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Letter

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Rh(III) and Ir(III)Cp* Complexes Provide Complementary Regioselectivity Profiles in Intermolecular Allylic C-H Amidation Reactions

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ABSTRACT: An efficient regioselective allylic C-H amidation of mono-, di-, and trisubstituted olefins has been developed. Specifically, the combination of dioxazolone reagents with RhCp* and IrCp* catalysts is reported to promote reactions with complimentary regioselectivites to those previously observed in Pd- catalyzed and Ag promoted Rh-catalyzed reactions. We report that catalyst matching with substrate class is essential for selective reactions. RhCp* complexes are required for high conversion and selectivities with *β*-alkylstyrene substrates, and IrCp* complexes are necessary in the context of unactivated terminal olefins.

KEYWORDS: C-H functionalization, allylic amidation, dioxazolone, π-allyl complex, RhCp, IrCp*, terminal olefins, disubstituted olefins*

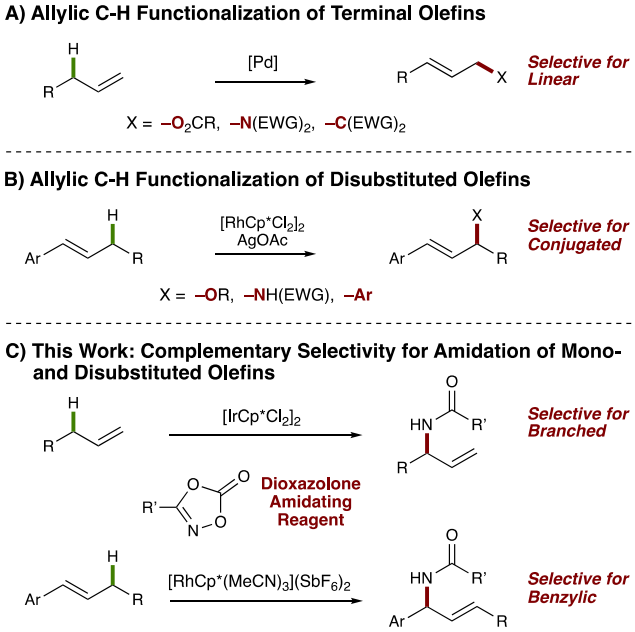
Allylic substitution reactions are established as versatile tools, strategically employed as key steps in the total synthesis of many biologically relevant molecules.[1] Underpinning their broad application is the development over many years of a selection of catalysts based on different transition metals, with different ligand sets, that allow exquisite mechanism-based control of regioselectivity and stereoselectivity.[2] Critically, in palladium catalyzed reactions, it has been established that an outer-sphere attack of a nucleophile on a π-allyl complex favors formation of linear products, while inner-sphere reductive elimination mechanisms favor the branched isomers.[3]

C-H functionalization presents an attractive alternative to allylic substitution, in which the requisite π-allyl complexes can be accessed directly from their parent olefins, without the need for preinstallation of an allylic leaving group. However, these technologies remain in their infancy and limitations in substrate scope, regioselectivity, and stereocontrol hamper their widespread adoption.

The work of White and co-workers has shown that palladium complexes are effective for allylic C-H functionalization and a variety of C-C,[4] C-N,[5] and C-O[6] bond forming reactions have been demonstrated (Scheme 1A).[7] However, these palladium-catalyzed reactions are limited to terminal olefins and generally require activated nucleophiles. Moreover, in intermolecular reactions they predominantly deliver linear products, with a single notable exception in which a catalyst system was developed to provide branched selectivity for allylic acetoxylation reactions.[6c]

Recently, building on Cossy's report of an intramolecular allylic amination reaction,[8] we established that RhCp* complexes are suitable catalysts for intermolecular C-H functionalization of di- and trisubstituted olefins, and demonstrated a significantly expanded nitrogen[9] and oxygen[10] nucleophile scope (Scheme 1B). Subsequent studies by Glorius and coworkers have further expanded the synthetic utility of these systems, demonstrating that electron-rich aromatic compounds,[11a] and arylboroxines[11b] can be utilized as nucleophiles for allylic C-C bond formation. Although the mechanistic underpinning of these Rh-catalyzed oxidative C-H functionalization processes using stochiometric silver salts as oxidants have not yet been experimentally elucidated, Cossy and co-workers propose a Rh(III/I) catalytic cycle.[8]

