpha$ -proton in the nitrile. The oxidative addition of  $L_nNi(0)$  to the  $\alpha$ -C–H bond affords the hydrido- $\alpha$ -cyanobenzyl nickel complex **11**, which may form an equilibrium with the N-bound zwitterionic intermediate **12**. The Michael addition of **11** or **12** to the vinyl ketone delivers

the nickel complex **13**, which eliminates the organic product via proton transfer and regenerates the  $Ni(0)$  species. However, we could not exclude the reaction pathway involving  $Ni(II)$  as the catalyst,<sup>3d,13,14</sup> which may be formed in situ. As suggested by a reviewer, PhNHTs may also play a role as a “proton shuttle”<sup>18</sup> to promote the proton transfer from the benzylic position of the nitrile to the  $\alpha$ -position of the ketone product.<sup>19</sup>

In summary, we have disclosed an efficient nickel(0)-catalyzed addition of benzyl nitriles to vinyl ketones. The reaction provides a novel and efficient protocol for the synthesis of  $\alpha$ -functionalized benzyl nitriles with a wide range of structural diversity under mild reaction conditions while obviating the use of strong base. The work would be potentially useful toward the development of an enantioselective variant using chiral nitrogen ligands. Further investigations into the reaction mechanism and the explorations of related transformations using benzyl nitriles are in progress.

## ■ ASSOCIATED CONTENT

## SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c02074>.

Experimental details and spectroscopic characterization of all products and new substrates and crystal data and structural refinement for **3a**, (PDF)

## Accession Codes

CCDC 2077284 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto: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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