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Palladium-Catalyzed Allyl−Allyl Reductive Coupling of Allylamines or Allylic Alcohols with H_2 as Sole Reductant

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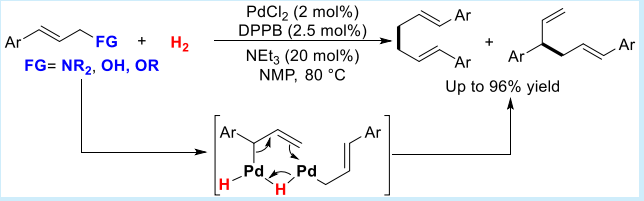
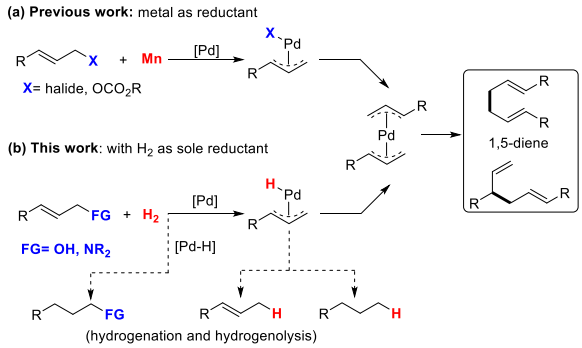
ABSTRACT: Catalytic carbon−carbon bond formation building on reductive coupling is a powerful method for the preparation of organic compounds. The identification of environmentally benign reductants is key for establishing an efficient reductive coupling reaction. Herein an efficient strategy enabling H_2 as the sole reductant for the palladium-catalyzed allyl−allyl reductive coupling reaction is described. A wide range of allylamines and allylic alcohols as well as allylic ethers proceed smoothly to deliver the C−C coupling products under 1 atm of H_2. Kinetic studies suggested that the dinuclear palladium species was involved in the catalytic cycle.



The transition-metal-catalyzed reductive coupling reaction, which avoids the individual preparation and intricate handling of hazardous organometallics, has emerged as a powerful strategy for the synthesis of organic compounds.[1] As a result, the chemistry of these transformations has been the subject of intense scrutiny in recent years.[2−6] Two major thrusts have dominated the research in this area. The first encompasses the expansion of the usefulness of C−C bond-forming reactions and other transformations.[2−6] The second major thrust involves the pursuit of effective and environmentally benign reductants, as stoichiometric amounts of reductants are generally required to maintain the catalytic cycle. However, the reductants employed in these reactions are critically limited to a large amount of reducing metals,[4] organometallics,[5] and other reducing agents that are sensitive to air and moisture.[6] These undoubtedly suffer from some fatal drawbacks including the formation of a large amount of undesirable waste, catalyst poisoning, and lower atom efficiency.

The catalytic reductive coupling of allylic electrophiles is an important synthetic method for the construction of 1,5-dienes, which are common structural motifs in natural products and synthetic intermediates.[7,8] Despite the fact that substantial efforts have been devoted to such Würtz-type reductive coupling reactions,[9] a superstoichiometric amount of metal, such as Mn, Mg, or Zn, is still required as the reductant in most of these reactions (Figure 1A).[10] One attractive approach to circumvent this problem is to use H_2, the cleanest and least expensive renewable chemical feedstock, as the sole reductant. However, a significant hurdle preventing the development of such a process is that hydrogenation of the unsaturated C=C bond[11] or hydrogenolysis of the C−X bond would compete with the desired C−C bond-forming reaction (Scheme 1b).[12] Mechanistically, the undesired competitive hydrogenation process is thought to be initiated by the metal-hydride species, and the hydrogenolysis reaction might result from the reductive elimination of allylmetal hydride species (Scheme 1b). To chemoselectively generate the metal hydride from H_2 and facilitate the key C−C bond-forming reductive elimination process, a catalyst that not only could activate H_2 but also does not display hydrogenative reactivity toward the C=C bond and could facilitate the self-transmetalation of the allylmetal hydride to form the diallylmetal species is required. Herein we report an unprecedented palladium-catalyzed allyl−allyl reductive coupling of allylamines, allylic alcohols, and allylic

