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One Step Selective Counterion Dependent Formation of Conjugated Chiral N-Sulfinylimines from Aldehydes

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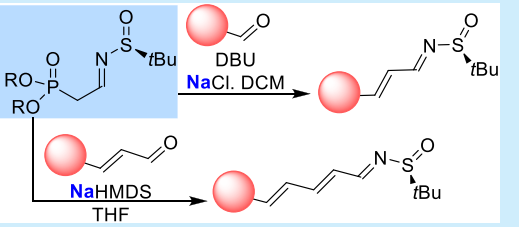
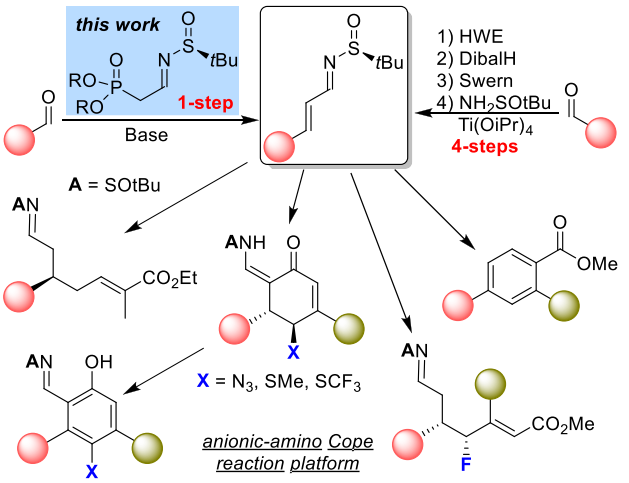
ABSTRACT: We report a detailed study on the synthesis and aldehyde vinylogation applications of chiral N-sulfinyl imine phosphonate reagents. Two complementary scalable reagent routes, from trialkyl phosphites and methyl phosphonates, respectively, are presented. This reagent class enables significant streamlining in synthesis of conjugated Ellman imines from aldehydes, which can now be accomplished in a single step compared to a more classic 4-step redox-based approach. Aldehyde vinylogation optimizations have revealed significant counterion effects and unexpected competing reaction challenges that needed to be addressed to achieve high yields.



A few years ago, we reported a new asymmetric anion-accelerated amino Cope rearrangement platform that involved the union of an ester dienolate, lithium counterion, and a conjugated chiral sulfinylimine (Scheme 1). We have

Scheme 1. Streamlining Synthesis of Conjugated Sulfinylimines for Anionic Amino-Cope Cascade Platform



shown that chiral cyclohexenone products are obtained with 3-substituted dienolates, while chiral acyclic products of the opposite configuration are realized with 2-substituted dienolates.[1] When heteroatom substituents are placed at the 4-position of the dienolates, chiral cyclohexenones with a second stereocenter, anti to the first, can be realized for certain substituents (N_3, SMe and SCF_3), while, when a 4-fluoro substituent was employed, an acyclic product with syn-stereochemical relationship of the newly formed centers was formed.[2] Treatment of the cyclohexenone products with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) yields complex phenol products in only 2-steps from the sulfinylimine.[3] With the success of this new program established and many investigative avenues currently underway,[4] it became apparent that we needed to improve how to make the chiral conjugated chiral sulfinylimine starting material (in box), which until now we had been made using a classic 4-step sequence from an aldehyde starting material involving (1) Horner−Wadsworth−Emmons (HWE) reaction, (2) ester reduction with diisobutylaluminum hydride (DIBAL-H), (3) Swern oxidation, and (4) an Ellman imine condensation using $Ti(OiPr)_4$.[5] Two years after our first amino-Cope efforts was reported, we came across the first and only example of utilizing the imino phosphonate reagent shown (highlighted in blue) for total synthesis of jatrophalactam by the Ding group[6] to accomplish the same overall transformation in a single step. This represents a streamlining synthesis gamechanger for our amino-Cope research program and for anyone planning to use conjugated chiral sulfinylimines, which is why we embarked on developing large scale synthesis routes to assemble this exciting new class of reagents and optimize their use for vinylogation of a wide variety of aldehydes. These efforts have uncovered fascinating insights into these reagents, their counterion dependence, unexpected competing side reaction pathways, and the need for different reaction conditions for conjugated vs nonconjugated aldehydes.

