

Proceedings

Terminal Alkynes Hydroamination Catalyzed by Copper Nanoparticles †

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Abstract: The copper-catalyzed regioselective intermolecular hydroamination of terminal alkynes with amines has been accomplished. The reaction was effectively catalyzed by copper nanoparticles supported on montmorillonite K10 (CuNPs/MK10), and afforded the intended imines in good conversions. Then, imines were transformed into the corresponding amines after treatment with NaBH_3CN . The catalyst could be recovered and reused in several cycles.

Keywords: hydroamination; metal catalysis; copper nanoparticles

1. Introduction

Nitrogen-containing compounds, such as amines, enamines, and imines, are valuable and commercially important bulk chemicals, industrial chemicals, and pharmaceuticals [1]. The hydroamination (HA) is a reaction that involves the direct formation of a new C-N bond by addition of an amine to a C-C π -bond. HA is one of the most atom efficient processes and can be performed under catalysis mediated by a wide range of metals, being especially versatile the late-transition metals [2]. Unlike these expensive metal sources, cheaper and more sustainable metals such as copper have received relatively limited attention [3]. Thus, most of the Cu-catalyzed hydroamination reactions have been described in an intramolecular fashion to afford N-heterocycles, while the intermolecular version of this reaction is still explorable. On the other hand, our group have a broad experience in the synthesis of novel catalysts, based on metal nanoparticles which can be immobilized on different supports. This type of catalysts have shown very high activity and selectivity in a wide range of organic transformations [4].

Here we report our results on the HA reaction between terminal alkynes and different amines catalyzed by copper nanoparticles supported on montmorillonite K10 (CuNPs/MK10). The reaction was regioselective towards the Markovnikov product in the majority of cases studied. The heterogeneous and low cost CuNPs/MK10 catalyst was fully characterized, and showed high activity and good recyclability.

2. Materials and Methods

2.1. Materials and Equipment

Reagents employed were analytical grade. THF and CH_2Cl_2 were freshly distilled over sodium/benzophenone or CaH_2 , respectively. All starting materials were of the best available grade (Aldrich, Merck, Cymit) and were used without further purification. Commercially available copper (II) chloride dihydrate was dehydrated upon heating in oven (150 °C, 45 min) prior to use for the preparation of CuNPs. Column chromatography was performed with Merck silica gel 60 (0.040–0.063

μm , 240–400 mesh) and hexane/EtOAc as eluent. Reactions were monitored by thin-layer chromatography on silica gel plates (60F-254) visualized under UV light. TEM and STEM images, together with EDX and EELS spectra, were obtained with a FEI Tecnai G2 F20 coupled to an EDAX detector and a Quantum SE 963 Gatan Imaging Filter (GIF). The samples were prepared by casting a drop of the corresponding sample dispersion on a holey carbon copper grid, and then evaporating off the solvent at room temperature. Copper content in the supported catalyst was determined by ICP-AES, in a Spectro Arcos instrument. CuNPs/MK10 samples were dissolved through conventional digestion for 72 h in a HNO_3/HCl 1:1 mixture.

2.2. General Procedure for CuNPs Catalyst Synthesis

Anhydrous copper (II) chloride (404 mg, 3 mmol) was added to a suspension of lithium (63 mg, 9 mmol) and 4,4'-di-*tert*-butylbiphenyl (DTBB, 80 mg, 0.3 mmol) in THF (10 mL) at room temperature under a nitrogen atmosphere. The reaction mixture, which was initially dark blue, rapidly changed to black, indicating that the suspension of copper nanoparticles was formed. This suspension was diluted with THF (10 mL) followed by the addition of the corresponding support (2.4 g). The resulting mixture was stirred for 1 h at room temperature, quenched with water and then filtered off. The solid was washed with EtOH (3×5 mL) and dried under vacuum.

