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ARTICLE

Catalytic Hydroboration of Aldehydes, Ketones, Alkynes and Alkenes Initiated by NaOH

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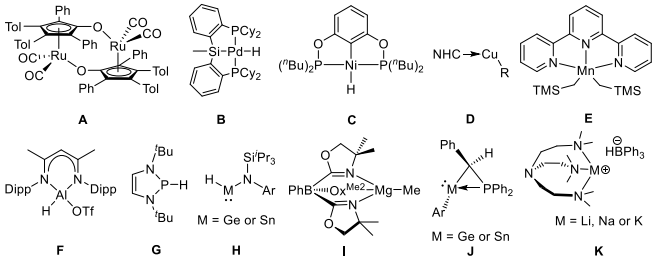
Commercially available NaOH powder is shown to be an efficient transition-metal-free initiator for the catalytic hydroboration of aldehydes, ketones, alkynes and alkenes with HBpin and 9-BBN under mild conditions. Combined experimental and theoretical studies suggest that the catalytically active species is a boron hydride generated in situ from the reaction mixture.

Introduction

Organoboranes have become a class of versatile synthetic intermediates for several important organic transformations (e.g. the Suzuki–Miyaura reaction and Brown hydroboration reaction) in both academic and industrial processes.[1] In contrast to other organometallic compounds, organoboranes are widely available and an extensive library of structures can be generated by the hydroboration of unsaturated compounds, one of its most remarkable advantages.[2] The pursuit of efficient methods for direct hydroboration of unsaturated bonds dates back to the middle of the twentieth century when Brown *et al.* pioneered the hydroboration of alkenes with sodium borohydride-aluminum chloride.[3] Following this, great efforts have been placed into catalytic hydroboration employing pinacolborane (HBpin) or catecholborane (HBcat), which emerges as an efficient and atom economic protocol for the preparation of numerous organoboranes.[4]

Hydroborations relying on well-defined transition metal catalysts have flourished in particular. Numerous transition-metal complexes (Scheme 1, A-E) involving Ru,[5] Mo,[6] Pd,[7] Cu,[8] Au,[9] Ni,[10] Fe,[11] Ti,[12] Zr,[13] Mn,[14] Hg,[15] Cd,[15] Rh[16] and Ir[17] have displayed excellent catalytic activity in the hydroboration of unsaturated bonds, resulting in the formation of various valuable organoboranes. In addition, recent progress in main-group catalysts (Scheme 1, F-K) based on Al,[18] P,[19] Ge,[20] Sn,[20a] Mg,[21] Ga[22] and alkali metals[23] as well as Lewis acid/Lewis acid-base pairs[24] has achieved tremendous success for the hydroboration of carbonyl compounds and imines with high efficiency and selectivity. However, the need for high catalyst loading coupled with the presence of heavy metal impurities in some cases leads to a high economic cost. The complicated preparation of well-designed catalysts also hindered the application of these reactions. In this regard, the development of efficient and transition-metal-free processes would significantly change synthetic strategies for the hydroboration in a sustainable and atom-economic manner.[25] Here, we report the first easy-to-handle, convenient, and versatile hydroboration of various aldehydes, ketones, alkynes and alkenes with B-H compounds using commercially available NaOH powder.



Scheme 1 Selected examples of transition metal complexes (**A**-**E**) and main group catalysts (**F**-**K**) for hydroboration reactions.

Results and Discussion

We reasoned that, as the typical Lewis acids, boranes could readily form adducts with nucleophiles (Scheme 2), leading to the weakening of B–H bonds with enhanced hydride character,[11c,24d] which would thus facilitate the hydroboration processes. Indeed, natural bond orbital (NBO) calculations at the M06-2X/TZVP level of theory supported our hypothesis (Scheme 2). The more negatively charged hydrogens of the B–H bond suggested that the Lewis acid-base adducts feature a stronger hydride character, compared to the corresponding