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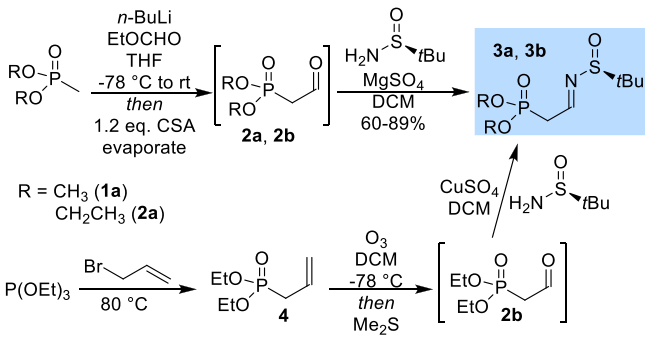
We started our efforts by focusing on developing scalable routes to make this new class of chiral sulfinylimine phosphonate reagents. Toward that end, we have developed two complementary routes from readily available commercial building blocks (Scheme 2). Of these two our preferred route

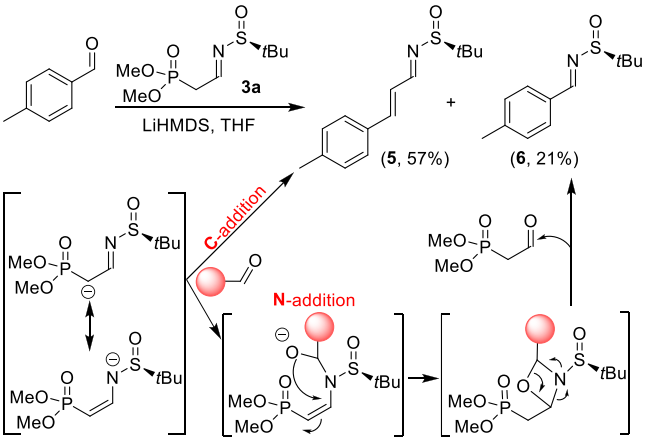
Scheme 2. Scalable Syntheses of Chiral Sulfinylimine Phosphonate Reagents 3a and 3b



commences with lithiation of dimethyl methyl phosphonate (R = Me, **1a**), which also works equally well with diethyl methyl phosphonate **1b**), followed by trapping of the resulting anion with ethyl formate. Quenching the reaction with 1.2 equiv of camphorsulfonic acid (CSA) enables direct telescoping of the intermediate known aldehyde[7] after evaporation of solvent and addition of dichloromethane and magnesium sulfate ($MgSO_4$) along with the chiral sulfinamide auxiliary to afford the desired reagents (**3a** and **3b**) in an overall yield of 60−89%. In this sequence, the residual CSA in partnership with magnesium sulfate drives imine formation. In the complementary approach, a neat Arbuzov reaction between triethyl phosphite and allyl bromide forms diethyl allylphosphonate **4**, which is then subjected to ozonolysis and a dimethylsulfide (DMS) workup to furnish crude aldehyde **2b**. After evaporation of solvent, imine formation is driven by copper sulfate ($CuSO_4$) to yield **3b**. It is worth noting that the diethyl acetal of the central aldehyde our two routes proceed via (diethyl 2,2-diethoxyethylphosphonate) is commercially available and can be deprotected to form the aldehyde, but we concluded it was too expensive as source material ($10+ per gram).

With only a single example of using these reagents reported in the literature,[6] much remains to be learned about their reaction behaviors, scope, limitations, and broader potential. In this context it is important to note that imine phosphonates have been developed and utilized in the past to convert aldehydes into conjugated aldehyde via vinylogation followed by deprotection of the intermediate conjugated imines. Examples of N-R imine substituents that have been explored include t-butyl (*t*-Bu),[8] cyclohexyl (Cy),[9] phenyl (Ph),[10] dialkylhydrazone (NR_2),[11,12] tosylhydrazone (NHTs),[13] and oxime (OR).[14] When benchmarking published reaction conditions as part of our optimization journey, we quickly encountered an unanticipated competing pathway, not previously reported, wherein, in addition to the desired Horner−Wadsworth−Emmons type vinylogation product, we isolated significant amount of an aryl imine, which had not undergone vinylogation (Scheme 3). We postulate that this is a case of initial C- vs N-addition to the aldehyde, with C-addition pathway being the expected one and the N-addition one opening the door for an intramolecular oxy-Michael cyclization onto vinyl phosphonate forming an intermediate