The copper-on-montmorillonite catalyst was characterized by different techniques. The copper content in the catalyst, ca. 3.5–3.8 wt%, was determined by inductively coupled plasma-mass spectrometry (ICP-MS). Analysis by TEM revealed the presence of copper nanoparticles homogenous distributed on montmorillonite support. Copper nanoparticles can be distinguished with an approximate size of 1–3 nm (Figure 1c,d, red circles). Energy-dispersive X-ray (EDX) analysis on various regions showed copper on the sample (Figure 2b top). Performing Electron Energy Loss Spectroscopy (EELS) confirmed the presence of copper after background subtraction (Figure 2b bottom).

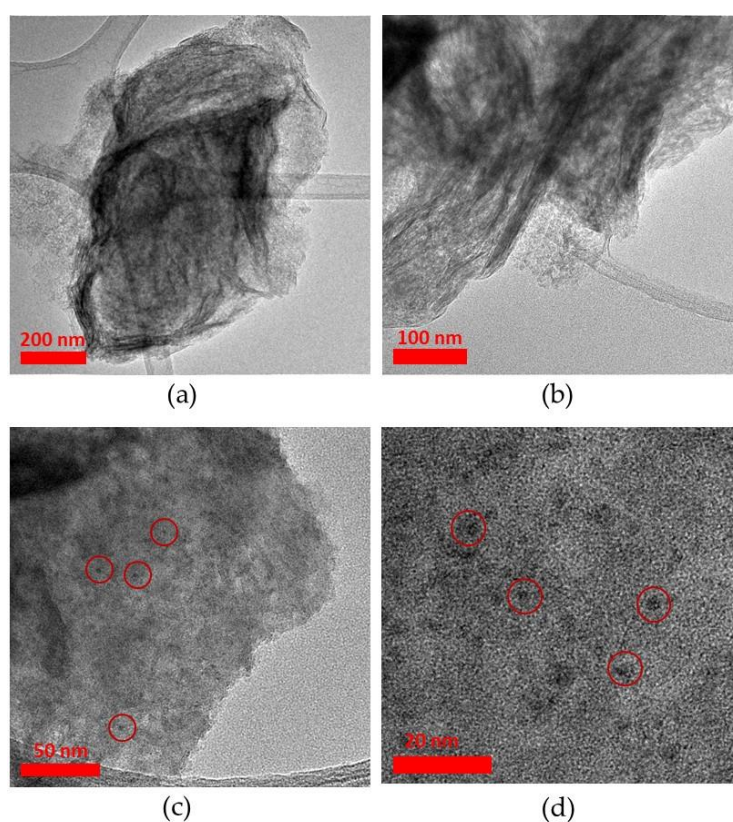


Figure 1. (a,b) TEM images of montmorillonite K10 showing nest-like form. (c,d) TEM image of catalyst CuNPs/MK10. CuNPs with a size of 1–3 nm can be appreciated homogeneously distributed in the sample.

