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▍Catalysis

Regio- and Diastereoselective Dimerization of Diazo Carbonyls: A Cooperative Catalytic Approach to Complex Scaffolds with Four Contiguous Stereocenters

Martin Petzold,[a] Andre Günther,[a] Peter G. Jones,[b] and Daniel B. Werz*[a]

Abstract: Starting from readily available *o*-diazoacyl-substituted arene carboxylates, scaffolds with the 5,9-epoxycyclohepta[b]pyran-2(3*H*)-one core were obtained by cooperative Rh[II], Lewis and Brønsted acid catalysis. Four new bonds, three functional groups (lactone, ketal, and alcohol) and four contiguous stereocenters are formed during this regio- and diastereoselective process in a single synthetic step. Intensive optimization and mechanistic studies, including the trapping, isolation, and elucidation of reaction intermediates, led to a plausible mechanistic scenario. The reaction is proposed to involve carbonyl ylides but also transient species of the ketocarbene equilibrium that undergo a cascade of cycloaddition and skeletal rearrangements.

Carbenes and metal carbenoids are versatile intermediates for numerous synthetic transformations. Whereas cycloaddition and simple rearrangement reactions have been known for almost a century,[1] in more recent years C−H and X−H insertion reactions have come into play.[2] The Davies group has performed intensive research in the field of C−H activation by using carbene precursors and has successfully developed methods that allow the C−H insertion even in the presence of olefin units.[3] Furthermore, insertion into heteroatom−H bonds has also been successfully realized, as is demonstrated by a recent example for the selective protection of hydroxy groups in monosaccharides.[4] However, carbenes and carbenoids also allow insertion into C−X bonds.[5] These latter reactions commonly proceed through the intermediate generation of ylides. Impressive examples involve the generation of polyether macrocycles (Lacour[6]) but also oxyalkynylations of carbenes by hypervalent iodine reagents (Waser[7]) and, most recently, photochemically induced transformations such as fluoroetherifications or insertion reactions into chalcogen–carbon bonds (Koenigs[8]). However, the versatility of carbenes is not limited to C−X or X−H insertion reactions; they also have found application in olefination and [1+*m*+*n*] annulation reactions and in the formation of complex heterocyclic motifs.[9]

Besides these direct transformations, other reactions exploit the highly reactive nature of carbenes, generating at first various types of fleeting intermediates. Early work in this field involves the transformations developed by Padwa and co-workers in which the decomposition of an appropriate carbene precursor in the neighborhood of a carbonyl moiety leads to carbonyl ylides that selectively transmute into other (heteroatom-containing) 1,3-dipoles.[10] Carbonyl ylides are also able to react in various kinds of (3+*n*)-cycloaddition reactions.[11,12] Doyle reported their (3+2)-cycloaddition reaction with cyclopropenes (Scheme 1A).[12] In 2019, our group developed the transformation with a donor—acceptor cyclopropane, and very recently the Schneider group employed such an in situ generated 1,3-dipole in a (4+3)-cycloaddition reaction with *ortho*-quinone methides.[13]