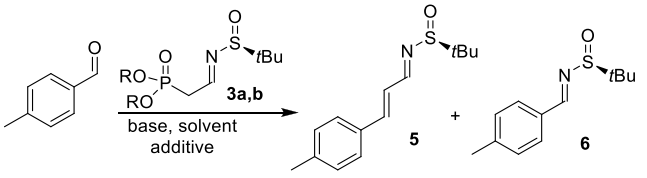
Scheme 3. Lithium Mediated C- vs N-Addition to Aldehyde—Unexpected Reaction Pathway



1,3-oxazetidine en route to the undesired aryl imine product. With a competing pathway established, we set out to optimize the vinylogation process while suppressing this unwanted reaction pathway.

We used para-tolualdehyde as a model substrate for our vinylogation optimization studies (Table 1). As discussed, using lithium bis(trimethylsilylamide) (LiHMDS), which was employed in the only reported example, we achieved the desired vinylogation results and formation of **5**, except this was

Table 1. Aldehyde Vinylogation Optimization Studies[a]



entry	base (equiv)	additive	solvent (M)	ratio (**5**:**6**)	**5** yield (%)
1	LiHMDS (1.2 equiv)	none	THF (0.5 M)	4:1	42
2	LiHMDS (1.5 equiv)	none	THF (0.5 M)	3:2	57
3	NaHMDS (1.5 equiv)	none	THF (0.5 M)	7:1	79
4	KHMDS (1.5 equiv)	none	THF (0.5 M)	nd	12
5	DBU (1.2 equiv)	1.2 equiv LiCl	MeCN (0.1 M)	2:3	18
6	DBU (1.2 equiv)	1.2 equiv NaCl	MeCN (0.1 M)	1:0	71
7	DBU (1.2 equiv)	1.2 equiv KCl	MeCN (0.1 M)	1:0	71
8	DBU (1.2 equiv)	1.2 equiv NaCl	MeCN (0.25 M)	1:0	69
9	DBU (1.2 equiv)	1.2 equiv NaCl	DCM (0.25 M)	1:0	64
10	DBU (1.2 equiv)	1.2 equiv NaCl	MeCN (0.5 M)	1:0	78
11	DBU (1.2 equiv)	1.2 equiv NaCl	DCM (0.5 M)	1:0	84
12	DBU (1.5 equiv)	1.2 equiv NaCl	DCM (0.5 M)	1:0	**90**

[a]All reactions used 1.2 equiv of phosphonates **3a** or **3b** and were run for 24 h at room temperature. Entries 1−11 used **3b**, while entry 12 used **3a**. nd = not determined.