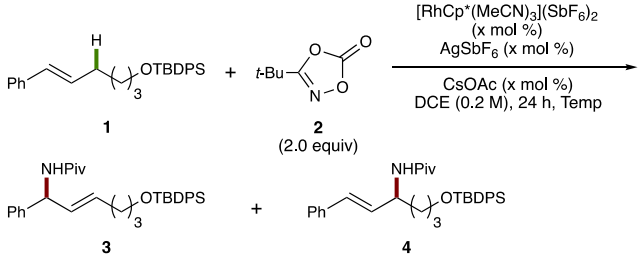
Scheme 1. Intermolecular Allylic C-H Functionalization of Olefins



We hypothesized that dioxazolones, established as oxidative amidating reagents by Chang and coworkers in directed sp^2 C-H functionalization processes,[12] would operate through a Rh(III/V) catalytic cycle inducing an inner-sphere reductive

elimination of a metal-nitrenoid species and potentially provide complimentary regioselectivity in allylic C-H functionalization reactions.[13] Such an outcome would significantly enhance both the strategic utility and our understanding of RhCp*-catalyzed allylic C-H functionalization. During the preparation of this manuscript, consistent with this hypothesis, Rovis and Glorius demonstrated that IrCp* complexes promote branch selective allylic amidation reactions of unactivated terminal olefins.[14] In this manuscript, we report that RhCp* and IrCp* complexes exhibit different reactivity profiles with different classes of olefin, and that while IrCp* complexes are required for more selective reactions of unactivated terminal olefins, RhCp* complexes are significantly more effective for regioselective amidation of *trans*-disubstituted olefins (Scheme 1C).

Table 1. Reaction Development for Allylic C-H Amidation of Disubstituted Olefins

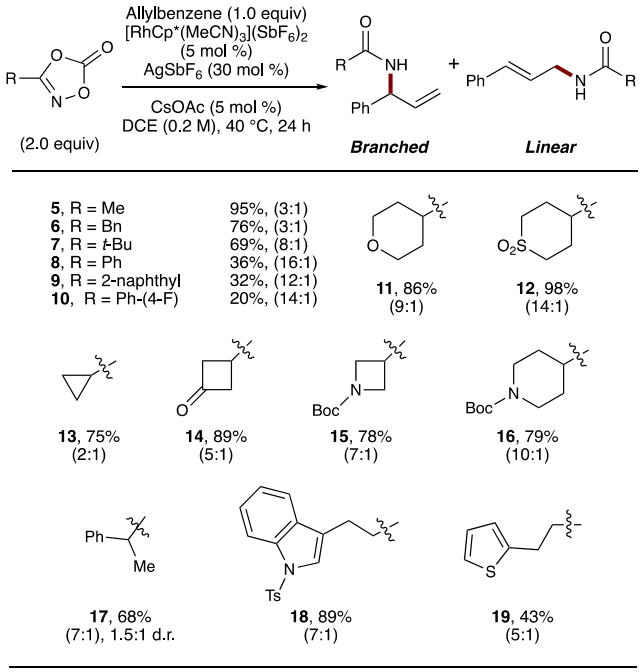


Entry	[Rh] (mol %)	$AgSbF_6$ (mol %)	CsOAc (mol %)	Temp (° C)	Yield[a] (%)	r.r[a]
1	5	0	5	40	29	6:1
2	5	20	5	40	78	13:1
3[b]	5	0	5	40	25	7:1
4	5	20	5	60	68	9:1
5[c]	**5**	**30**	**5**	**40**	**84(78)**	**16:1**
6	5	50	5	40	27	14:1
7	0	20	5	40	0	—
8	5	20	0	40	0	—
9[d]	5	20	20	40	7	N.D

[a]Yields and product ratios (**3**:**4**) were determined by ^{1}H NMR using 1,4-dinitrobenzene as an internal standard in the crude reaction mixture. [b]20 mol % of $NaSbF_6$ was used instead of $AgSbF_6$. [c]Isolated yield in parentheses. [d]≤5% quantities of conjugated aryl-diene were observed.

