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Rh-Catalyzed General Method for Directed C−H Functionalization via Decarbonylation of *in-Situ*-Generated Acid Fluorides from Carboxylic Acids

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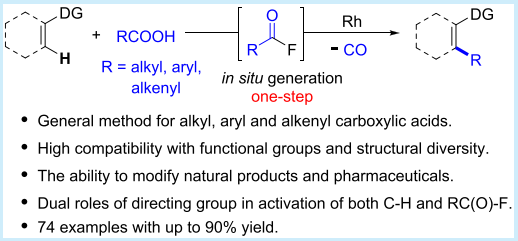
ABSTRACT: A Rh-catalyzed decarbonylative C−H coupling of *in-situ*-generated acid fluorides with amide substrates bearing *ortho*-Csp^2−H bonds has been developed. This method enables alkyl, aryl, and alkenyl carboxylic acids to undergo decarbonylative coupling with C−H bonds of (hetero)-aromatic or alkenyl amides in generally good yields via the *in situ* conversion of carboxylic acids into acid fluorides and also allows for the functionalization of a series of structurally complex carboxyl-containing natural products and pharmaceuticals as well as pharmaceutical amide derivatives.



By virtue of the ubiquity, structural diversity, and nontoxicity of carboxylic acids, the exploration of catalytic methods for their conversion to valuable products has been an attractive area of chemical research.[1] The last two decades have witnessed dramatic advances in the development of decarboxylative cross-coupling reactions.[1−5] Specifically, (hetero)aryl carboxylic acids have been demonstrated to participate in a considerable variety of decarboxylative cross-coupling reactions via Ag- or Cu-mediated nonredox decarboxylation with high functional group tolerance, which, however, requires ortho-substituted groups. The oxidative decarboxylation-based cross-coupling reactions of aryl carboxylic acids allow the substrate scope to be expanded beyond ortho-substituted (hetero)aryl carboxylic acids, but they are currently limited to only a few types of reactions.[3] As for alkyl carboxylic acids, the widespread adoption of an oxidative decarboxylation mode has brought about the discoveries of diverse decarboxylative cross-coupling reactions,[1a,4,5] which have recently been facilitated by the strategy of the merger of photocatalysis and transition-metal catalysis.[1a,5] As a result of the formation of alkyl radical intermediates in the oxidative decarboxylation, these reactions preferentially work for alkyl carboxylic acids that generate relatively stable radical intermediates, such as benzylic, α-amino, α-oxy, and secondary alkyl carboxylic acids.[1a,4,5] Recently, the catalytic methods for decarbonylative cross-coupling reactions of carboxylic acid derivatives have been significantly developed to provide an alternative approach to the utility of abundant carboxylic acids as starting materials for organic syntheses.[6−10] The remarkable achievements in this area showcase that nearly all kinds of carboxylic acid derivatives including esters,[7] acid anhydrides,[8] amides,[9] and acid halides[10] can undergo such reactions. To date, the vast majority of these established catalytic methods have applied to only (hetero)aryl carboxylic acid derivatives. The challenges posed by the achievement of efficient decarbonylative cross-coupling reactions of common alkyl carboxylic acid derivatives may stem from the lower activity of their C(O)−X bonds (X = heteroatom) toward oxidative addition to low-valent metal catalyst species compared with (hetero)aryl carboxylic acid counterparts and the tendency of alkyl carboxylic acid derivatives to generate olefin side products via β-hydride elimination upon the occurrence of oxidative addition and subsequent decarbonylation.[11] The realization of decarbonylative cross-coupling reactions of alkyl carboxylic acid derivatives by overcoming the aforementioned challenges is highly desired in that they are much more available than the currently used alkylating reagents.