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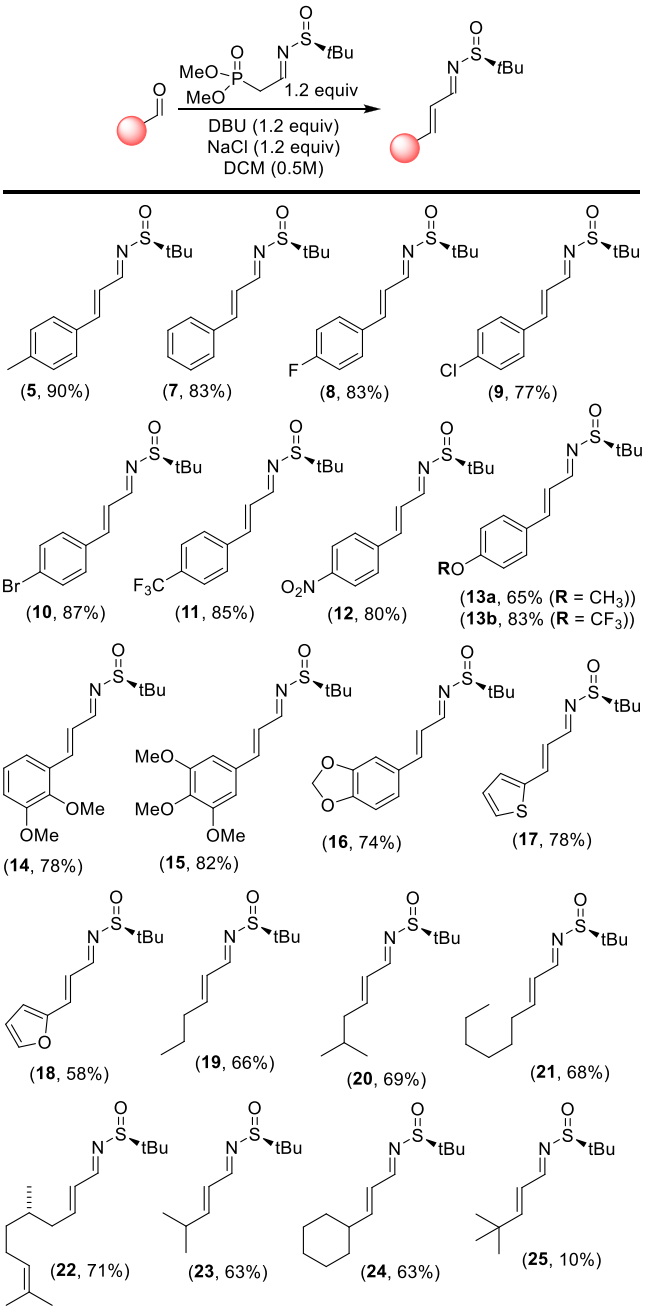
accompanied by formation of significant amount of unwanted imine **6** (Table 1, entries 1−2) and yields left significant room for improvement. Interestingly, when the counterion was changed from lithium to sodium (NaHMDS, entry 3) and potassium (KHMDS, entry 4), respectively, we learned that sodium offered a notable improvement in yield and selectivity, while potassium resulted in a poor vinylogation outcome. We wondered if the mild lithium chloride amine base Horner−Wadsworth−Emmons conditions reported by Roush and Masamune[15] might be more suitable for realizing our vinylogation goals. First attempt employing these conditions employing lithium chloride (LiCl) and 1,8-dizabicyclo[5.4.0]-undec-7-ene (DBU) as base in acetonitrile (MeCN) afforded the product (**5**) in only 18% yield and very poor **5**/**6** ratio (entry 5). Notably, we soon learned how significant role counterions played in pursuing this new optimization direction as it was revealed that switching from lithium to sodium and potassium chloride the yield jumped to 71% for **5** with none of the unwanted side product (**6**) observed (entries 6 and 7). With these exciting results we set out to further optimize with focus on sodium counterion as it had been revealed to be superior in both NaHMDS (entry 3) and NaCl/DBU (entry 6) optimization directions. We next surveyed the impact of solvents, equivalents, reaction concentration, and steric impact of phosphonate reagents (**3a** vs **3b**). These studies revealed that increasing the reaction concentration to 0.5 M improved the isolated yield of **5** to 78% and 84% if the reaction was run in acetonitrile or dichloromethane (DCM), respectively (entries 10 and 11). Final improvements were accomplished by using phosphonate **3a**, affording **5** as a single product in 90% isolated yield (entry 12).

The optimized aldehyde vinylogation conditions have been applied to 20 aromatic, heteroaromatic, and alkyl aldehydes (**5**, **7**−**25**, Scheme 4). Aromatic and heteroaromatic aldehydes deliver the desired conjugated imine products in generally very good yields, with some dip in yields for anisaldehyde (**13**) and 2-furanaldehyde (**18**). Alkyl aldehydes, despite having enolizable protons, also perform well with yields in the mid- to high sixties (**19**−**24**). When sterics are pushed to their limited, the yield drops significantly in the case of pivalaldehyde (**25**).