Scheme 1. Palladium-Catalyzed Allyl−Allyl Reductive Coupling with H_2 as the Sole Reductant



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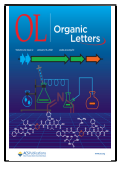

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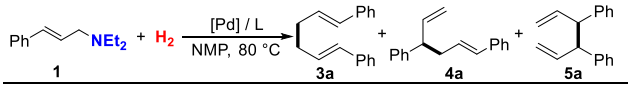
ethers with H_2 as the sole reductant under mild reaction conditions. Our strategy relies on the heterolytic cleavage of the H−H bond by the *in situ* formed Pd−N or Pd−O bond from allylamines or allylic alcohols via the cleavage of the C−N bond or C−O bond.

We commenced our studies by treating (*E*)-*N*,*N*-diethyl-3-phenylprop-2-en-1-amine with 1 atm of H_2 and a catalytic amount of palladium catalyst at 80 °C in *N*-methyl-2-pyrrolidone (NMP). The commonly used $PdCl_2/PPh_3$ was found to be capable of promoting the C−C bond-forming reaction, giving the 1,5-dienes **3a** and **4a** in 39% combined yield in a 1:1 ratio. The branched 1,5-diene **5a** was not detected at all. Further optimized reaction conditions by the screening of phosphine ligands disclosed that the monodentate phosphine ligands such as Cy_3P did not give the desired products (Scheme 2, entry 2). Bidentate phosphine ligands

Scheme 2. Optimization of the Reaction Conditions[a]



entry	[Pd]	L	solvent	yield (%)	**3a**/**4a**
1[b]	$PdCl_2$	PPh_3	NMP	39	49:51
2[b]	$PdCl_2$	PCy_3	NMP	0	-
3	$PdCl_2$	BINAP	NMP	<5	-
4	$PdCl_2$	DPPB	NMP	81	49:51
5	$PdCl_2$	DPPPen	NMP	65	50:50
6	$PdCl_2$	DPPH	NMP	65	46:54
7	$PdCl_2$	DPPF	NMP	38	43:57
8	$PdCl_2$	Xantphos	NMP	0	-
9[c]	$PdCl_2$	DPPB	NMP	82	49:51
10[c]	$PdCl_2$	-	NMP	0	-
11[c]	$PdBr_2$	DPPB	NMP	0	-
12[c]	$Pd(TFA)_2$	DPPB	NMP	36	50:50
13[c]	PdI_2	DPPB	NMP	0	-
14[c]	$Pd_2(dba)_3$	DPPB	NMP	0	50:50
15[c]	$PdCl_2$	DPPB	DMA	70	48:52
16[c]	$PdCl_2$	DPPB	CH_3CN	0	-
17[c]	$PdCl_2$	DPPB	DMF	80	50:50
18[c]	$PdCl_2$	DPPB	DMA	70	48:52
19[c]	$PdCl_2$	DPPB	THF	74	50:50
20[c]	$PdCl_2$	DPPB	1,4-dioxane	75	45:55

[a]Reaction conditions: **1** (0.5 mmol), [Pd] (2 mol %), ligand (2.5 mol %), solvent (0.5 mL), H_2 (1 atm), 80 °C, 24 h. The ratio (**3a**/**4a**) was determined via analysis of the crude reaction mixture with GC and GC-MS. Isolated yield. [b]Ligand (4.4 mol %). [c]12 h.

with different bite angles, like BINAP, DPPF, DPPE, DPPH, and Xantphos, were then examined, and it was found that DPPB was the most efficient for the present reaction to deliver the desired products in 81% combined yield with excellent E/Z selectivity (>99:1). We could reduce the reaction time to 12 h (Scheme 2, entry 9). Control experiments demonstrated that no desired products were obtained in the absence of ligand (Scheme 2, entry 10). Moreover, the reactivity was also strongly dependent on the palladium precursor. The simple $PdCl_2$ proved to be the optimal precursor (Scheme 2, entries 11−13). The solvent examination demonstrated that the polar solvents including dimethylformamide (DMF), dimethylacetamide (DMA), and tetrahydrofuran (THF) were suitable for the present reaction, and NMP was the best solvent.

