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Nickel-catalyzed highly regioselective hydrocyanation of alkenes with $\text{Zn}(\text{CN})_2^\dagger$

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The first general and regioselective nickel-catalyzed hydrocyanation of terminal alkenes with $\text{Zn}(\text{CN})_2$ using an air-stable and inexpensive nickel(II) salt as the precatalyst has been established. The strategy avoids the use of the volatile and hazardous reagent HCN. Aryl/heteroaryl alkenes are effectively converted to branched nitrile derivatives, while aliphatic alkenes or active alkenes are transformed to linear nitriles with good to excellent regioselectivity.

Introduction

Nitriles are versatile building blocks that can be converted into amines, isocyanates, amides, aldehydes, carboxylic acids, esters and heterocycles, not only in the laboratory but also on the industrial scale.¹ They have also found many applications in materials, pharmaceuticals, cosmetics, and agrochemicals.² In particular, due to the important properties such as hydrogen binding affinity to target proteins and metabolic stability of the nitrile functional group in pharmaceuticals, currently, over 30 nitrile-containing drugs are marketed, and more than 20 additional nitrile-containing leads are tested in clinical trials.³

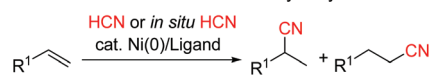
Transition-metal-catalyzed hydrocyanation of alkenes (addition of HCN to alkenes) provides a concise and highly atom-economical access to alkyl nitriles (Scheme 1).^{4–7} The most remarkable application of this reaction is the DuPont adiponitrile (a precursor of Nylon 6,6) process from 1,3-butadiene by nickel catalysis with a production of 1 million tons per year.⁸ However, these methods usually have the following drawbacks: (1) the hydrogen cyanide gas is extremely toxic, and is not easy to handle in a normal laboratory. Recently, acetone cyanohydrin^{7h–i} and TMS-CN/MeOH^{7j} have been explored as less volatile precursors for generating HCN *in situ*, but they still pose a significant risk. (2) The substrate scope in these reactions was quite limited. Most of the studies concentrated on the hydrocyanation of aryl alkenes, while there are few examples with non-activated aliphatic alkenes⁹ as the sub-

strates, possibly due to the low reactivity of these alkenes, and the high instability of the alkyl-metal intermediates which can be deactivated by β -hydride elimination, or forming the inactive dicyanonickel(II) complexes, *etc.*^{4c,7d} (3) Although Markovnikov selectivity can be usually achieved for aryl alkenes, the selectivity control of aliphatic alkenes still remains a challenge.^{4c} Therefore, it is of high importance to develop much safer, efficient, and regioselective catalyst systems. Recently, Morandi *et al.*¹⁰ reported elegant Ni-catalyzed transfer hydrocyanation of alkenes using isovaleronitrile as a HCN donor. Low to high linear-to-branched regioselectivities were observed for both aryl and aliphatic terminal alkenes. In this system, the air sensitive $\text{Ni}(\text{COD})_2$ and AlMe_2Cl (as a Lewis acidic additive) were used. During our manuscript preparation, Pd-catalyzed transfer hydrocyanation of alkenes with *anti*-Markovnikov selectivity using 1-methylcyclohexa-2,5-diene-1-carbonitrile as a HCN source was reported.^{6b} Nevertheless, the highly regioselective hydrocyanation by util-

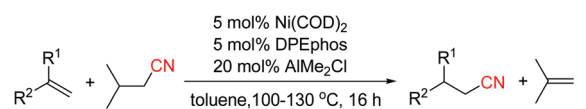
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Previous work: traditional alkene hydrocyanation



2016, Morandi *et al.*: transfer hydrocyanation



○ low to high linear selectivity (48% to >95%) for aryl and aliphatic alkenes

This work: direct cyanation



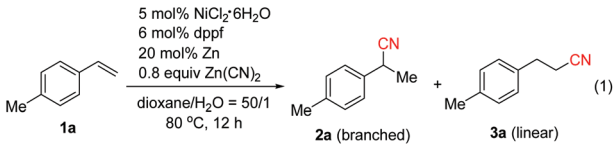
Scheme 1 Nickel-catalyzed cyanation reactions of alkenes.