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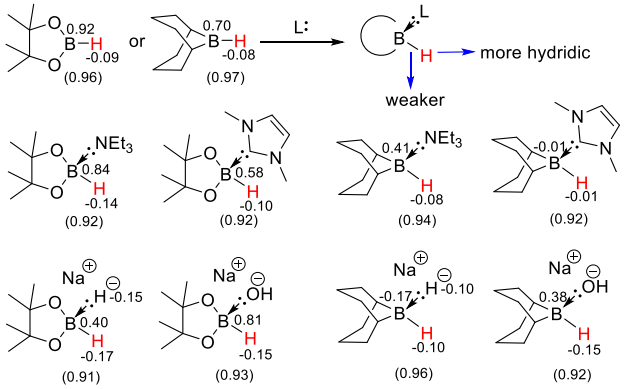
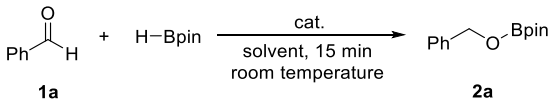
Electronic Supplementary Information (ESI) available: experimental procedure, characterization crystallographic and computational details, crystallographic details, NMR spectra, CIF file. CCDC 1503838. See DOI: 10.1039/x0xx00000x

boranes. Further, the coordination of Lewis bases could efficiently decrease the electron deficiency of the boron center, resulting in a weaker B–H bond (relative to HBpin or 9-borabicyclo[3.3.1]nonan (9-BBN)), supported also by the smaller Wiberg bond indices (WBIs).



Scheme 2 NBO analysis of HBpin, 9-BBN and the ensuing adducts. Selected NBO charges are given in atomic units. WBIs are given in parentheses.

Table 1 Optimization of the reaction conditions.[a]



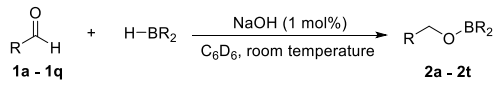
1a **2a**

Entry	Cat.	Loading (mol%)	Solvent	Yield (%)[b]
1	-	-	C_6D_6	<5
2	Et_3N	5	C_6D_6	35
3	^{t}BuOK	5	C_6D_6	82
4	NaOH[c]	5	C_6D_6	92
5	NaH	5	C_6D_6	99
6	IMes	5	C_6D_6	99
7	NaOH[d]	5	C_6D_6	99
8	NaOH[d]	1	C_6D_6	99
9	NaOH[d]	1	$CDCl_3$	99
10	NaOH[d]	1	THF-d_8	99

[a] Reaction conditions: benzaldehyde (1.00 mmol), HBpin (1.02 mmol), solvent (0.4 mL), room temperature. Catalyst loading relative to benzaldehyde. [b] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Pellets. [d] Powders.

On the basis of the calculations, we started our investigation employing benzaldehyde (**1a**) and HBpin as model substrates at room temperature. Deuterated solvents were employed for the convenience of NMR monitoring. The control experiment showed that without catalysts the reaction only gave trace amount of product **2a** (Table 1, entry 1). Next, some common and commercially available Lewis bases (*ie*. Et_3N, ^{t}BuOK, and NaOH (pellets); Table 1, entries 2-4) were used as catalysts for the reaction. Gratifyingly, the desired hydroboration product **2a** was formed in a good yield of 84% employing ^{t}BuOK as the catalyst (entry 3). Stronger Lewis bases such as alkali hydride NaH and *N*-heterocyclic carbene 1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes)[26] were also evaluated and both provided very high yields of **2a** (entries 5-6). Kawabata *et al.* discovered that powdered alkali hydroxides showed better solubility in organic solvents, have great specific surface area and high reactivity in alkylation reactions.[27] Illuminated by the previous reports, powdered NaOH was investigated and a high yield of 99% was obtained (entry 7). Even when the catalyst loading was decreased to 1 mol%, the hydroboration product **2a** was obtained in excellent yield after 15 minutes (entry 8). Encouraged by these promising results, solvents were briefly screened and C_6D_6, $CDCl_3$ and THF-d_8 were found to be suitable for the reaction (entries 8-10).