Various allylic compounds with different leaving groups were then evaluated for the reductive coupling reactions under the optimized reaction conditions. As summarized in Scheme 3, substrates containing different leaving groups exhibited distinct

Scheme 3. Effect of the Leaving Groups[a]

entry	X	additive	yield (%)	**3a**/**4a**
1	NEt_2	-	82	49:51
2	$N(i\text{-}Pr)_2$	-	86	50:50
3	NCy_2	-	50	49:51
4	NHBn	-	90	50:50
5	NTsBn	-	0	-
6	OH	-	0	-
7	OAc	-	0	-
8	OH	NEt_3	82	45:55
9	OAc	NEt_3	68	49:51
10	Cl	NEt_3	11	54:46

[a]Reaction conditions: allylic compound (0.5 mmol), $PdCl_2$ (2 mol %), DPPB (2.5 mol %), NMP (0.5 mL), H_2 (1 atm), 80 °C, 12 h. The ratio (**3a**/**4a**) was determined via analysis of the crude reaction mixture with GC and GC-MS. Isolated yield. NEt_3 (20 mol %).

reactivities. For the allylamines with NEt_2, $N(i\text{-}Pr)_2$, or NHBn as leaving groups, the desired products could be produced in moderate to excellent yields, whereas no reaction occurred when NBnTs was utilized as the leaving group. Interestingly, no desired reaction was observed under these conditions when allylic alcohol and allyl acetate were utilized as substrates. Consequently, to solve this problem, the modified reaction conditions were identified by introducing 20 mol % of Et_3N into the reaction system. Thereby, using the newly optimized reaction conditions, the desired C−C bond coupling products were obtained in 82 and 68% yield, respectively. However, the allylic chloride was not applicable for the present reaction, even with Et_3N as an additive.

With the optimized conditions established, we first investigated the scope of the allylamines. Aromatic allylamines bearing either an electron-donating or an electron-withdrawing group on the phenyl ring exhibited good reactivity and gave the 1,5-diene products **3** and **4** in good yields in an almost 1:1 ratio in all cases (Scheme 4). It was even more intriguing that generally no hydrogenation or hydrogenolysis product was observed. Substituents at different positions on the arenes could be tolerated. In addition to phenyl-substituted allylamines, naphthyl-substituted allylamine was also a suitable substrate for this reaction, generating the corresponding coupling products (**3h** and **4h**) in high yields with moderate regioselectivity, although a prolonged reaction time was required. Moreover, the reaction of heteroaryl-substituted allylamine *N*-benzyl-3-(furan-2-yl)prop-2-en-1-amine (**1i**) also proceeded smoothly to provide the desired products in good yields. In addition, the substrate with substituted groups on the allylic skeleton was examined. For the reactions of three-substituted aryl allylamines (**1j**−**m**), we could obtain similar good results to give the linear 1,5-dienes as the major products. It is pointing out that the regioselectivity varied swiftly with the variation of the substituent. For example, the reaction proceeded with excellent regioselectivity for substrates containing a phenyl group or chloride at the γ-position (**1l**,**m**). A lower selectivity was observed when a methyl group was installed into the γ-position (**1j**,**k**). β-Substituted

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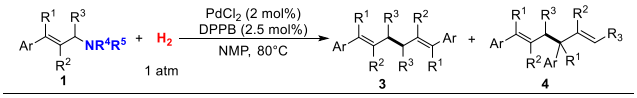
Scheme 4. Substrate Scope for Allylic Compounds