ization of inexpensive and Earth-abundant metal catalysts is still quite rare and highly desirable. Recently, we have reported a highly efficient nickel-catalyzed hydrocyanation reaction of alkynes with $\text{Zn}(\text{CN})_2$ using $\text{Ni}(\text{acac})_2/(\text{neocuproine})/\text{Mn}$ as the catalyst system in the presence of water.¹¹ However, when we applied these reaction conditions to alkenes, no desired products were observed. In order to achieve the hydrocyanation of alkenes, we made great efforts. Herein we report the first nickel-catalyzed hydrocyanation of terminal alkenes that (a) utilizes relatively less toxic $\text{Zn}(\text{CN})_2$ as the cyano source while obviating the use of the hazardous HCN, (b) accommodates both aryl and aliphatic alkenes with wide functional group tolerance, (c) displays high regioselectivity for both aryl and aliphatic alkenes in which the branched or linear regioselectivity was found to be strongly influenced by the substitution patterns of the substrates, and (d) proceeds under mild reaction conditions (80 °C) using the air stable and inexpensive nickel(II) salts as the precatalyst¹² without the addition of air-sensitive additives (Scheme 1).

Results and discussion

We initially investigated the cyanation reaction of aryl alkene **1a**. After a thorough optimization study of the nickel catalysts, ligands, additives and solvents,¹³ we discovered that the use of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (5 mol%), dppf (6 mol%) and Zn powder (20 mol%) enabled the reaction to take place in dioxane/ H_2O (50:1) at 80 °C. The desired product **2a** with Markovnikov selectivity was formed efficiently in 89% yield, along with a linear product **3a** in 3% yield (Table 1, entry 1). The high regioselectivity is possibly attributed to the formation of the more stable η^3 -benzylnickel cyanide (π -allyl nickel complex) intermediate. Subsequently, the effect of the amount of water was investigated. Neither **2a** nor **3a** was obtained when increasing the amount of water (Table 1, entry 2). Possibly, higher cyanide concentration in this case caused catalyst poisoning. The addition of one or two equivalents of water resulted in lower product yields and regioselectivity (Table 1, entries 3 and 4). Screening of other nickel catalysts showed that $\text{NiCl}_2(\text{DME})$ displayed higher catalytic activity (Table 1, entries 5 and 6). As expected, PPh_3 was not effective in this reaction. It was known that phosphite type ligands displayed the best performance in Ni(0)-catalyzed hydrocyanation of alkenes using HCN. However, in our case, the use of $\text{P}(\text{OPh})_3$ failed to give any desired products, possibly owing to its lower stability in water (Table 1, entry 7). It was suggested that bidentate ligands with larger bite angles promote the reductive elimination and diminish the formation of a dicyanonickel(II) complex^{Ab,7d} in the hydrocyanation reaction. In our case, bidentate phosphine ligands with small bite angles such as dppp and dppb,¹⁴ or DPEphos with a bite angle of 105°^{Ab} afforded the products in low yields and selectivity (Table 1, entry 8), while Xantphos with a large bite angle ($\beta = 114^\circ$)^{Ab} showed higher efficiency than dppf (Table 1, entry 9). After brief screening of the solvents, THF was found to give products with comparable yields