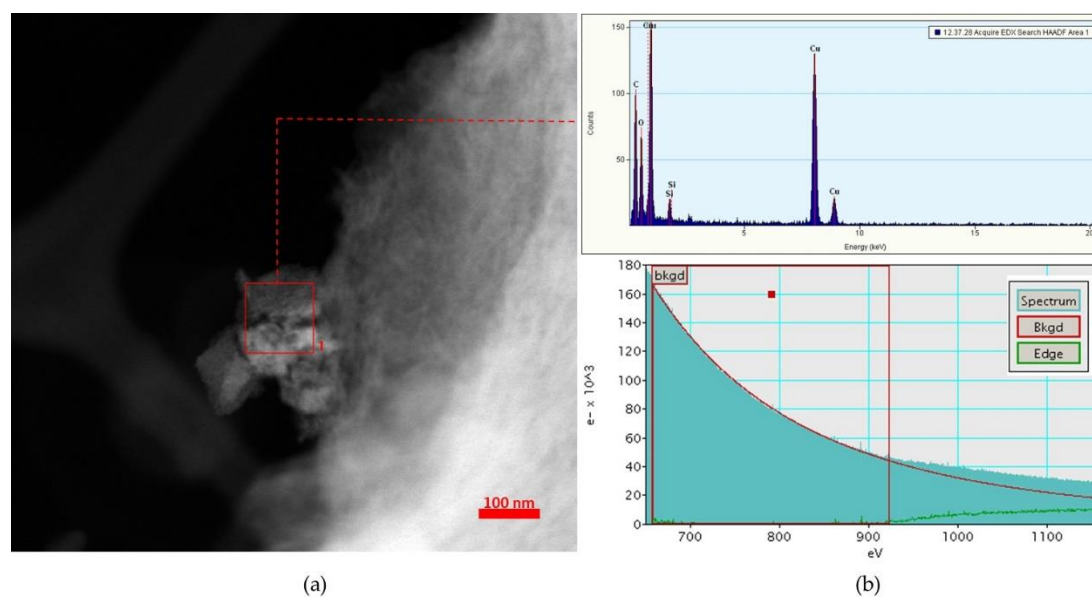


Figure 2. (a) TEM image of CuNPs/MK10 catalyst. (b) Top: EDX profile from red square. Bottom: Background subtraction in EELS confirming the presence of copper.

2.3. General Procedure for HA Products Synthesis

A 100 mL Schlenk flask equipped with magnetic stir bar was loaded with the corresponding amine (0.5 mmol), the CuNPs/MK10 catalyst (30 mg, 3 mol%), and the alkyne (0.5 mmol), in 0.8 mL of solvent (a mixture of xylenes). Dodecane (50 μ L) as internal standard for GC-MS was also added to the reaction mixture. The Schlenk tube was sealed with a ground glass cap and heated in a silicone bath at the desired temperature under vigorous stirring.

After 12–17 h, the sealed tube was cooled to room temperature, and an aliquot was filtered off *through* celite in order to check the conversion of the starting amine by GC-MS. The crude reaction mixture was centrifuged for recovering the catalyst which was sequentially washed with toluene, THF and finally with EtOH (1 mL each washed) several times. Isolation of the imine products is possible after fractional distillation under reduced pressure [5]. However, in most cases, conversions into the imine products were almost quantitative, and the reduction step to the corresponding amines was carried out without further purification.

2.4. General Procedure for HA Product Hydrolysis

After recovery of the catalyst, the crude reaction mixture from HA reaction was placed into a round bottom flask and diluted with Et₂O (4 mL). Then, diluted HCl (10%, 2 mL) was added and the mixture was vigorously stirred for 20 min. Then the organic layer was separated and dried, and an aliquot was taken and prepared for GC-MS analysis.

2.5. General Procedure for Reduction of Imines to Amines

The crude product from the HA reaction (0.5 mmol assuming quantitative yield) was diluted with 2 mL of THF. Then, 2.5 equivalents of NaBH₃CN were added (95%, 83 mg, 1.25 mmol) and stirred during 30 min. Then, a solution of *p*-toluenesulphonic acid (15 mol% in 2 mL of THF) was added dropwise, and stirred over 2–4 h more [6]. During this time, a small portion of bromocresol green was used as indicator, maintaining the solution in an orange-yellow colour (indicating acidic pH) [7]. After that, diluted HCl (2%, 4 mL) was added and stirred for 1 h. Finally, the resulting solution was neutralized up to pH 7–8, and the corresponding amine was extracted with Et₂O (3 \times 3 mL). The combined organic layers were washed first with water, then with brine and dried over MgSO₄. Then, after filtration, volatiles were removed under vacuum. The amine product was then purified by flash column chromatography on silica gel.

2.6. Recycling of the CuNPs/MK10 Catalyst

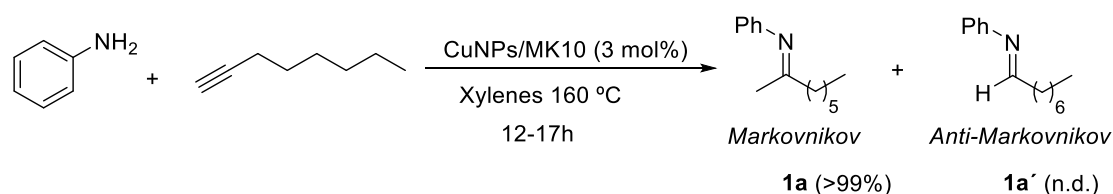
A 100 mL Schlenk flask equipped with magnetic stir bar was loaded with the amine (3 mmol), the catalyst (180 mg, 3 mol%), the alkyne (3 mmol), the reaction solvent (mixture of xylenes, 2.4 mL) and dodecane (50 μ L) as internal standard for GC-MS analysis. The Schlenk tube was sealed with a ground glass cap, was heated in a silicone bath at 160 $^{\circ}$ C under vigorous stirring.