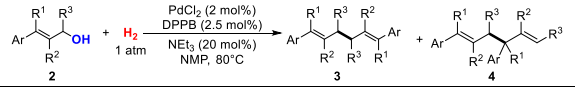
1		3	4	yield (3/4)
1a	Ar = Ph	3a	4a	90%, (50:50)
1b	Ar = 4-*t*-BuC$_6$H$_4$	3b	4b	87%, (47:53)
1c	Ar = 2-CH$_3$C$_6$H$_4$	3c	4c	78%, (43:57)
1d	Ar = 4-FC$_6$H$_4$	3d	4d	70%, (48:52)
1e	Ar = 4-ClC$_6$H$_4$	3e	4e	72%, (44:56)
1f	Ar = 3-MeOC$_6$H$_4$	3f	4f	84%, (50:50)
1g	Ar = 4-Me$_2$NC$_6$H$_4$	3g	4g	88%, (49:51)
1h[b]	Ar = 1-naphthyl	3h	4h	79%, (30:70)
1i	Ar = 2-furyl	3i	4i	88%, (44:56)
1j	Ar = Ph, R^1 = Me	3j	4j	85%, (63:37)
1k	Ar = 4-ClC$_6$H$_4$, R^1 = Me	3k	4k	85%, (61:39)
1l[b]	Ar = Ph, R^1 = Cl	3l	4l	49%, (97:3)
1m[b]	Ar = Ph, R^1 = Ph	3m	4m	70%, (99:1)
1n[c]	R^2 = F	3n	4n	52%, (44:56)
1o[d]	R^2 = CO$_2$Me	3o	4o	65%, (25:74)
1p[e]	Ar = Ph	3p		83%
1q[e]	Ar = 4-MeC$_6$H$_4$	3q		87% (96%)[f]
1r[e]	Ar = 3-MeC$_6$H$_4$	3r		94%
1s[e]	Ar = 4-ClC$_6$H$_4$	3s		78%

[a]Reaction conditions: **1** (0.5 mmol), $PdCl_2$ (2 mol %), DPPB (2.5 mol %), H_2 (1 atm), NMP (0.5 mL), 80 °C, 12 h. Isolated yield. The ratios of **3**/**4** within parentheses were determined by analysis of the crude reaction mixture with GC and GC-MS. [b]24 h. [c]120 °C. [d]$PdCl_2$ (5 mol %), DPPB (6.25 mol %). [e]18 h. [f]**1r** (5 mmol), $PdCl_2$ (0.1 mol %), DPPB (0.125 mol %), H_2 (1 atm), NMP (5 mL), 80 °C, 72 h.

substrates (**1n,o**) exhibited lower reactivity to give the 1,5-dienes in moderate yields under slightly modified conditions. In contrast, the α-substituted allylamines (**1p−s**) could produce the corresponding dienes in 78−94% yields as a single regioisomer (**3q−t**). However, the aliphatic-substituted allylamines were not applicable in this reaction because the hydrogenolysis reaction took place to significantly inhibit the coupling reaction. Notably, the reductive coupling on a 5 mmol scale of **1r** was found to be completed in 72 h in the presence of 0.1 mol % of catalyst, yielding 1.07 g of diene **3r** (96% yield). Most of the products **3** and **4** could be isolated through flash chromatography, although the regioselectivities of these reactions were not satisfying.

The catalytic protocol was also successfully amenable to a wide range of allylic alcohols (**2a−s**) in the presence of 20 mol % of NEt_3, which acted as a base for promoting the H_2 to reduce the Pd(II) to the Pd(0) species (Scheme 5).[13] Similar to allylamines, the reactions proceeded well, allowing the preparation of the corresponding 1,5-dienes in good to excellent yields (Scheme 5). In addition, the tertiary alcohol **2t** could be smoothly transferred to hexa-1,5-diene-1,1,3,4,6,6-hexaylhexabenzene in 93% yield with excellent regioselectivity and 65:35 diastereoselectivity. Having demonstrated that the process is compatible with a wide range of allylamines and allylic alcohols, the investigation of the scope with respect to the compounds containing multiallylic backbones was also undertaken. As summarized in Scheme 6, tertiary diallylamines

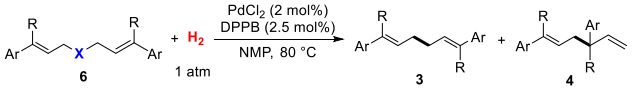
Scheme 5. Substrate Scope for Allylic Alcohols[a]