Table 1 Optimization of reaction conditions

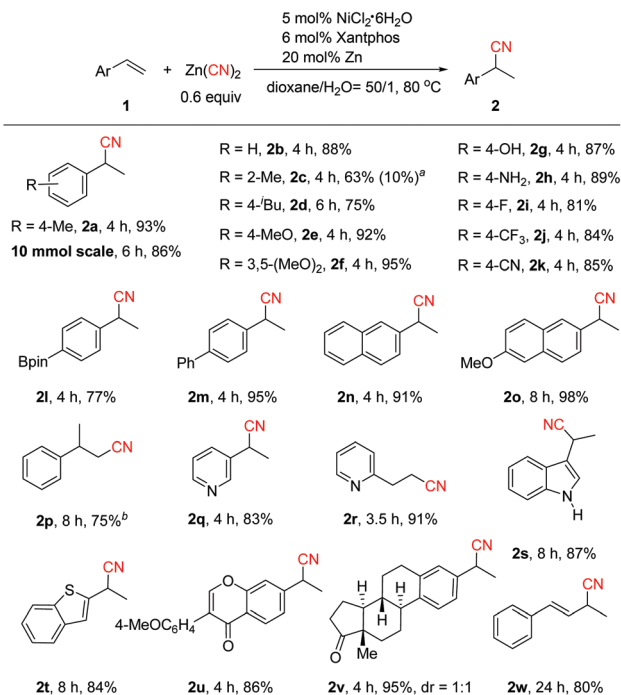


Entry	Deviation from the conditions shown in eqn (1)	Yield ^a (%)	
		2a	3a
1	None	89	3
2	Dioxane/ $\text{H}_2\text{O} = 25/1$	0	0
3	1.0 equiv. H_2O was used	33	9.5
4	2.0 equiv. H_2O were used	75	10
5	$\text{NiCl}_2(\text{DME})$ instead of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$	87	4
6	$\text{Ni}(\text{acac})_2$ instead of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$	0	0
7	10 mol% PPh_3 or $\text{P}(\text{OPh})_3$ instead of 6 mol% dppf	0	0
8	dppp, dppb or DPEphos instead of dppf	3–37	0–8
9	Xantphos instead of dppf	96	1
10	Xantphos instead of dppf, MeCN or DMF instead of dioxane	26–49	0–33
11	Xantphos instead of dppf, THF instead of dioxane	95	1
12 ^b	Xantphos instead of dppf, 0.6 equiv. $\text{Zn}(\text{CN})_2$ were used	97	1
13 ^{b,c}	Without $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, Xantphos or Zn	0	0
14 ^{b,c}	Without H_2O	25	0

^a Determined by ¹H NMR of the crude reaction mixture using mesitylene as an internal standard. ^b The reaction time was 4 h. ^c 0.6 equiv. $\text{Zn}(\text{CN})_2$ were used.

and selectivity to those obtained with dioxane (Table 1, entries 10 and 11). Lowering the amount of $\text{Zn}(\text{CN})_2$ to 0.6 equivalents could also afford **2a** in excellent yield within 4 h, and only a trace of linear isomer **3a** was detected (Table 1, entry 12). Control experiments indicated that the reaction could not take place without either $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, Xantphos or Zn (entry 13). It is worth noting that the yield of **2a** decreased to 25% without the addition of water, emphasizing again the importance of water (Table 1, entry 14).

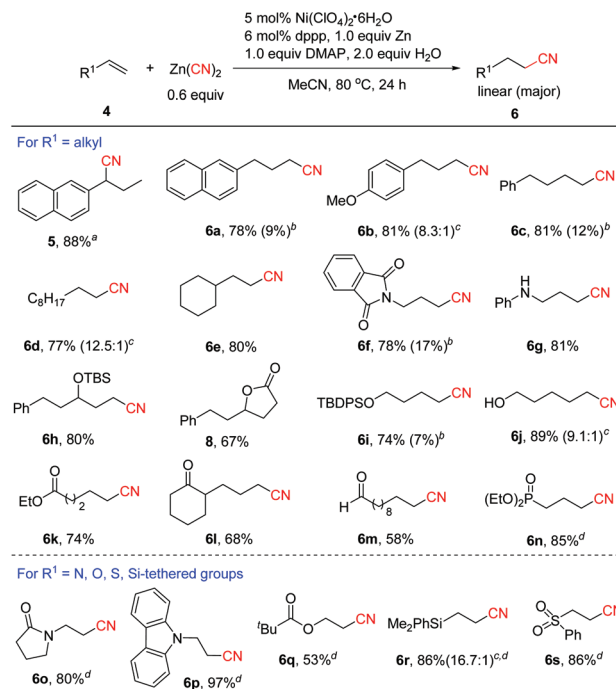
With the optimized reaction conditions in hand (Table 1, entry 12), the scope of the aryl alkenes was first evaluated (Scheme 2). Gratifyingly, a wide range of styrenes were suitable for this reaction, and generally the corresponding branched nitriles were obtained in good to high yields with excellent regioselectivity. Electrically neutral styrene provided **2b** in 88% yield. Only small amounts of product **2c** derived from sterically hindered 2-methylstyrene were formed. However, replacing Xantphos by dppf and increasing the amount of Zn to one equivalent enhanced the reaction efficiency significantly, leading to **2c** and linear product **3c** in 63% and 10% yields, respectively. We envisioned that the use of a stoichiometric amount of Zn might cause a facile reduction of inactive Ni(II) species generated during the reaction process to Ni(0), and using adequate amounts of Ni(0) should be the key to the success of this reaction. Alkenes bearing electron-donating groups on the aryl ring such as *p*-^tBu, *p*-MeO, and 3,5-(MeO)₂ or even with the highly challenging free hydroxyl and amino groups turned out to be efficient substrates (**2d–2h**). Notably, product **2d**, a precursor of the famous drug ibuprofen, could