Latest studies have mainly focused on reactions of these in situ generated fleeting intermediates with dipolarophiles. When no other reaction partners in the reaction of **1** are present and Rh[II] is the sole active catalyst, the well-known C_2-symmetric dimerization products **2** are formed (Scheme 1B).[14,15] However, from our previous studies we realized that cooperative catalysis[16] using Rh[II], Lewis acid and Brønsted acid provides access to more complex oligocyclic scaffolds **3**, which had been isolated in traces (Scheme 1C), but eluded structural characterization before we obtained X-ray diffraction data. The formation of these structures can be traced back to the involvement of transient species in the ketocarbene equilibrium[1,17] and skeletal rearrangements triggered by Brønsted and Lewis acid.
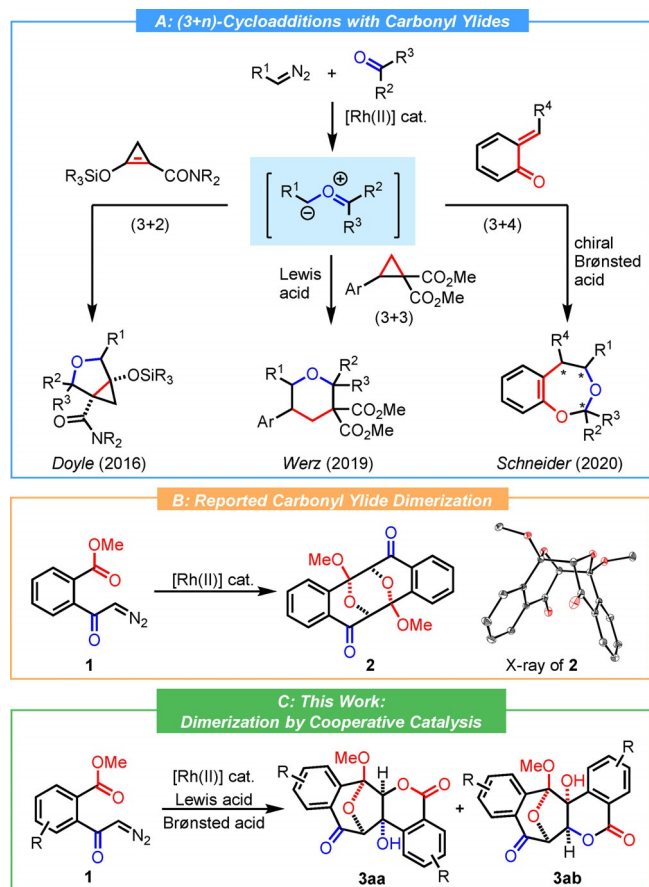
Because we were struck by the structural complexity that could be generated in a single synthetic operation, we started to investigate conditions that lead to the novel oligocyclic systems **3**. At the beginning of our investigations, we chose diazo compound **1a** as model substrate to determine the optimal conditions for this cooperative annulation cascade. Our initial results (Table 1, entries 1 and 2) gave a low yield and a poor

[a] *M. Petzold, A. Günther, Prof. Dr. D. B. Werz*
Technische Universität Braunschweig
Institute of Organic Chemistry
Hagenring 30, 38106 Braunschweig (Germany)
E-mail: d.werz@tu-braunschweig.de

[b] *Prof. Dr. P. G. Jones*
Technische Universität Braunschweig
Institute of Inorganic and Analytical Chemistry
Hagenring 30, 38106 Braunschweig (Germany)

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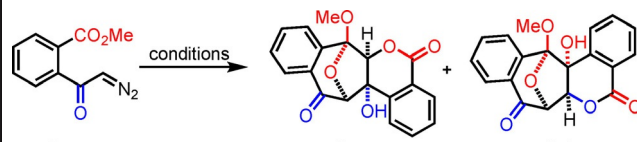**Scheme 1.** (3+n)-Cycloaddition reactions of in situ generated carbonyl ylides, reported carbonyl ylide dimerization and our work.

Table 1. Optimization of the reaction conditions.[a]