Based on our goal to broadly establish reaction conditions for the regioselective functionalization of terminal, di- and trisubstituted olefins, we initiated our study by examining the amidation of disubstituted olefin **1** (Table 1). *t*-Bu-Dioxazolone **2** was chosen as the amidating reagent along with $[RhCp^*(MeCN)_3](SbF_6)_2$ as the precatalyst to allow for selective introduction of additives. CsOAc was used as a soluble carboxylate base to promote concerted metalation-deprotonation (CMD) of the allylic proton. Reacting olefin **1** with 2.0 equivalents of dioxazolone **2** at 40 °C for 24 hours successfully afforded allylic amides **3**/**4** with a preference for benzylic amide **3** (Table 1, entry 1, 29%, 6:1). A short survey of additives quickly identified that $AgSbF_6$ promoted higher yields and selectivity for the benzylic amide product (entry 2, 78%, 13:1). Using $NaSbF_6$ instead of the silver-salt resulted in lower yield and selectivity similar to the additive-free conditions (entry 3, 25%, 7:1). At this stage the exact role of the silver salt remains unknown, although it is plausible that it activates the dioxazolone for oxidative addition to the Rh(III) species, and remains coordinated during the C-N bond forming step, thus impacting both the efficiency and regioselectivity of the reaction. Increasing the loading of $AgSbF_6$ to 30 mol % resulted in an improved yield and regioselectivity (entry 5, 84%, 16:1) but, further addition of the additive lead to a significant loss in yield (entry 6, 27%). Control experiments in which either the RhCp* precatalyst or the CsOAc were left out of the reaction did not produce amide product supporting the intermediacy of a Rh-π-allyl intermediate obtained by carboxylate assisted CMD (entries 7-8). The relative ratios of CsOAc to RhCp* complex proved critical for efficient reaction, with excess carboxylate suppressing the generation of amide products (7%, entry 9). It is likely that the excess acetate sequesters the rhodium as catalytically inactive $RhCp^*(OAc)_2$.

Table 2. Effects of Dioxazolone Substitution for Branched Selective Allylic C-H Amidation

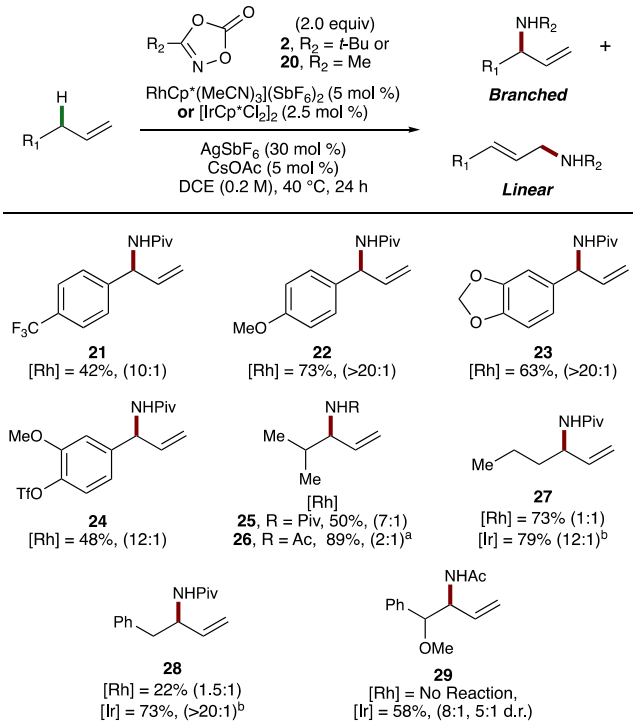


Yields are of isolated amide products and the regiomeric ratio of amide products (branched:linear) was obtained by analysis of the ^{1}H NMR spectra of the crude reaction mixtures.