Scheme 2 Scope of aryl/heteroaryl alkenes. Isolated yields. ^a 6 mol% dpfp and 1.0 equiv. Zn were used. The isolated yield of the minor regioisomer is shown in parentheses. ^b 5 mol% NiCl₂·6H₂O, 6 mol% dpfp, 1.0 equiv. Zn, 0.5 equiv. ZnI₂ and 2.0 equiv. H₂O were used in MeCN.

be obtained in 75% yield. Electron-deficient aryl alkenes bearing a *p*-F, *p*-CF₃ or *p*-CN group also worked well (**2i–2k**). Boron-substituted aryl alkene **1l** was well tolerated in the reaction, while the Bpin moiety remained intact. The reaction could be applied to biaryl or naphthyl substituted alkenes [**2m**, **2n** and **2o** (a precursor of the drug naproxen)]. 1,1-Disubstituted styrene transformed to **2p** smoothly in 75% yield under modified reaction conditions with ZnI₂ as the additive. ZnI₂ possibly behaves as a Lewis acid to coordinate with the CN group which promotes the reductive elimination step.^{4c,7a,15} The substrate scope could also be extended to heteroaryl-substituted alkenes (**2q**, **2s–2t**). To our surprise, the use of 2-vinylpyridine led to linear product **2r** in 91% yield exclusively. We envisioned that pyridyl may act as a coordinating group to form a five-membered metal chelate ring¹⁶ that stabilizes the C(sp³)-Ni intermediate and facilitates the linear product formation. In addition, the high efficiency of this method in the hydrocyanation of formononetin (**2u**) and estrone (**2v**) derivatives demonstrates its potential value in late-stage functionalization of medicinally relevant compounds. Hydrocyanation of 1,3-diene was also successful (**2w**, 80% yield), which could not be cyanated by the transfer hydrocyanation reaction.¹⁰ The practicality of this method was elucidated by the gram-scale synthesis of **2a** (86% yield).

Next, the substrate scope of aliphatic alkenes was examined (Scheme 3). Under the standard conditions for aryl alkenes, unexpectedly, 2-allylnaphthalene was converted to branched nitrile **5** in 88% yield, which was likely formed through alkene