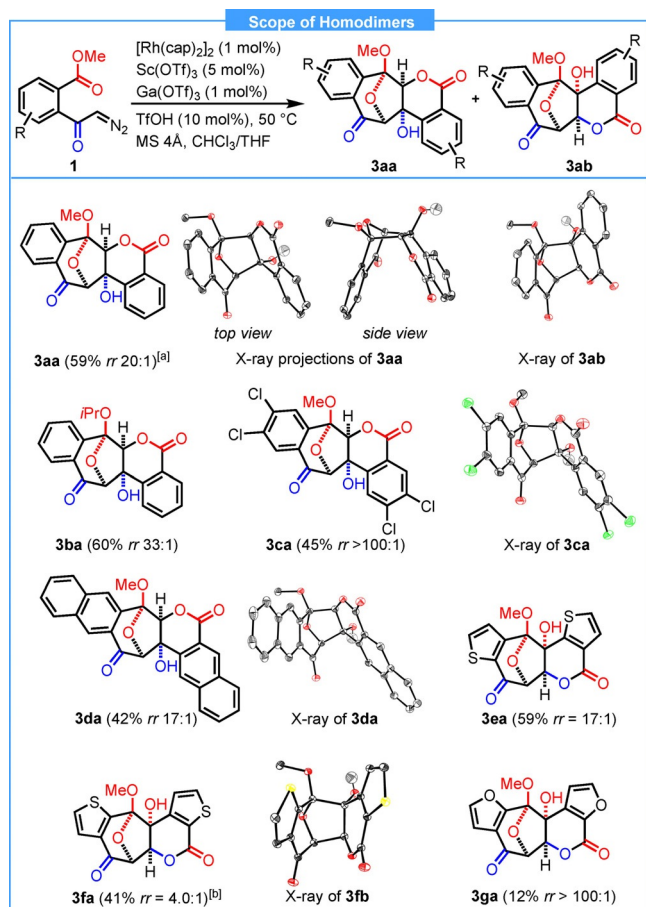| Entry	Rh[II] cat.	Lewis acid	Solvent	3 [%]	rr (3 aa/3 ab)
1	$Rh_2(cap)_4$	$Sc(OTf)_3$	PhMe	19	2.5:1
2	$Rh_2(cap)_4$	$Sc(OTf)_3$	$CHCl_3$	23	3.7:1
3	$Rh_2(cap)_4$	$Sc(OTf)_3$	THF	28	19:1
4	$Rh_2(cap)_4$	$Sc(OTf)_3$	PhMe/THF	60	16:1
5	$Rh_2(cap)_4$	$Sc(OTf)_3$	$CHCl_3$/THF	**74**	**20:1**
6[b]	$Rh_2(cap)_4$	$Sc(OTf)_3$	$CHCl_3$/THF	34	13:1
7[c]	$Rh_2(cap)_4$	$Sc(OTf)_3$	$CHCl_3$/THF	61	15:1
8[d]	$Rh_2(cap)_4$	$Sc(OTf)_3$	$CHCl_3$/THF	**59**	**20:1**
9[e]	$Rh_2(cap)_4$	$Ga(OTf)_3$	$CHCl_3$/THF	5	2.1:1
10[d]	–	$Sc(OTf)_3$	$CHCl_3$/THF	0	–
11	$Rh_2(cap)_4$	–	$CHCl_3$/THF	0	–
12[d,f]	$Rh_2(cap)_4$	$Sc(OTf)_3$	$CHCl_3$/THF	2	42:1
13[d,g]	$Rh_2(cap)_4$	$Sc(OTf)_3$	$CHCl_3$/THF	34	10:1
14[d]	$Rh_2(OAc)_4$	$Sc(OTf)_3$	$CHCl_3$/THF	45	11:1
15[d]	$Rh_2(pfb)_4$	$Sc(OTf)_3$	$CHCl_3$/THF	37	17:1

[a] Reaction conditions: $Sc(OTf)_3$ (5 mol%), Rh_2L_4 (1 mol%), TfOH (10 mol%), MS 4 Å (60 mg), $T = 50 °C$. Catalysts and additives were dissolved in 2 mL of solvent and a solution of **1a** (250 μmol) in 1 mL of solvent was added within 4 h. [b] This batch of $Sc(OTf)_3$ did not contain other rare earth metal triflates as trace impurities. [c] $Lu(OTf)_3$ (1 mol%) was used to dope $Sc(OTf)_3$. [d] $Ga(OTf)_3$ (1 mol%) was used to dope $Sc(OTf)_3$. [e] No $Sc(OTf)_3$ was used. [f] No MS 4 Å. [g] No TfOH. Yields and regioisomeric ratios were determined by HPLC. rr = regioisomeric ratio, THF = tetrahydrofuran, pfb = perfluorobutyrate, cap = ε-caprolactamate, L = ligand, TfOH = triflic acid.

selectivity, except in the case of coordinating THF as solvent (entry 3). Solvent mixtures increased both yield and selectivity (entries 4 and 5). At that stage, we observed that the addition of other trace metal modifiers had a significant positive effect on the reaction outcome and were indeed required to achieve reproducible results (entries 6–8). Unfortunately, results given in entry 5 could never be reproduced. Crossover experiments with these metal salts and appropriate control experiments (entries 9–13) revealed that additives strongly affect yield and selectivity. Lastly, other Rh[II] sources were examined (entries 14 and 15, for full optimization details, see Supporting Information); it turned out that $Rh_2(cap)_4$ showed the best performance with respect to yield and selectivity.