Having developed conditions for an efficient benzylic/branch selective allylic C-H amidation, we sought to establish the functional-group tolerance for a range of alkyl-, aryl-, and heterocyclic-substituted dioxazolones using allylbenzene as a simple model olefin (Table 2). High yields (75-95%) of allylic amides are observed for substrates with smaller substituents (**5-6, 13-15, 18-19**), with selectivities for the branched isomer ranging from 3:1 to 7:1. Dioxazolones bearing larger substituents, like *t*-Bu-dioxazolone **2**, were also efficient (**7**, 69%, 8:1). However, despite providing the highest regioselectivities (12:1 – 16:1), aryl substituents on the dioxazolone resulted in generally lower yields (**8-10**, 20-36%). We speculate that resultant aryl-substituted amide products engage in iterative directed sp^2 C-H amidations and prevent further allylic amidations.[15] Amidation with dioxazolones derived from cyclic ethers, sulfones, and ketones produced excellent yields (**11-12**, **14**, 86-98%) with good regioselectivities (5:1 – 14:1). Boc-protected azetidine and pipiridine were compatible dioxazolones under the reaction conditions and produced the corresponding amides with high yields and regioselectivities (**15**, 78%, 7:1; **16**, 79%, 10:1). A

dioxazolone bearing an α-stereocenter gave the corresponding amide in good yield and regioselectivity but only limited diastereoselectivity was observed (**17**, 68%, 7:1, 1.5:1 d.r.). Dioxazolones bearing electron rich heterocycles were also demonstrated to be effective reagents (**18**, 89%, 7:1 and **19**, 43%, 5:1). The general trends we observed are that dioxazolones with either larger α-substituents or substituents that are inductively withdrawing provide the highest selectivities and yields of branched amide products.

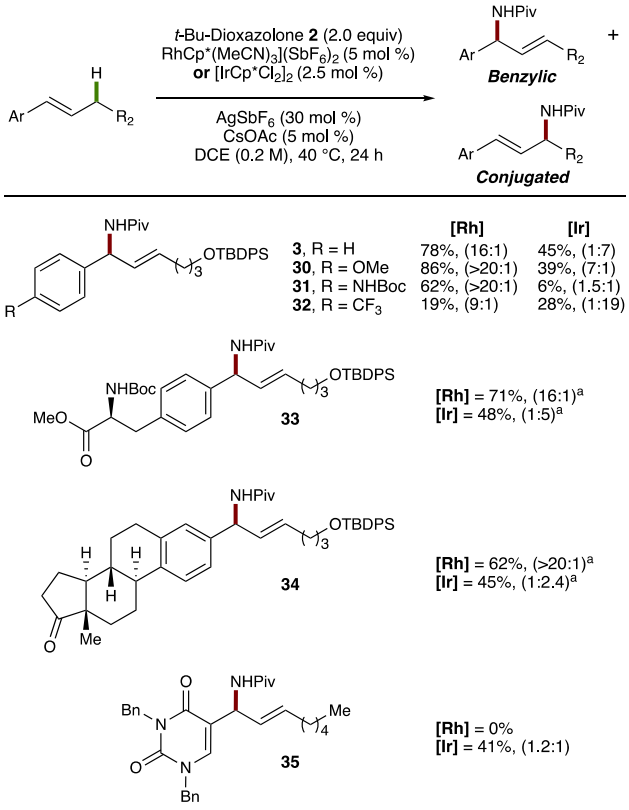
Table 3. Effects of the Olefin Substituent on the Branched Selective Allylic C-H Amidation of Terminal Olefins.



Yields are of isolated amide products and the regiomeric ratio of amide products (Branched:Linear) was obtained by analysis of the ^{1}H NMR spectra of the crude reaction mixtures. [a]Reaction was run at 60 °C. [b]40 mol % $AgSbF_6$ was used.