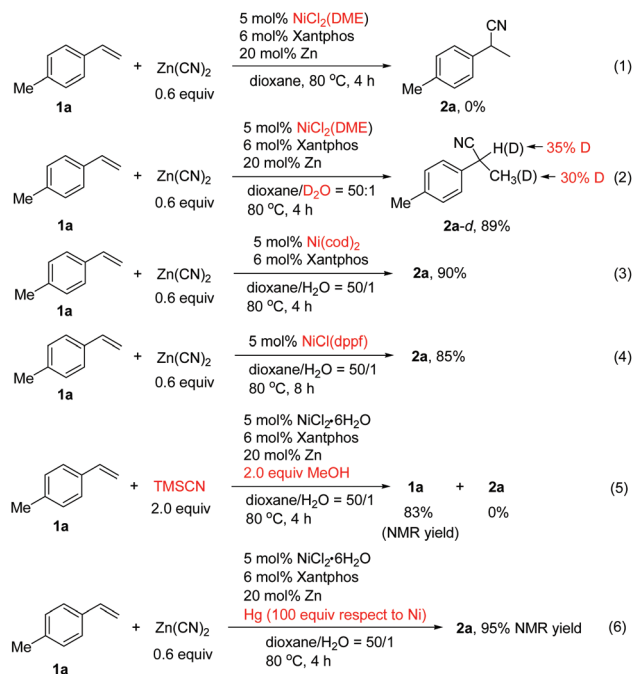


Scheme 3 Scope of aliphatic alkenes. Isolated yields. ^a 5 mol% NiCl₂·6H₂O, 6 mol% Xantphos, 20 mol% Zn, dioxane/H₂O = 50/1. ^b The yields of the branched nitrile **7** are shown in parentheses. ^c Overall yields of **6** and **7**, and the ratio of **6**:**7** is shown in parentheses. ^d 5 mol% NiCl₂·6H₂O, 6 mol% dpfp, 20 mol% Zn and 2.0 equiv. H₂O were used in MeCN at 80 °C for 12 h.

isomerization followed by hydrocyanation. In fact, the alkene isomer of 2-(prop-1-enyl)naphthalene **4a'** (*E/Z* = 33.3:1) could be isolated in 94% yield at the early stage of the reaction. The results clearly indicated that nickel hydride was formed during the process since it was known that Ni-H species could catalyze the isomerization of alkenes.¹⁷ In order to avoid the alkene isomerization, we re-optimized the reaction conditions.¹³ Inspired by our recent work on nickel-catalyzed cyanation of aryl halides with Zn(CN)₂^{18a} using DMAP as a co-ligand,¹⁸ after many trials, we found that the reaction proceeded with good to high linear selectivity in the presence of 5 mol% Ni(ClO₄)₂·6H₂O, 6 mol% dpfp, 1.0 equiv. of Zn, 2.0 equiv. of H₂O and 1.0 equiv. of DMAP in MeCN at 80 °C. In particular, DMAP was found to play an important role in improving the regioselectivity, since without DMAP, branched product **5** was formed in high yield (89%) in the case of 2-allylnaphthalene.¹³ The large change in regioselectivity might be attributed to the steric effect around the alkylnickel cyanide intermediate in which DMAP coordinates to the metal and increases the steric bulkiness around nickel. Thus the less hindered linear alkylnickel cyanide intermediate is favored leading to the linear product. The scope of aliphatic alkenes was then investigated under the revised conditions. For example, the reaction of the same substrate of 2-allylnaphthalene with Zn(CN)₂ afforded linear product **6a** in 78% yield, along with 9% of branched product **7a**. Alkenes with alkyl side chains bearing aryl functional groups were transformed to **6b–6c** in high yields with

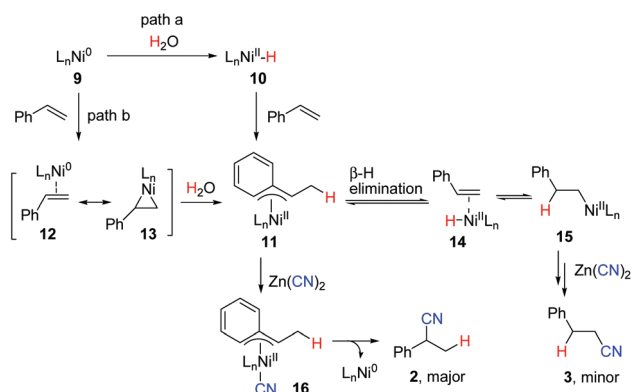
good linear selectivity. Common alkenes without any functional groups such as 1-decene and sterically congested vinylcyclohexane could also be cyanated efficiently (**6d–6e**). Excellent linear selectivity was observed in the latter case due to the steric effect of the cyclohexyl group. Allylic amine derivatives were confirmed to be valuable substrates for this reaction to afford the desired linear nitriles in 78%–81% yields (**6f–6g**). TBS-protected secondary allylic alcohol was compatible and showed excellent linear selectivity (**6h**). Unexpectedly, when allylic alcohol 5-phenylpent-1-en-3-ol **4t** was employed as the substrate, lactone product **8** was obtained *via* sequential hydrocyanation/cyclization. Thus, the reaction provided a concise and efficient route to lactones. Protected and unprotected primary alcohols were well tolerated (**6i–6j**). It was noted that unprotected alcohols were not suitable for the transfer hydrocyanation reaction.¹⁰ Excellent linear selectivity (**6k–6m**) was also achieved with aliphatic alkenes containing ester, keto and aldehyde groups. In the case of diethyl allylphosphonate, we found that the reaction proceeded more efficiently to afford **6n** in 85% yield using 5 mol% NiCl₂·6H₂O, 6 mol% dppf, 20 mol% Zn, and 2.0 equiv. H₂O without the addition of DMAP. Encouraged by this result, we further explored the hydrocyanation of a series of activated alkenes under the conditions for the formation of **6n**. Notably, all these reactions occurred with excellent anti-Markovnikov selectivity, and various N, O, Si or S-containing groups were well tolerated (**6o–6s**).