With the optimized reaction conditions in hand, we investigated the scope of this annulation (Scheme 2). Changing the ester moiety to iPr furnished the desired product **3b** in good yield and selectivity, while benzyl esters were not successfully converted. Chlorine substituents attached to the backbone (**3c**) and extended π-systems (**3d**) worked smoothly although the yield was moderate. Thiophene-containing backbones provided the pentacyclic structures **3e** and **3f** in yields up to 59%. Surprisingly, the predominantly formed regioisomer was the opposite of that observed for non-heterocyclic backbones. The same holds true for a furan backbone; however, only a poor yield of 12% was observed. Predominantly, diols of type

6 (Figure 2) were isolated that relate to the intermediate formation of sensitive oxiranes **4** (cf. Scheme 3).

Whereas the compounds in Scheme 2 are built from two fragments of the same diazo precursor, we also investigated the use of two different diazo precursors to form heterodimers. When electronically very similar π-systems are employed, only a slight preference for one of the heterodimers is observed (Figure 1). In contrast, when we used an indol-derived substrate a clear-cut preference for one of the heterodimers was observed. As a competing reaction, the homodimers of the non-heterocyclic precursors are also formed; however, the regioisomers of type **3ab** were not detected in any case of heterodimerization.

Trapping and control experiments led us to propose a plausible mechanistic hypothesis for the formation of these complex oligocyclic products. Amongst a multitude of potential products there is a strong preference for one regioisomer. In this isomer four contiguous stereocenters are generated, whereby two stereocenters are not independent of each other. Thus, theoretically four different pairs of enantiomers might be formed; however, only one is observed.

In the initial step the Rh[II] catalyst triggers the elimination of nitrogen (Scheme 3 A). The emerging carbene **B** is either able to cyclize to carbonyl ylide **A** or undergo a carbene migration to **D** through the formation of an oxirene intermediate **C** (keto-carbene equilibrium). Carbonyl ylide **A** reacts with the starting

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Scheme 2. Scope of the cooperative annulation cascade for the construction of homodimers **2**. The annotation **a** represents β- and **b** γ-hydroxyketones. Stated yields represent isolated yields. The regioisomeric ratio (*rr*) was determined by ¹H NMR spectroscopy. [a] Large scale reaction: 2.1 mmol, 52% isolated yield, *rr* = 33:1. [b] PhMe/THF was used as a solvent.
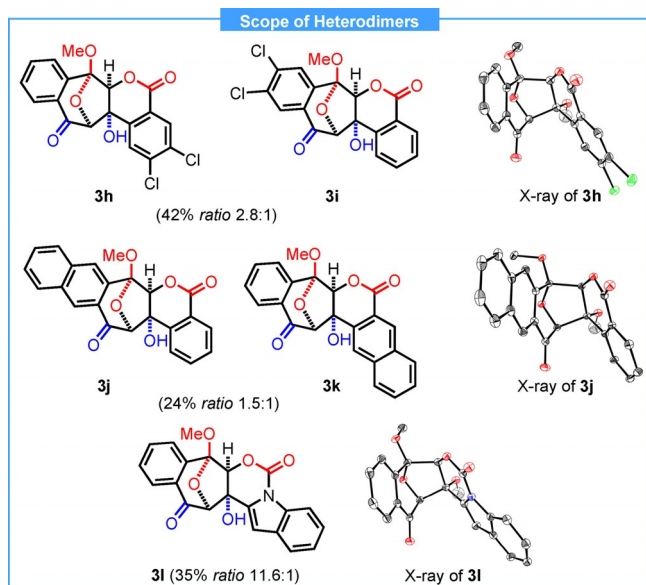

Figure 1. Heterodimerization products from various substrates **1**.

material **1a** to afford orthoester **E**, which is consecutively transformed via Rh catalysis into ylide **F**. Upon activation with Sc(OTf)₃ **F** rearranges to **3aa**. We attribute the fact that sterically more congested V-shaped molecules are formed to the initial formation of the less sterically encumbered stereoisomer of **E** during the (3+2)-cycloaddition. This orientation determines the stereochemistry of **3aa**.