We next decided to explore if conjugated aldehydes, such as cinnamaldehyde, could be homologated using imine phosphonate **3a**. Optimized DBU conditions employed for non-conjugated aldehydes afforded the desired conjugated homologated product **26** (Table 2), albeit in lower yield with highest yield (57%, entry 3)) obtained when sodium chloride was used as additive with potassium chloride fairing slightly worse (43%, entry 4) and lithium chloride barely affording any product (10%, entry 5). Switching back to silyl amide bases, **26** could be formed in 41% using LiHMDS (entry 6). The counterion switching to sodium resulted yet again in a drastic improvement in yield delivering **26** in 74% (entry 7) when NaHMDS and 2 equiv of **3a** were used at 0.5 M concentration. Changing concentration and equivalents of NaHMDS or **3a** lowered yields (entries 8−10).

Scope studies for vinylogation of conjugated aldehydes with phosphonate **3a** in the presence of NaHMDS as presented in Scheme 5 for ten representative substrates (**26**−**35**, aryl, heteroaryl, and alkyl). Overall, aromatic and heteroaromatic conjugated aldehydes performed well affording desired imine vinylogation products in yields ranging from 51% to 74%. Conjugated alkyl aldehydes, perillaldehyde, and decenal

Scheme 4. Reaction Scope for Aryl and Alkyl Aldehydes



formed imine products **33** and **34** in 42% and 38%, respectively, while crotonaldehyde fared poorly as a substrate.

We have established that a trifluoromethyl ketone also works under our optimized DBU conditions to afford **36** in 83% yield (Scheme 6). Interestingly, the corresponding acetophenone does not work. Furthermore, methyl substituted imine phosphonate **37** successfully transforms 4-bromo benzaldehyde into imine **38** in very good yield. We are delighted to report for the first time that an all-carbon quaternary center can be selectively installed in our amino-Cope products (**39**). Extensive base and counterion studies revealed that cesium carbonate in acetonitrile coupled with an iodide leaving group delivered all carbon quaternary products **40** and **41** in 88% and 97% isolated yields and as single stereoisomers, respectively. Interestingly, when methyl triflate was employed using the same reaction conditions, the selectivity could be reversed now

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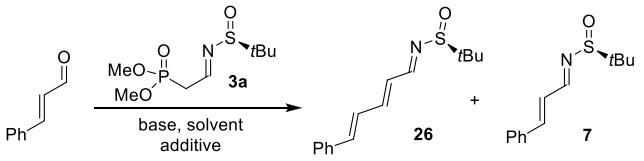
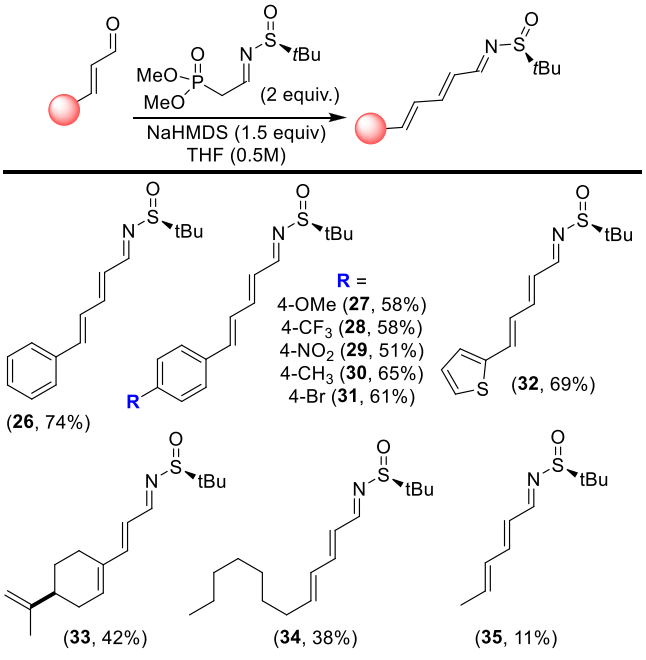
Table 2. Cinnamaldehyde Optimization Studies[a]