Our interest in the decarboxylative cross-coupling of carboxylic acids[12] prompted us to explore the transition-metal-catalyzed general method for decarbonylative coupling of both (hetero)aryl and alkyl carboxylic acid derivatives with (hetero)arenes via functional-group-directed C−H activation.[13] We envisioned that in this target reaction, the directing groups of substrates not only enhance the reactivity of the C−H bonds and the reaction selectivity by positioning metal centers closely proximal to the C−H bonds[13] but also exert an effect on the activation and transformation of carboxylic acid derivatives as coupling partners by turning the electron density of metal catalyst centers (Scheme 1A). In light of this speculation, the proper directing groups used for C−H bond

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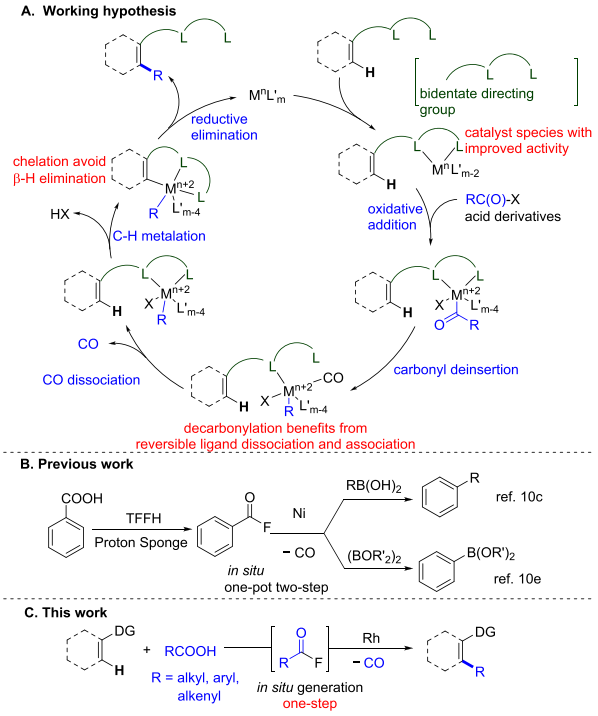
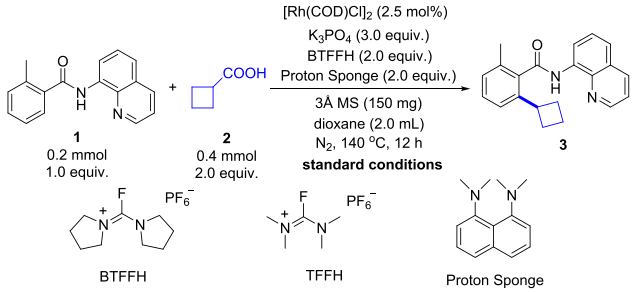
Scheme 1. (A) Working Hypothesis, (B) Previous Work, and (C) This Work



activation may improve the activity of metal catalysts toward the oxidative addition of acyl C−X (X = heteroatom) bonds in carboxylic acid derivatives and also accelerate decarbonylation of the resulting acyl−metal intermediates via flexible ligand dissociation and association process.[7,10b] In addition, the coordination of the directing groups to metal catalysts may prevent *β*-hydride elimination of the alkyl−metal complex intermediates to olefin side products.[14] Realizing the dual roles of the directing group, we established a general method for the Rh-catalyzed decarbonylative Csp^2−H coupling of *in-situ*-generated alkyl, alkenyl, and (hetero)aryl acyl fluorides with aromatic and olefinic *N*-(quinolin-8-yl) carboxamides.[15] Herein we report the discovery and development of this method.

Considering that acyl fluorides feature a good balance between stability and reactivity due to their moderate electrophilicity and are easy to handle and readily synthesized from abundant carboxylic acids,[6a,b] our exploration of the catalytic transformation of carboxylic acid derivatives focused on acyl fluorides. Inspired by the success made in the development of the catalytic method for the conversion of *in-situ*-generated acyl fluorides (Scheme 1B),[10c,e] we aimed at a one-pot procedure consisting of the *in situ* conversion of carboxylic acids to corresponding acyl fluorides and the metal-catalyzed cross-coupling of directing-group-containing arenes with the resultant acyl fluorides (Scheme 1C). After screening a series of arenes with varying mono- or bidentate directing groups (see the SI, Section III.C) as well as other reaction parameters, we achieved a Rh-catalyzed *ortho*-C−H alkylation of 2-methyl-*N*-(quinolin-8-yl)benzamide (**1**) with 2 equiv of cyclobutanecarboxylic acid (**2**) that was conducted under a dinitrogen atmosphere in dioxane (0.1 M) at 140 °C for 12 h in the presence of 2.5 mol % $[Rh(COD)Cl]_2$ as a catalyst, 2 equiv of 1-(fluoro(pyrrolidin-1-yl)methylene)pyrrolidin-1-ium hexafluorophosphate(V) (BTFFH), a proton sponge (2 equiv), K_3PO_4 (3 equiv), and 3 Å molecular sieves (150 mg) to deliver the expected product in 82% yield, as shown in entry 1 of Table 1. No reaction occurred when using N or Pd