To understand the impact of olefin substitution on the reaction outcome, we initially investigated a series of allylbenzene derivatives using *t*-butyl dioxazolone **2** as the amidation reagent (Table 3). Both electron-rich and electron deficient substrates were amidated with excellent regioselectivity (**21-23**, 10:1 – >20:1). The reactions with electron-rich substrates tended to proceed in higher yields. Allylic amidation of the eugenol-derivative proceeded smoothly with high regioselectivity and retention of the aryl-triflate moiety (**24**, 48%, 12:1) demonstrating compatibility with functional groups that might engage in competitive oxidative addition reactions during conventional allylic substitution reactions. Having established the broad applicability of the reaction conditions in the context of allylbenzene and its derivatives, we investigated the extension of this reaction to unactivated terminal olefins. In an initial reaction, the branched substrate 4-methylpentene, was amidated with the sterically demanding *t*-Bu-dioxazolone **2** providing product with respectable yield and regioselectivity (**25**, 50%, 7:1). However, when Me-dioxazolone **20** was used, although the reaction yield increased, the regioselectivity dropped significantly (**26**, 89%, 2:1). Furthermore, amidation of the straight chain terminal olefin 1-hexene proved to be entirely unselective, even with the sterically demanding *t*-Bu dioxazolone reagent (**27**, [Rh] = 73%, 1:1). In an attempt to solve this problem, we investigated alternative group IX metal complexes as catalysts for this substrate class. We were delighted to find that the use of $[IrCp^*Cl_2]_2$ as the pre-catalyst provided excellent regioselectivity and high yield of the branched product in the amidation of this simple unactivated olefin substrate (**27**, [Ir] = 79%, 12:1). 4-Phenylbutene showed a similar reactive profile with the Ir-catalyzed reaction affording higher yield and regioselectivity than the Rh-catalyzed process (**28**, [Rh] = 22%, 1.5:1; [Ir] = 73%, >20:1). Amidation of 4-methoxy-4-phenylbutene further highlighted the difference in reactivity between the Rh and Ir catalysts. In this case the RhCp* complex was completely ineffective, but the IrCp* catalyst delivered the product in good yield and regioselectivity, and with useful levels of diastereoselectivity (**29**, 58%, 8:1 r.r., 5:1 d.r.).

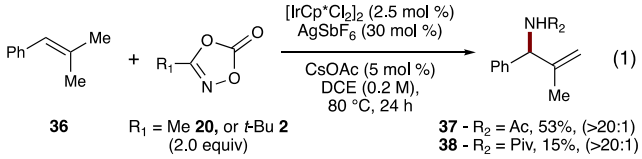
Table 4. Comparison of RhCp* vs. IrCp* for the Allylic Amidation of Disubstituted Olefins.



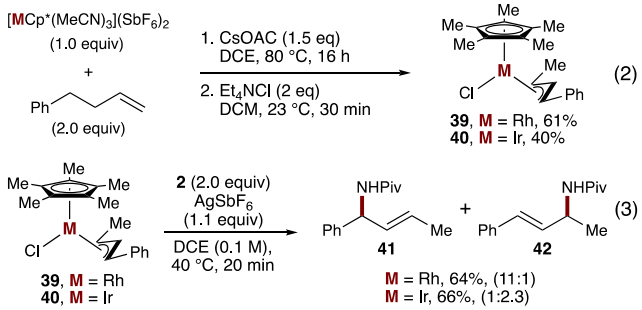
Yields are of isolated amide products and the regiomeric ratio of amide products (Benzylic:Conjugated) was obtained by analysis of the ^{1}H NMR spectra of the crude reaction mixtures. [a]Isolated as 1:1 mixture of diastereomers.

To complete our initial investigation of this novel allylic amidation reaction, we addressed the generality of benzylic-selective amidation of *β*-alkyl styrene substrates (Table 4). Although our initial reaction optimization had identified $[RhCp^*(MeCN)_3](SbF_6)_2$ as an excellent catalyst for these compounds, the improved performance of $[IrCp^*Cl_2]_2$ in the amidation of unactivated terminal olefins caused us to evaluate both catalysts. Surprisingly, the two catalysts showed significantly different reactivity profiles across a broad range of these disubstituted olefin substrates. For **3**, **30-31**, and **33-35**

the RhCp*-catalyzed reactions gave uniformly good yields and excellent selectivities for the benzylic amidation isomer (62-86%, 16:1 – 20:1 r.r.). The electron-deficient **32** was amidated in low yield but retained the same sense of regioselectivity (19%, 9:1). However, the IrCp* complex gave comparatively low yields (6-48%) and regioselectivities that were strongly substrate dependent. Electron deficient and neutral *β*-alkyl styrenes (**3**, **32**-**34**) were amidated with a preference for the conjugated regioisomer, but *β*-alkyl styrenes with electron donating substituents favored the benzylic regioisomer (**30**, **31**). We note that functional group compatibility differences also emerged during this study. In the case of Boc-protected aniline **31**, the RhCp* complex is an effective catalyst (62%, >20:1 r.r.) but the substrate proved unstable under the IrCp* reaction conditions, and only a 6% yield was observed. In contrast, the uracil-derivative was incompatible with the Rh-catalyzed conditions, but the iridium catalyst was able to promote formation of amide products (**35**, 41%, 1.2:1).