Another possibility for the construction of **3aa** is given by the (3+2)-cycloaddition of oxirene **C** with ylide **A** furnishing **4a**. In the absence of Lewis acid, **4a** was isolated.[18] When **4a** was treated with Sc(OTf)₃ both regioisomers **3aa** and **3ab** were detected, with a strong preference for **3aa**. The regioisomer **3ab** was exclusively obtained when **4a** was treated with TfOH. Scheme 3B provides a hypothetical Sc(OTf)₃-catalyzed mechanism involving, inter alia, epoxide opening and concomitant Wagner–Meerwein rearrangement for the conversion of **4a** to **3aa** (for more details see Supporting Information). A plausible mechanism for the generation of its regioisomer **3ab** is provided in Scheme 3C.

We consider as a first step the activation of the oxirane moiety by Brønsted acid. A Wagner–Meerwein type aryl shift leads to ring contraction and affords, upon lactonization and hydrolysis, bislactone **5**, which was isolated and elucidated by X-ray crystallography. A subsequent domino cascade triggered by protonation of the lactones yields **3ab**.

In addition, this mechanistic scenario can explain the predominant formation of the regioisomers **3ab** when electron-donating arene units are attached to the carbene (Scheme 2).
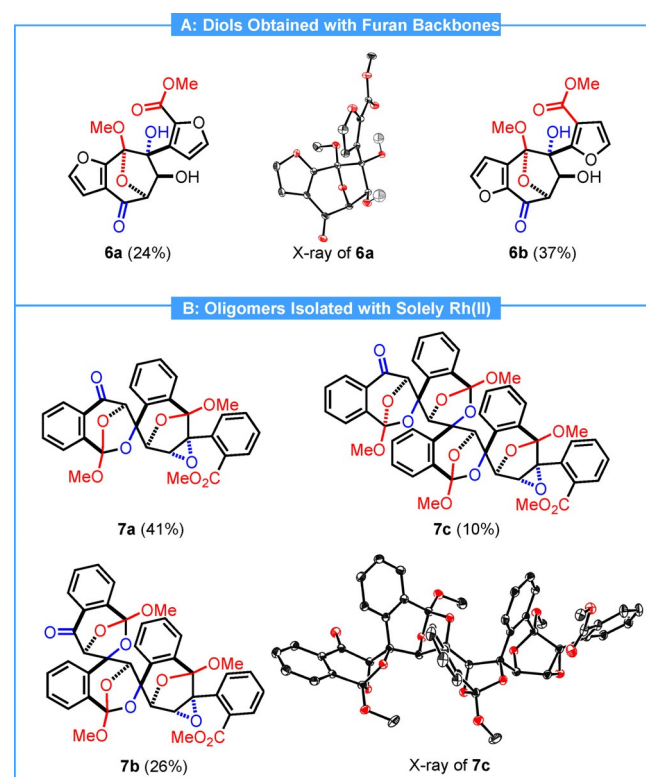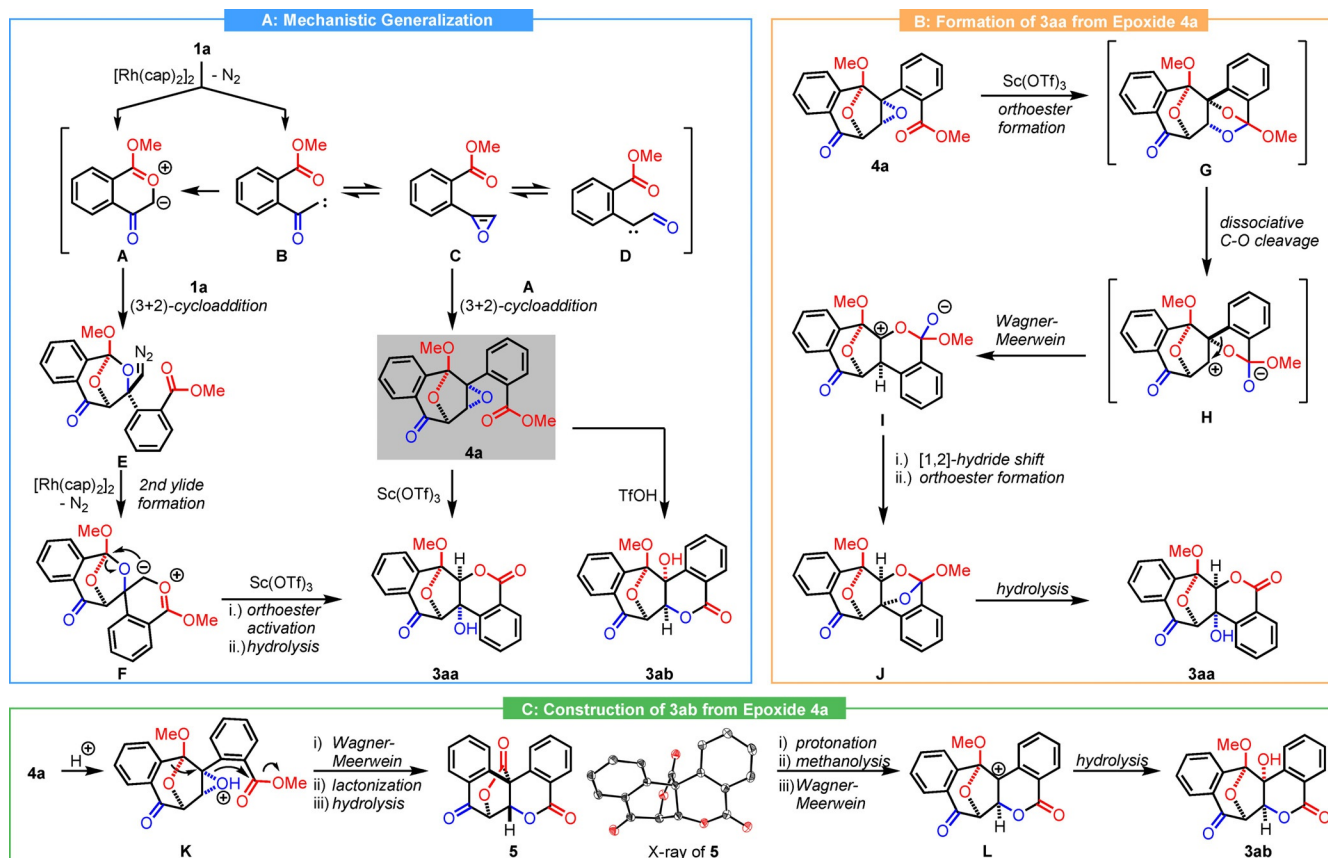