Table 2 Scope of hydroboration with aldehyde substrates.[a]



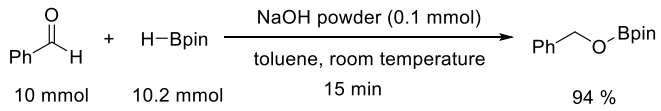
1a - 1q **2a - 2t**

Product	Yield (%)[b]	Product	Yield (%)[b]
2a	99	**2b**	95
2c	96	**2d**	95[c]
2e	97	**2f**	99
2g	93[c]	**2h**	98
2i	96	**2j**	97
2k	99	**2l**	93
2m	99	**2n**	95[d]
2o	98[d]	**2p**	94[e]
2q	88[e]	**2r**	92[e]
2s	91[e]	**2t**	99

[a] Reaction conditions: benzaldehyde (1.00 mmol), HBpin (1.02 mmol), NaOH (0.01 mmol), C_6D_6 (0.4 mL), room temperature, 15 minutes. [b] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction was conducted for 1 hour. [d] 2 equiv of HBpin were employed. [e] Reaction conditions: benzaldehyde (1.00 mmol), 9-BBN (0.5 M in THF, 1.10

mmol), NaOH (0.01 mmol), THF-d_8 (0.5 mL), room temperature, 2 hours.

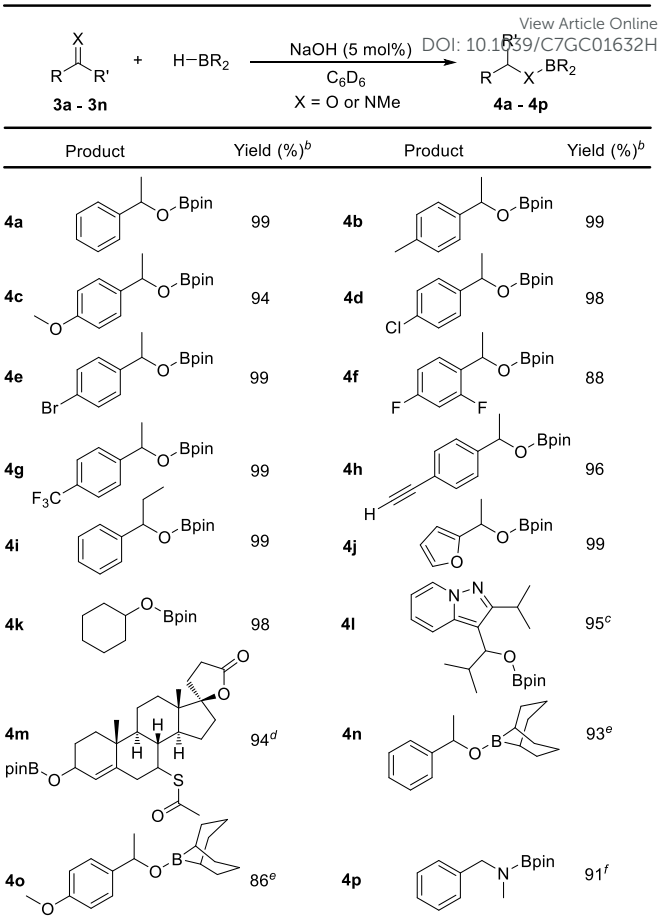
With the optimized reaction conditions in hand, we explored the scope of this reaction with various aldehydes (Table 2). Both electron-donating and electron-withdrawing (**2b**-**k**) aromatic groups were well tolerated and gave excellent yields under standard conditions. It is worth noting that even with a bulky substituent on the arylaldehyde, the hydroboration can still be effectively performed with a high yield of 98% (**2h**). Aliphatic aldehydes were also tolerated and afforded the corresponding borate esters in good yields (**2l**: 93%, **2m**: 99%). Terephthalaldehyde (**1n**) and isophthalaldehyde (**1o**) could also be used as suitable substrates to give the corresponding diborate esters in a high yield of 95% (**2n**) and 98% (**2o**), respectively. In addition to HBpin, 9-BBN and HBcat were also compatible with this reaction, affording the desired hydroboration products **2p**-**t** in excellent yields. Notably, a large-scale reaction of **1a** (10 mmol) with HBpin (10.2 mmol) was employed in a toluene solution under the optimized conditions and delivered **2a** in 94% yield (Scheme 3).



Scheme 3 Large-scale reaction of benzaldehyde with HBpin.