entry	base (equiv)	additive	solvent (M)	3a (equiv)	26 yield (%)
1	DBU (1.2 equiv)	1.2 equiv NaCl	DCM (0.5 M)	1.2	49
2	DBU (1.5 equiv)	1.5 equiv NaCl	DCM (0.5 M)	1.5	54
3	DBU (2.0 equiv)	2.0 equiv NaCl	DCM (0.5 M)	2.0	57
4	DBU (1.2 equiv)	1.2 equiv KCl	DCM (0.5 M)	1.2	43
5	DBU (1.2 equiv)	1.2 equiv LiCl	DCM (0.5 M)	1.2	>10
6	LiHMDS (1.5 equiv)	none	THF (0.5 M)	2.0	41
7	NaHMDS (1.5 equiv)	none	THF (0.5 M)	2.0	74
8	NaHMDS (1.5 equiv)	none	THF (0.5 M)	2.0	32
9	NaHMDS (1.5 equiv)	none	THF (0.5 M)	1.5	53
10	NaHMDS (1.2 equiv)	none	THF (0.5 M)	1.2	21

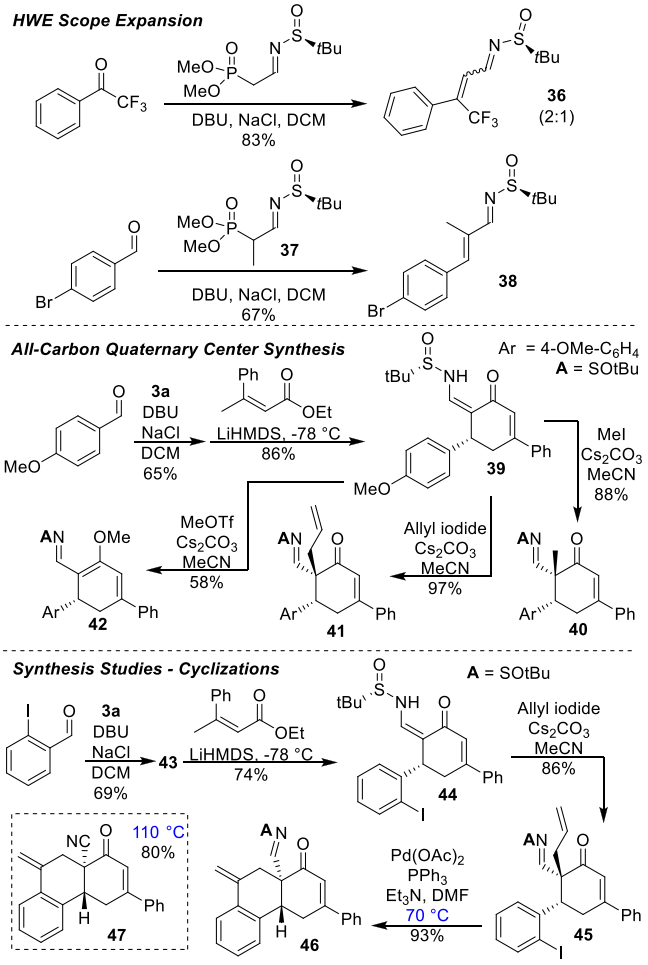
[a]All reactions run for 24 h.

Scheme 5. Reaction Scope for Conjugated Aldehydes



favoring O-alkylated product **42** albeit in lower 58% isolated yield. Bringing these new advances forward toward building complex structures selectively and efficiently is showcased for 2-iodo benzaldehyde, which is converted in 2-steps to **44** employing the new HWE and amino-Cope chemistry. All-carbon quaternary center installation then yields **45**, which can be subjected to intramolecular Heck cyclization conditions at variable temperatures resulting in selective and high yielding formation of decalin products **46** or **47**, respectively, by running the Heck cyclization at 70 or 110 °C respectively. All

Scheme 6. Scope Expansion—All Carbon Quaternary Center Formation—Synthetic Application Examples



the steps in this 4-step sequence are C−C bond forming with no redox or protecting steps.

In conclusion, we report a useful new aldehyde vinylogation reaction for forming conjugated chiral sulfinylimine products in a single step from an aldehyde instead of 4-steps using classic reactions. Applications using our amino-Cope reaction platform highlight the streamlining power of these reactions in accessing all carbon quaternary centers and complex chiral cyclic products.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c04102.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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