To probe the reaction mechanism, we carried out various control experiments.¹³ It was found that no desired product was formed from **1a** using NiCl₂(DME) as the catalyst in the absence of water (Scheme 4, eqn (1)). Deuterium labeling experiments using D₂O produced deuterated **2a-d** in 89% yield in which deuterium is found in both the benzylic position and methyl group (Scheme 4, eqn (2)). The results implied that the hydrogen source for hydrocyanation comes from water. The scrambling of the deuterium between the benzylic and homobenzylic carbon atoms of **2a-d** indicated that nickel hydride addition to the alkene is reversible, and it is possible that the resulting η³-benzyl nickel species equilibrates with a linear alkylnickel intermediate.^{7g} The Ni(cod)₂ or Ni(I) complex of NiCl(dppf) could also catalyze the reaction efficiently in the absence of the reductant (Scheme 4, eqn (3) and (4)). It is unlikely that the reaction goes through Ni(I) species involving transmetalation of Ni–Cl with Zn(CN)₂ to form a Ni(I)–CN species followed by addition to the alkene and protonation, since it is hard to explain the observed regioselectivity and deuterium labeling results.¹³ We suggest that in the case of the Ni(I)-catalyzed reaction, the Ni(I) species might undergo a disproportionation reaction to afford Ni(0) and Ni(II) complexes, in which Ni(0) is the real active species for the reaction. Employing TMSCN/MeOH as the *in situ* HCN donor resulted in no formation of **2a** under the standard conditions for **2a** (Scheme 4, eqn (5)). Additionally, the mercury poisoning experiments indicated that the reaction was not inhibited, implying that a heterogeneous system might not be involved (Scheme 4, eqn (6)).



Scheme 4 Control experiments.

Although more efforts should be made to make the reaction mechanism clear, based on the above results, we tentatively propose the following reaction mechanism represented by hydrocyanation of styrene shown in Scheme 5. In path a, Ni(0) complex **9**, formed *via* reduction of NiCl₂·6H₂O with Zn, reacts with water to give a LnNi(II)–H intermediate **10** either by oxidative addition of water^{19,20} or by an unclear process. Migratory insertion of styrene into the Ni–H bond affords η³-benzyl nickel(II) complex **11**. A fast equilibrium between **11** and **15** *via* intermediate **14** exists, but **11** is more favored due to its higher stability. Subsequent transmetalation of **11** with Zn(CN)₂ followed by reductive elimination provides branched nitrile **2** selectively. Alternatively, complex **10** may first react with Zn(CN)₂ to generate a H–Ni–CN species followed by insertion and reductive elimination to give **2**. The reaction of nickel



Scheme 5 Possible reaction mechanism.

π -alkene complex **12/13** with H₂O may also afford the same intermediate **11** (path b). In the case of aliphatic alkenes, linear products **6** were observed as the major products, which were formed through the less hindered alkyl nickel complex (type **15**).

Conclusions

In summary, we have described a first general and highly regioselective method for alkene hydrocyanation using relatively less toxic Zn(CN)₂ as the cyano source and the air-stable nickel(II) salt as the precatalyst. The regioselectivity of these reactions was found to depend remarkably on the nature of terminal alkenes. Preliminary mechanistic studies indicate that the Ni(COD)₂ or diphosphine-ligated nickel(I) chloride complex also displays high catalytic activity without the need for the reductant for this transformation. This method might find wide utility in pharmaceutical chemistry for drug discovery and development. Further investigations on the detailed reaction mechanism and application of this chemistry are in progress.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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