2		3	4	yield (3: 4)
2a	Ar = Ph	3a	4a	82%, (45:55)
2b	Ar = 4-*t*-BuC$_6$H$_4$	3b	4b	77%, (43:57)
2c	Ar = 2-CH$_3$C$_6$H$_4$	3c	4c	72%, (40:60)
2d	Ar = 4-FC$_6$H$_4$	3d	4d	68%, (45:55)
2e	Ar = 4-ClC$_6$H$_4$	3e	4e	70%, (36:64)
2f	Ar = 3-MeOC$_6$H$_4$	3f	4f	71%, (39:61)
2g	Ar = 4-Me$_2$NC$_6$H$_4$	3g	4g	71%, (44:56)
2h[b]	Ar = 1-naphthyl	3h	4h	66%, (22:78)
2i	Ar = 2-furyl	3i	4i	72%, (42:58)
2j	Ar = Ph, R^1 = Me	3j	4j	86%, (53:47)
2k	Ar = 4-ClC$_6$H$_4$, R^1 = Me	3k	4k	86%, (54:46)
2l[b]	Ar = Ph, R^1 = Cl	3l	4l	37%, (82:18)
2m[b]	Ar = Ph, R^1 = Ph	3m	4m	86%, (87:13)
2n[c]	R^2 = F	3n	4n	41%, (38:62)
2o[d]	R^2 = CO$_2$Me	3o	4o	49%, (12:88)
2p	Ar = Ph	3p	(dr = 52:48)[e]	80%
2q	Ar = 4-MeC$_6$H$_4$	3q	(dr = 55:45)[e]	90%
2r	Ar = 3-MeC$_6$H$_4$	3r	(dr = 50:50)[e]	92%
2s	Ar = 4-ClC$_6$H$_4$	3s	(dr = 50:50)[e]	76%
2t[c]		3t	(dr = 65:35)[e]	93%

[a]Reaction conditions: **2** (0.5 mmol), $PdCl_2$ (2 mol %), DPPB (2.5 mol %), NEt_3 (0.1 mmol), H_2 (1 atm), NMP (0.5 mL), 80 °C, 18 h. Isolated yield. The ratios of **3**/**4** within parentheses were determined by analysis of the crude reaction mixture with GC and GC-MS. [b]24 h. [c]120 °C. [d]$PdCl_2$ (5 mol %). [e]Diastereoselectivity was determined by ^{1}H NMR analysis.

Scheme 6. Substrate Scope for Multiallylic Compounds[a]



entry	substrate	product	yield (3:4)
1	6a	3a + 4a	80% (50:50)
2	6b	3a + 4a	85% (50:50)
3	6c	3a + 4a	80% (50:50)
4	6d	3b + 4b	71% (48:52)
5	6e	3m + 4m	73% (64:36)
6[b]	6f	3a + 4a	65% (45:55)

[a]Reaction conditions: **6** (0.5 mmol), $PdCl_2$ (2 mol %), DPPB (2.5 mol %), H_2 (1 atm), NMP (0.5 mL), 80 °C, 12 h, isolated yield. The ratio of **3**/**4** within parentheses was determined by analysis of the crude reaction mixture with GC and GC-MS. [b]NEt_3 (0.1 mmol), 120 °C, 18 h.

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containing different groups on the N atom (**6a**−**c**) gave the desired product in good yields under standard reaction conditions. The reaction of allylic ether **6f** provided products **3a** and **4a** in a 65% combined yield.

To shed light on the mechanism of this reductive coupling reaction, kinetic studies of the standard reaction of **1a** were