Table 1. Optimization Studies of Decarbonylative C−H Coupling



entry	variation from the standard conditions	yield (%)[a]
1	none	**82 (80**[b]**)**
2	$Ni(COD)_2$ instead of $[Rh(COD)Cl]_2$	NA[c]
3	$Pd_2(dba)_3$ instead of $[Rh(COD)Cl]_2$	NA[d]
4	without proton sponge	62
5	without BTFFH	NA
6	without K_3PO_4	NA
7	without $[Rh(COD)Cl]_2$	NA
8	TFFH instead of BTFFH	76
9	Na_2CO_3 instead of K_3PO_4	46
10	without 3 Å MS	68
11	120 °C instead of 140 °C	54
12	100 °C instead of 140 °C	29
13	toluene instead of dioxane	37
14	1.0 mmol **1** scale	76[b]

[a]GC yield of **3**. [b]Yield of isolated **3**. [c]$Ni(COD)_2$ (10 mol %). [d]$Pd_2(dba)_3$ (5 mol %).

catalysts, which are regularly used for C−H activation and decarbonylation (entries 2 and 3).[6−10,13,15] According to literature reports,[10c] fluoro-formamidinium TFFH and a proton sponge were used as additives for the stoichiometric conversion of carboxylic acid **2** into acyl fluoride. A control experiment revealed that in the absence of a proton sponge, the C−H alkylation of **1** with **2** still proceeded, albeit in a lower yield of **3** (entry 4). However, BTFFH, K_3PO_4, and $[Rh(COD)Cl]_2$ all proved to be essential to this reaction (entries 5−7). The role of K_3PO_4 is to deprotonate the N−H bond of the directing group. Using TFFH as a fluorinating reagent gave a slightly lower yield than BTFFH (entry 8). Na_2CO_3 was used as a base, leading to much lower yield than K_3PO_4 (entry 9 vs entry 6). The removal of 3 Å molecular sieves from the reaction system reduced the yield (entry 10), presumably because a trace amount of water existing in reagents was detrimental to the reaction. When the reaction temperature was decreased from 140 to 120 or 100 °C, the reaction still occurred, the yields decreased (entries 11 and 12). A nonpolar solvent such as toluene led to a notable drop in yield (entry 13). When the reaction scale was increased from 0.2 to 1.0 mmol, the reaction yield was still maintained at a high level (entry 14).

With the optimized reaction condition in hand, we explored the generality of this method with respect to aliphatic carboxylic acids using **1** as the substrate (Scheme 2). To our delight, the expected alkylation was achieved with a vast set of primary and secondary alkyl groups successfully introduced on the ortho position of benzamides (**4**−**8**). Cyclic alkyl