This divergent reactivity was also seen in the amidation of trisubstituted olefin **36** with the RhCp* complex proving ineffective, and $[IrCp^*Cl_2]_2$ promoting highly regioselective reactions (>20:1 r.r.). Consistent with previous observations, Me-dioxazolone **20** afforded greater yields of amide product (**37**, 53%) compared to the sterically demanding *t*-Bu-dioxazolone **2** (**38**, 15%) (eq 1). The regioselectivity observed in these reactions mirrors the branched selectivity observed in terminal olefins, reflecting the similarities in the structures of the intermediate π-allyl complexes.



In an attempt to understand the regioselectivity differences observed for the RhCp* and IrCp* catalyzed reactions of disubstituted olefins, we prepared the corresponding discreet π-allyl complexes **39** and **40** from their respective MCp*-trisacetonitrile monomers *via* allylic C-H activation and subsequent isomerization of 4-phenylbutene (eq 2). When each of these complexes was subjected to *t*-Bu-dioxazolone **2** in the presence of $AgSbF_6$ as a halide scavenger, the corresponding amides were obtained in good yields and regioselectivities that mirrored the catalytic reactions (eq 3: Rh = 11:1; Ir = 1:2.3). These stoichiometric reactions are consistent with the hypotheses that the catalytic reactions proceed via cationic M(III)Cp*(π-allyl) complexes.

The structures of each complex were obtained by x-ray crystallography. The two structures are isomorphous and isostructural. In both cases the M-C bond adjacent to the phenyl group (M-C11; Rh = 2.2235(7) Å, Ir = 2.2095(17) Å) is slightly elongated compared to the M-C bond adjacent to the methyl substituent on the π-allyl component (M-C13; Rh = 2.2008(7) Å, Ir = 2.1813(17) Å). Although each of the M-C bond distances is slightly longer in the Rh-π-allyl complex **39** than they are in the analogous Ir-π-allyl complex **40**, there are no structural features that would explain the significant differences in regioselectivities that are observed under both catalytic and stochiometric reaction conditions. Detailed computational and experimental studies are ongoing in our laboratory to elucidate the origins of the complimentary reactivity observed in this study.

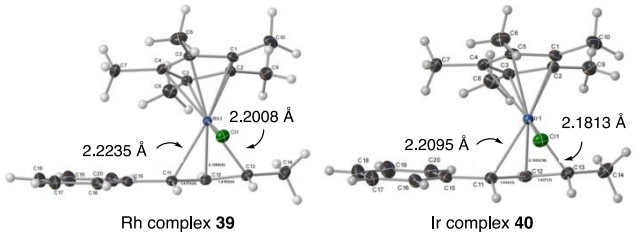


Figure 1. Crystal Structures of Disubstituted RhCp*- and IrCp*(π-allyl) Complexes. Key bond lengths for Rh complex 38: M-C11 = 2.2235(7) Å, M-C13 = 2.2008(7) Å, and for Ir complex 39: M-C11 = 2.2095(17) Å, M-C13 = 2.1813(17) Å.

In conclusion, we have developed a novel allylic amidation reaction that provides complimentary regioselectivities to those observed in previously disclosed allylic C-H functionalization reactions proceeding through organometallic π-allyl complexes. The synthesis and reactions of stochiometric Rh- and Ir-π-allyl complexes provide products with regioselectivities that are consistent with the catalytic reactions, and support a mechanism in which these π-allyl complexes are oxidized to fleeting M(V)-nitrenoid intermediates, that subsequently undergo inner-sphere reductive elimination. We observe that it is necessary to match the catalyst to the substrate class for efficient and selective reactions, with RhCp* catalysts proving necessary for *β*-alkylstyrene substrates, and IrCp* complexes required for unactivated terminal olefins. The origins of these subtle catalyst-substrate matching requirements remain the focus of ongoing mechanistic studies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, crystallography reports and analytical data (PDF),

Crystallographic data for **39** and **40** (CIF)

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Notes

The authors declare no competing financial interest

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