After 12–17 h, the pressure tube was cooled to room temperature, and an aliquot was filtered off through celite in order to check conversion of the amine by GC-MS analysis. The crude reaction mixture was centrifuged for recovering the catalyst. Then, the recovered catalyst was washed with toluene and thoroughly mixed until the solid was re-suspended in the liquid phase. The resulting mixture was then centrifuged, and the supernatant was decanted. The solid was washed with THF and then with EtOH, until the supernatant shows no suspended solid. Finally, the catalyst was dried under vacuum and weighted in order to reuse it in another HA reaction cycle (adjusting the reagents amount and maintaining a 3 mol% of catalyst loading). This same process was repeated during every reaction cycle.

3. Results and Discussion

The catalysts were prepared by addition of the support to a suspension of freshly prepared metal nanoparticles. The metal NPs were generated by fast reduction of the corresponding anhydrous metal chloride, using lithium dust and a catalytic amount of DTBB (4,4'-di-tert-butylbiphenyl, 10 mol%) as reducing system, in THF at room temperature as described in experimental section. The catalysts were ready for use as prepared, after filtration and drying, without any pre-treatment. Different inorganic materials such as activated carbon, TiO₂, zeolite Y (ZY), MgO, Al-MCM-41, MK10 or CeO₂ among others, were tested as supports for the metal NPs.

For the optimization of reaction conditions, aniline and 1-octyne were chosen as model starting reagents, using toluene as the solvent and heating at 110 $^{\circ}$ C. Then, it was necessary to use a mixture of xylenes as solvent in order to increase the temperature up to 160 $^{\circ}$ C. The best results under these conditions were obtained by using CuNPs/MK10 as the catalyst, showing a quantitative conversion of the starting aniline, with a 3 mol% catalyst loading (Scheme 1). Moreover, reaction was completely regioselective towards the Markovnikov HA product. Although the presence of the Markovnikov and the anti-Markovnikov products can be estimated by GC-MS, it is important to determine precisely the ratio between these products in order to evaluate the regioselectivity of the process. For this purpose, imines obtained by HA can be hydrolyzed with dilute hydrochloric acid, giving a ketone as one of the products in the case of Markovnikov addition, and an aldehyde in the case of the anti-Markovnikov product. Both the ketone and the aldehyde can be then determined by GC-MS more accurately than the corresponding imines.

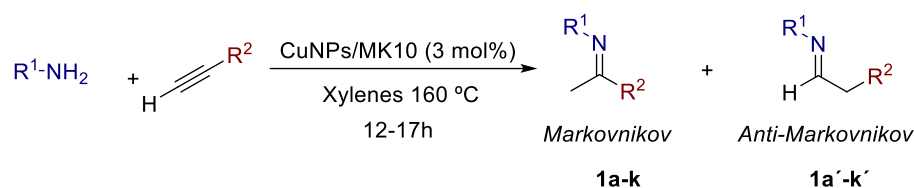


Scheme 1. HA reaction of aniline and 1-octyne catalyzed by CuNPs/MK10 giving quantitative conversion of Markovnikov product.

3.1. HA Scope for the Synthesis of Imines

With the optimized conditions in hand, different amines and alkynes were tested in the HA reaction affording the corresponding products showed in Scheme 2 and Figure 3. First of all, blank studies were developed by carrying out the reaction under the optimized conditions but with no catalyst and then, by using just one equivalent of CuCl₂. In both reactions, none of the products were detected. Regardless of the method used to promote the reaction, it is important to bear in mind that

both alkyne and amine groups are inherently nucleophilic [8]. For this reason it was necessary to carry out the reaction at high temperature and in the presence of the catalyst.



Scheme 2. HA reaction scope.