To expand the scope of this method, we next turned our attention to ketone substrates. The hydroboration of acetophenone (**3a**) with HBpin afforded the desired product **4a** in 99% yield. Ketones bearing methyl, methoxy, chloro, fluoro, bromo, trifluoromethyl and ethynyl groups afforded the corresponding borate esters in excellent yields (Table 3, **4a**-**h**). Notably, the ketone moiety displayed higher chemoselectivity over the chlorine (**4d**, 98%), bromine (**4e**, 99%) and alkyne (**4h**, 96%). Heteroaromatic ketones, such as furan-2-carbaldehyde, were also tolerated and the corresponding product **4j** was obtained in a high yield of 99%. Although longer reaction times were required compared to the standard conditions, biologically active compounds such as ibudilast (**3l**)[28] and spironolactone(**3m**)[29] were investigated and gave the corresponding borate esters in good yields (**4l**: 95% and **4**m: 94%). Furthermore, 9-BBN can also react with ketone substrates smoothly at room temperature, affording the desired hydroboration products **4n** and **4o** in good yields. Imines, easily accessible from carbonyl compounds and primary amines, are suitable precursors for the preparation of secondary amines. Thus, next we examined imines as substrates in the catalytic hydroboration reaction. Hydroboration of N-methyl-1-phenylmethanimine (**3p**) with HBpin proceeded within 6 hours at 90 °C to give borate ester **4p** in a good yield of 91%.

Table 3 Scope of hydroboration with ketone and imine substrates.[a]



[a] Reaction conditions: ketone or imine (1.00 mmol), HBpin (1.02 mmol), NaOH (0.05 mmol), C_6D_6 (0.4 mL), room temperature, 15 minutes. [b] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. *c* Reaction was conducted for 12 hours. [d] Reaction was conducted for 24 hours. [e] Reaction conditions: ketone (1.00 mmol), 9-BBN (0.5 M in THF, 1.10 mmol), NaOH (0.05 mmol), THF-d_8 (0.5 mL), room temperature, 2 hours. [f] Reaction was conducted at 90 °C for 6 hours.

Inspired by the above results, we then examined alkynes and alkenes as substrates (Table 4). Note that catalyst-free hydroboration of alkynes and alkenes with HBpin was reported by Knochel *et al*,[30] in which 2.0 equivalents HBpin, based on alkynes and alkenes, was necessarily needed for good yields. However, when the loading of HBpin was decreased to 1.4 equivalents, the hydroboration processes gave very poor yields in the absence of NaOH (Table 4, footnotes c and d). To our delight, the NaOH-initiated hydroboration of phenylacetylene (**5a**) with HBpin at 100 °C furnished the corresponding borate esters **6a** in high yields. Both electron-donating and electron-withdrawing aromatic groups bearing methyl, methoxy, fluoro and chloro were well tolerated in this reaction (**6a**-**e**). Substrates having a substituted group such as fluoro and chloro on the ortho position of phenyl ring only gave moderate to low yields (**6f**-**g**), indicating that steric hindrance affects the reaction yields. Unfortunately, internal alkynyl such as 1,2-diphenylethyne and methyl 3-phenylpropiolate only gave a trace amount of the desired hydroboration products. 2-Ethynylthiophene was also found to be suitable reaction