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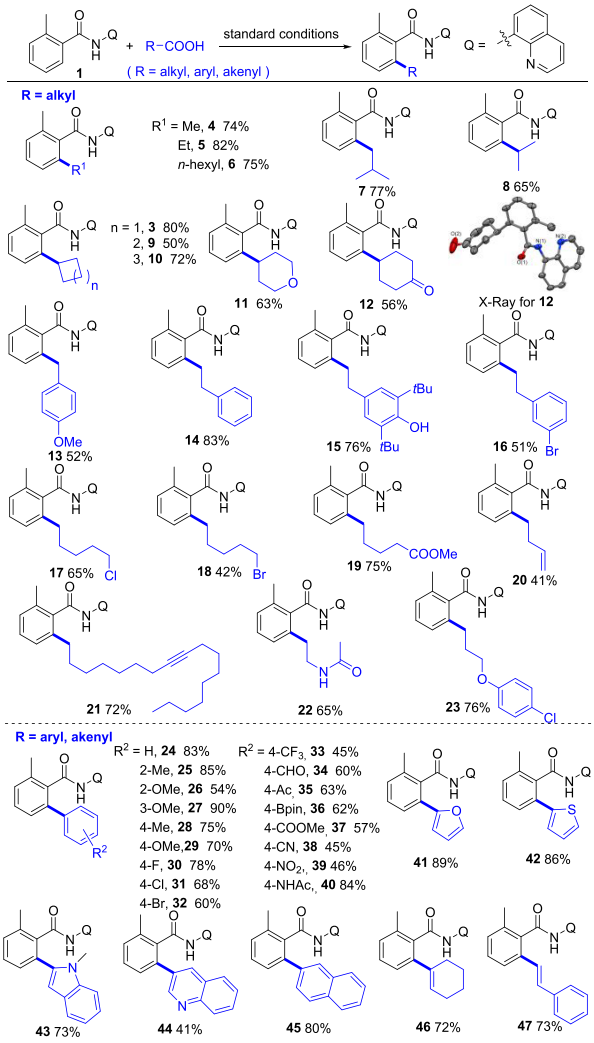
Scheme 2. Scope of Carboxylic Acids in Rh-Catalyzed Decarbonylative C−H Coupling

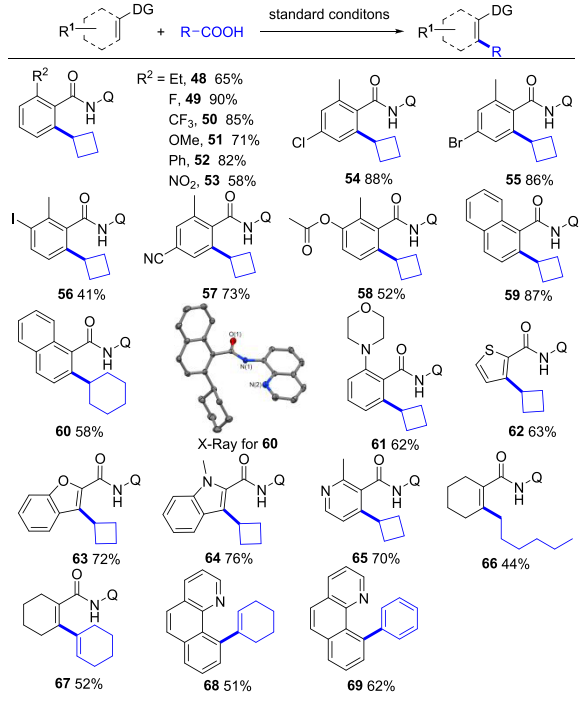


carboxylic acids with different ring sizes (**3**, **9**−**12**), including tetrahydropyran-4-yl-carboxylic acid (**11**) and 4-oxocyclohexanecarboxylic acid (**12**), delivered the corresponding alkylation products. No alkene side product was observed in the reactions of β-aryl-substituted propanoic acids (**14**−**16**) that are prone to forming stable styrene derivatives via β-hydride elimination, indicating that this transformation effectively excludes the undesired β−H elimination. Various functional groups on the linear aliphatic carboxylic acid scaffolds, such as chloro (**17**), bromo (**18**), ester (**19**), alkenyl (**20**), alkyne (**21**), acylamido (**22**), and phenyl alkyl ether groups (**23**), were all compatible. Interestingly, this method tolerated terminal C−Cl, C−Br, and C═C bonds (**17**, **18**, and **20**), demonstrating its chemoselectivity for acyl fluorides over alkyl chlorides or bromides and therefore offering a complement to the previous established C−H alkylation reactions using alkyl halides[15a,b,17b] or terminal olefins[16,17] as alkylating reagents. In addition, this reaction was allowed varying substituents from electron-donating methoxy (**13**) and hydroxy (**15**) groups to electron-withdrawing, active bromo (**16**) and chloro (**23**) groups on aryl rings existing in alkyl carboxylic acids.