Figure 2. A: Isolated hydrolyzed intermediates of furan substrates. B: Oligomers observed in the absence of Lewis and Brønsted acid. Compound **6a** was isolated as a by-product in the formation of **3g**.

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Scheme 3. A: Plausible mechanistic pathways for the multistage cooperative annulation cascade of diazo compounds **1**. To facilitate ease of understanding, [Rh] was omitted after the initial step. B: Rearrangement of epoxide **4a** via orthoester **G**. C: Wagner–Meerwein cascade of epoxide **4a** to afford regioisomer **3ab**.

A more electron-rich arene unit leads to a higher nucleophilicity of the adjacent carbonyl moiety, which is a prerequisite for the formation of oxirene-type intermediates. Further evidence for oxirene formation in the case of furan backbones is given by the generation of diols **6a** and **6b** (Figure 2), which are traced back to an intermolecularly formed and concomitantly hydrolyzed epoxide **4** (cf. Scheme 3 A). Further mechanistic evidence for the crucial role of Lewis and Brønsted acid participation is provided by oligomers **7**, which were isolated in moderate yield (Figure 2) when the reaction was conducted in the absence of those acids. These oligomers are the products of an initial (3+2)-cycloaddition of oxirene **C** with carbonyl ylide **A**, followed by further (3+2)-cycloaddition reactions of the respective carbonyl moiety with ylide **A**.

In conclusion, we have discovered an unprecedented dimerization cascade that transforms, through cooperative Rh^{II}, Lewis and Brønsted acid catalysis, a simple diazo carbonyl compound into oxygen-rich oligocyclic scaffolds. In a regio- and diastereoselective fashion four new bonds, three different functional groups and four contiguous stereocenters are formed in one step. Mechanistic investigations by the isolation and X-ray investigation of some intermediates and their subjection to specific reaction conditions revealed a complex framework of cycloaddition reactions also involving transient species of the ketocarbene equilibrium and skeletal rearrangements.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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