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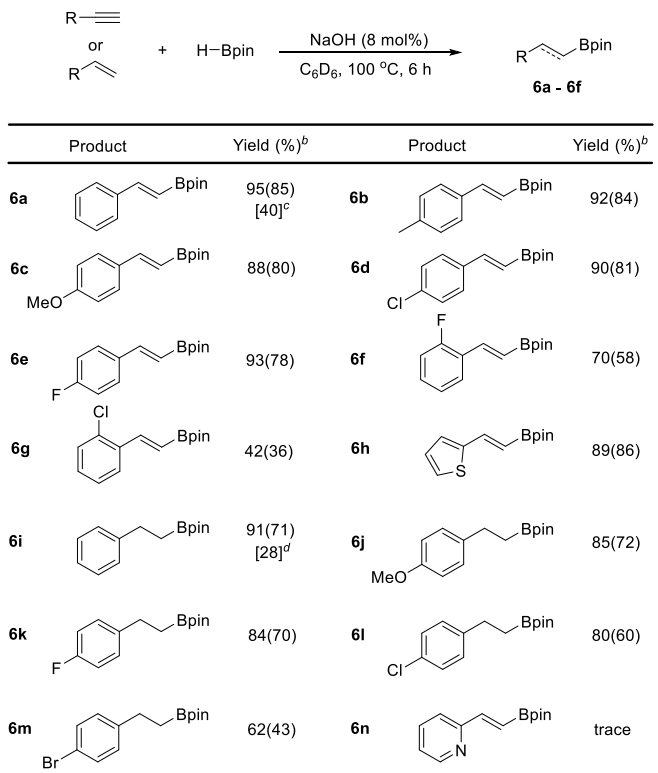
partners (**6h**). In addition, it is noticeable that this procotol could be employed in the hydroboration of alkenes (**5i**-**m**) without damaging the methoxy, fluoro, chloro, bromo functionalities, providing the ensuing alkyl-substituted dioxaborolanes (**6i**-**m**) in good to moderate yields.

Table 4. Scope of hydroboration with alkyne and alkene substrates.[a]



Product	Yield (%)[b]	Product	Yield (%)[b]
6a	95(85) [40][c]	**6b**	92(84)
6c	88(80)	**6d**	90(81)
6e	93(78)	**6f**	70(58)
6g	42(36)	**6h**	89(86)
6i	91(71) [28][d]	**6j**	85(72)
6k	84(70)	**6l**	80(60)
6m	62(43)	**6n**	trace

[a] Reaction conditions: alkyne or alkene (1.00 mmol), HBpin (1.40 mmol), NaOH (0.08 mmol), C_6D_6 (0.4 mL), 100 °C, 6 hours. [b] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Yields in parentheses are isolated yields after column chromatography on silica. [c] Reaction conditions: **5a** (1.00 mmol), HBpin (1.40 mmol), C_6D_6 (0.4 mL), 100 °C, 6 hours. [d] Reaction conditions: **5i** (1.00 mmol), HBpin (1.40 mmol), C_6D_6 (0.4 mL), 100 °C, 6 hours.

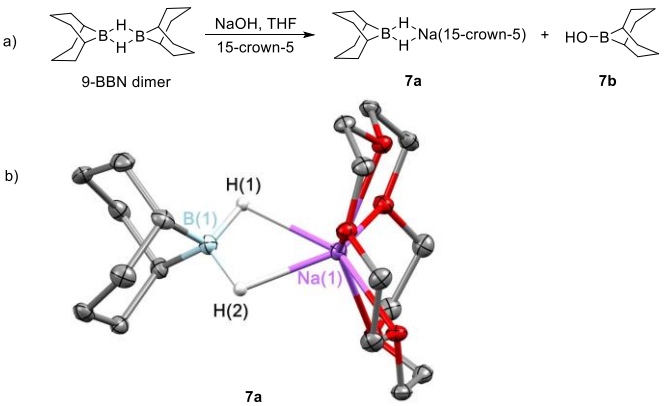
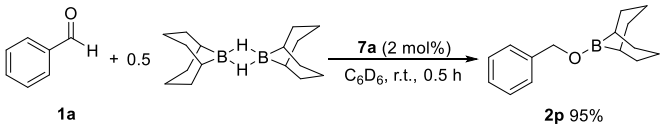


Fig. 1 (a) The reaction of 9-BBN with NaOH. (b) Molecular structure of **7a** with the anisotropic displacement parameters depicted at the 50% probability level. The hydrogen atoms except those on the B atom have been omitted for clarity.