Moreover, this method also enabled (hetero)aryl carboxylic acids to act as coupling partners for the *ortho*-C−H arylation of **1**. A broad spectrum of functional groups on the phenyl rings of the aryl carboxylic acids with different positions (**24**−**40**), whether they were electron-withdrawing or electron-donating groups, were tolerated well. Intriguingly, among these compatible functional groups, some were reactive groups, for instance, the formyl group (**34**) and Bpin substituents (**36**), which provided an entry into the further modification of these products. Various heteroaryl carboxylic acids (**41**−**44**) including quinoline carboxylic acid (**44**) as well as naphthalene carboxylic acid (**45**) were all amenable to this method. Both cyclic (**46**) and linear alkenyl carboxylic acids (**47**) also proved to be viable substrates to give the corresponding C−H alkenylation products in good yields. As such, investigating the scope of carboxylic acids demonstrated the great generality of this decarbonylative coupling reaction with respect to carboxylic acids.

Diversely decorated 8-aminoquinoline amides were evaluated for this method using cyclobutanecarboxylic acid as a coupling partner (Scheme 3). A wide range of 8-aminoquinoline benzamides that incorporate electron-neutral, electron-donating and electron-withdrawing substituents on arene rings underwent decarbonylative C−H alkylation in generally good yields (**48**−**61**). Heteroaryl substrates (**62**−**65**) also proved to be competent substrates for this C−H alkylation reaction. Interestingly, cyclohex-1-ene-1-carboamide was able to cross-couple both alkyl and alkenyl carboxylic acids to afford alkylation and alkenylation products, respectively, via the selective activation of the *ortho*-alkenyl C−H bond (**66**, **67**). Notably, benzo[*h*]quinolin bearing a monodentate directing group, which failed to work with alkyl carboxylic acids (see the SI, Section III.C), was found to react with both alkenyl and aryl carboxylic acids under the conditions established for 8-aminoquinoline amides. As shown in Scheme 3, benzo[*h*]-quinoline was able to react with cyclohex-1-ene-1-carboxylic

Scheme 3. Scope of 8-Aminoquinoline Amides and the Reaction of Benzo[*h*]quinoline with Aryl and Alkenyl Carboxylic Acids



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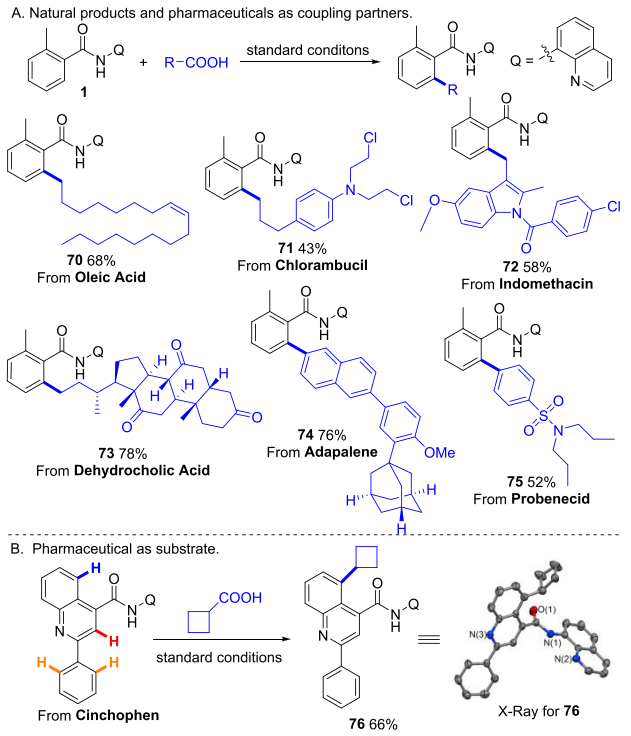
acid and benzoic acid to deliver the expected C−H alkenylation and arylation products (**68**, **69**), respectively.