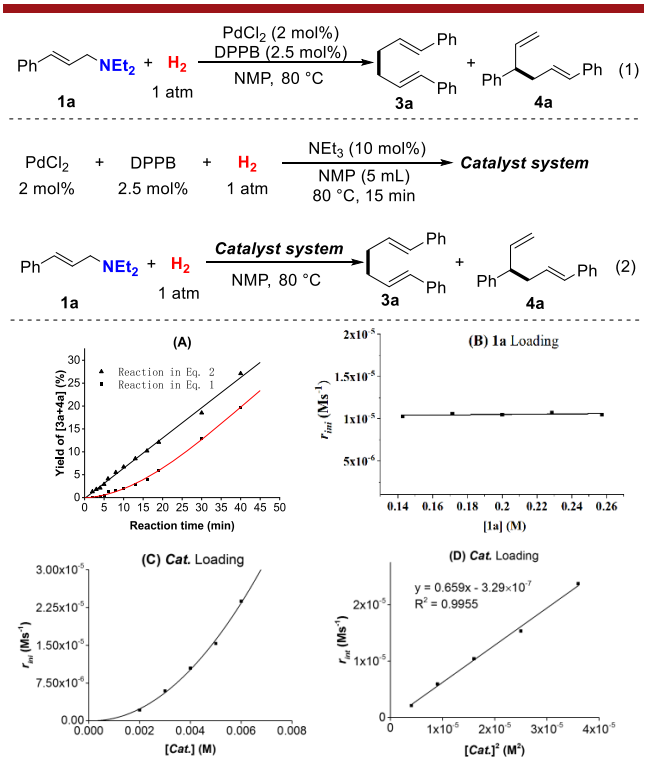

Figure 1. (A) Kinetic plots of the reaction in eq 1 and the reaction in eq 2. (B) Plot of initial rates with respect to **1a** showing zeroth-order dependence. (C,D) Plot of initial rates with respect to [*Cat.*] or $[Cat]^2$ showing second-order dependence.

conducted (Figure 1). The reaction profile showed that a relatively long induction phase was observed under the standard reaction conditions. However, the induction period disappeared when the palladium catalyst was aged in the presence of 10 mol % of Et_3N and 1 atm of H_2 for 15 min (Figure 1, eq 2). This result revealed that the catalytic active Pd(0) was most likely involved in and generated from the reduction of $PdCl_2$ with H_2 under basic conditions. Initial rates for the reaction were then investigated by changing the concentrations of **1a** and the catalyst. The result disclosed a zero-order dependence of the rate on the concentration of **1a**. A more marvelous occurrence is the observed second-order dependence of the rate on the concentration of the palladium catalyst, indicating that two palladium species are involved in the rate-determining step.

On the basis of the above results, we propose the following mechanism (Figure 2). The reduction of $PdCl_2$ by H_2 via σ-bond metathesis and the reductive elimination sequence in the presence of amine affords Pd(0). Oxidative addition of Pd(0) to the allylamine generates the π-allyl palladium **A**. H_2 coordinates to the palladium center and undergoes σ-bond metathesis to form the allylic palladium hydride species **C**.[13] The hydride-bridged dinuclear palladium species **D**[14] is formed, followed by rearrangement to generate the palladium dihydride species and the intermediate **E**. The complex **E**

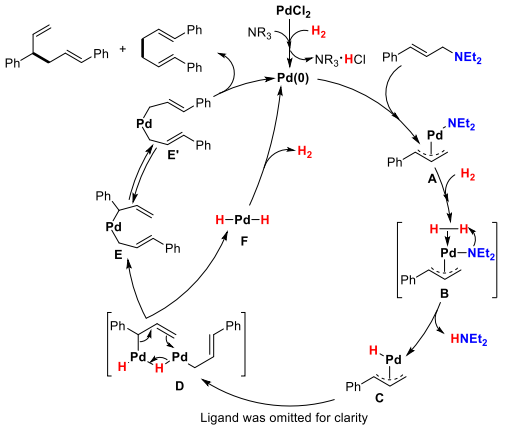

Figure 2. Proposed reaction mechanism.

might be transferred to **E′** through a $\sigma-\pi-\sigma$ transformation.[15] Reductive elimination takes place with the intermediate **E** or **E′** to form the C−C coupling product **3** or **4** and regenerate Pd(0). The palladium dihydride species **F** would also undergo reductive elimination to regenerate Pd(0) while releasing H_2.

In summary, for the first time, the most environmentally benign H_2 has been identified, which is an effective reducing agent for the palladium-catalyzed allyl−allyl reductive coupling reactions. Allylamines, allylic alcohols, and allylic ethers were applied as coupling partners, which enabled the reductive coupling reaction to proceed under 1 atm of a H_2 atmosphere. This newly designed transformation tolerates a broad range of allylic compounds, leading to 1,5-dienes in good yields. Kinetic studies suggest that the formation of the dinuclear palladium species from self-transmetalation is the rate-determining step. Further research is currently under way to obtain a detailed understanding of the reaction mechanism and the application of this strategy in other reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03865.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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