To gain insight into the mechanism, we employed a stoichiometric reaction of HBpin with NaOH in THF at room temperature. White precipitates were obtained immediately after a THF solution of HBpin was added dropwise. The white precipitates were filtrated and collected, but showed very poor solubility in all usual organic solvents. Note that the group of Clark showed the formation of a complex mixture containing boron-bound hydrides by treatment of a stoichiometric equivalent of ^{t}BuONa with HBpin.[23b] It is highly possible that any of the borohydride derivatives serve as the active hydride source in the reaction mixture. In contrast, treatment of 9-BBN dimer with NaOH in a molar ratio of 1:1 immediately led to a clear colorless solution (Fig. 1a). The in situ ^{11}B NMR spectrum revealed a clean transformation with a broad peak at 55.98 ppm assigned to **7b**[31] and a triplet resonance at –17.65 ppm (J = 74.1 Hz), which collapses into a singlet upon proton decoupling, indicating the presence of a BH_2 fragment. Adding 15-crown-5 into the reaction mixture allowed the formation of colorless needle crystals of **7a**. X-ray diffraction analysis confirmed the boron hydride structure of **7a** with an anionic tetracoordinate boron center (Fig. 1b).[32] We found that **7a** could efficiently catalyze the hydroboration of **1a** with 9-BBN (Scheme 4), prompting us to consider that **7a** is likely the catalytically active species.



Scheme 4 **7a**-catalyzed hydroboration of **1a** with 9-BBN.

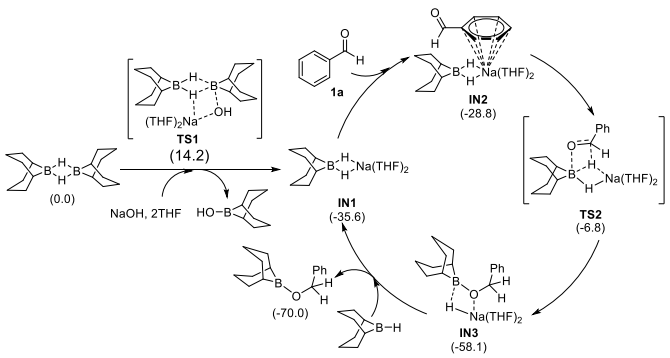


Fig. 2. Proposed mechanism. Free energies are given in kcal mol^{-1} employing 9-BBN as the substrate.

On the basis of above analysis, a plausible reaction mechanism of hydroboration of carbonyl compounds with 9-BBN was proposed and supported by density functional theory (DFT) calculations at the SMD-M06-2X/6-311++G(2d,p)//M06-2X/6-31G(d) level of theory (Fig. 2).[33] As the initial step, the generation of boron hydride **IN1** is not energy-demanding (activation barrier of 14.2 kcal mol^{-1}) and highly exothermic (-18.6 kcal mol^{-1}), which could be mainly attributed to the formation of the strong B–O bond. The approach of **1a** toward **IN1** results in the formation of an intermediate **IN2** (-28.8 kcal mol^{-1}) featuring the Na^+–π interaction.[34] Subsequently, the hydridic B–H bond in **IN1** would allow insertion of **1a** via a four-

membered ring transition state **TS2** (-6.8 kcal/mol) with an activation barrier of 28.8 kcal mol^{-1} (**IN1**→**TS2**). Finally, the hydroboration product extrusion (-70.0 kcal mol^{-1}) with the aid of a 9-BBN completes the catalytic cycle to regenerate the catalytically active species **IN1**. We note that the results and the interpretations presented here might be insufficient to support the generation of H_2Bpin anion from the reaction of HBpin and NaOH. Another possible mechanism consists of coordination of NaOH to boron as the reactive species cannot be ruled out.

Conclusion

In conclusion, we have developed a general and efficient catalytic hydroboration of aldehydes, ketones, alkynes and alkenes using powdered NaOH as the initiator. Utilizing this low toxic, commercially available, cheap, and stable powder as the initiator instead of environmentally unfriendly transition metals is extremely attractive. Coupled with its remarkable substrate tolerance, high chemo-selectivity, and good yields mean that this method will be appealing for organic synthesis. In contrast to the observations that the proposed active hydride source could not be isolated in the reaction of ^{t}BuONa with HBpin,[23b] we have successfully isolated a boron hydride **7a**. Preliminary mechanistic study revealed that **7a** is the catalytically active specie generated in situ in the reaction, which also paves a new way to produce the anionic H_2BR_2 species. Further studies of this newly discovered catalytic system are the subject of on-going investigation.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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The acknowledgements come at the end of an article after the conclusions and before the notes and references.

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