To further explore the synthesis application of this method, we applied this protocol to the late-stage diversification of carboxyl-containing natural products and pharmaceuticals (Scheme 4). Structurally complex carboxylic acids including

Scheme 4. Late-Stage Diversification of Natural Products and Pharmaceuticals



natural products such as oleic acid (**70**) and pharmaceuticals such as chlorambucil (**71**), indomethacin (**72**), dehydrocholic acid (**73**), adapalene (**74**), and probenecid (**75**) smoothly underwent decarbonylative coupling reaction in good yields. Intriguingly, the high regioselectivity of this method was observed in the case of the pharmaceutical amide derivative cinchophen, a carboxyl-containing medicine. As shown in Scheme 4, the 8-aminoquinoline amide derivative of cinchophen possesses four possible reaction positions in the directed C−H functionalization reaction: 8-aminoquinoline-directed C3−H and C5−H bonds on the quinoline framework and two quinoline nitrogen-directed *ortho*-C−H bonds on the phenyl substituent. Interestingly, the amide derivative of cinchophen reacted with cyclobutanecarboxylic acid to exclusively generate the C5−H alkylation product in 66% yield (**76**).

Aiming at the identification of acyl fluorides as active intermediates, a series of control experiments were performed. 3-Phenylpropanoyl fluoride in 93% yield was detected in the fluorating process (see the SI, Section IV.A); then, the generated 3-phenylpropanoyl fluoride successfully reacted with **1** to afford **14** in 86% yield (see the SI, Section IV.B). Moreover, The reaction of **1** with benzoyl fluoride directly generated **24** in 85% yield (see the SI, Section IV.C). In addition, a great amount of CO was determined under the standard conditions (see the SI, Section IV.D). All of these results verify that this reaction undergoes the decarbonylative C−H coupling of *in-situ*-generated acyl fluorides from carboxylic acids.

The observed conversion of 3-phenylpropanoic acid into styrene using benzo[*h*]quinoline as a substrate (see the SI, Section III.C) points to the possibility that this decarbonylative C−H coupling reaction may occur via the decarbonylative elimination of alkyl acid fluorides to alkenes and the subsequent hydrocarbonation of the resultant alkenes (see the SI, Section IV.E).[16,17] If this mechanism was operable, then the reactions of some structurally symmetrical alkyl acids, such as tetrahydropyran-4-yl-carboxylic acid and 4-oxocyclohexane-carboxylic acid, would produce a mixture of two regioisomers because two carbon atoms of the double bond of the supposed alkenes from these carboxylic acids have no electronic bias; however, the decarbonylative C−H coupling reactions of tetrahydropyran-4-yl-carboxylic acid and 4-oxocyclohexanecarboxylic acid occurred exclusively at their *ipso*-carbon atoms, which rules out the possibility that the reaction of alkyl carboxylic acids goes through the formation of alkene intermediates. The previously mentioned observation and illation demonstrate that the *β*-hydride elimination of the alkyl−metal complex intermediates to olefin side products is restrained by using the transformable 8-aminoquinoline bidentate directing group.

In conclusion, we have developed a general method for the Rh-catalyzed decarbonylative C−H coupling of readily available carboxylic acids with (hetero)aromatic and alkenyl amides containing transformable 8-aminoquinoline as a bidentate directing group via the *in situ* generation of acid fluorides from the corresponding carboxylic acids. By implementing this protocol, a diverse variety of alkyl, aryl, and alkenyl carboxylic acids all acted as building blocks for the 8-aminoquinoline-directed *ortho*-C−H functionalization of a broad range of (hetero)aromatic amides and alkenyl amides. Additionally, this Rh-catalyzed protocol possesses a high compatibility with functional groups and a structural diversity of substrates, as exemplified by the late-stage functionalization of a series of complex natural products and pharmaceuticals. Moreover, we consider that the key to achieving this Rh-catalyzed general method is the identification of 8-aminoquinoline as a bidentate directing group for C−H bond activation, which concurrently engages in the activation and transformation of acid fluorides, in particular, avoiding *β*-hydride elimination by coordinating to metal catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01103.

X-ray crystallographic data for the product **12**, **60**, and **76**; detailed experimental procedures; characterization data; ^{1}H, ^{13}C, and ^{19}F NMR spectra of compounds; and mechanistic studies (PDF)

Accession Codes

CCDC 2061286, 2061288, and 2061290 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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