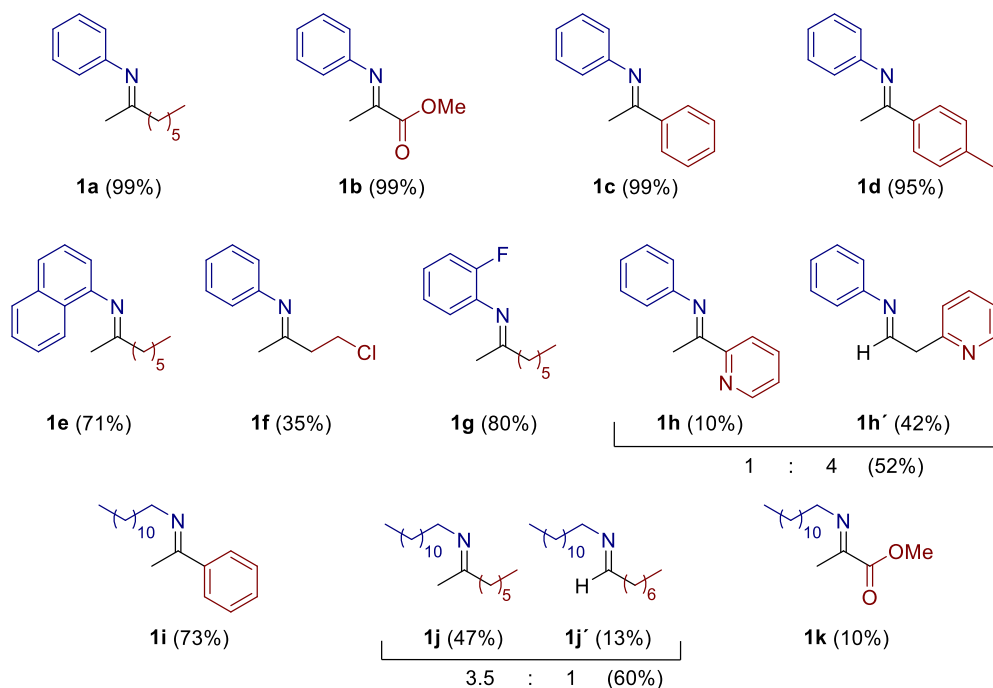


Figure 3. HA products. In parentheses conversion of the starting amine determined by GC-MS using dodecane as internal standard.

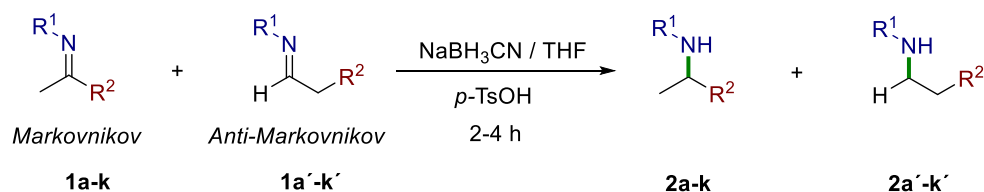
Aromatic amines, such as aniline or 1-naphthylamine afford, in the presence of 1-octyne, good to quantitative conversion (Figure 3, **1a** and **1e**). Reaction of aniline with alkyne was also effective when terminal alkynes such as phenylacetylene, 1-ethynyl-4-methylbenzene or methyl propiolate were tested instead of an aliphatic alkyne, affording the corresponding HA products in quantitative yields (Figure 1, **1b**, **1c** and **1d**). In the case of 2-fluoroaniline, in the presence of 1-octyne, the HA worked in 80% conversion (Figure 1, **1g**). Especially interesting are the products obtained in the reaction of aniline with 2-ethynylpyridine (Figure 1, **1h** and **1h'**). In this case, the HA reaction worked in a moderate conversion (52%), being the only case studied in which the anti-Markovnikov imine was the major product. By comparing 2-ethynylpyridine and phenylacetylene as starting alkynes, the results were notably different, showing that the pyridine ring is clearly interacting with the catalyst in a negative way.

On the other hand, an aliphatic amine such as dodecyl amine was also tested in few cases, in presence of methylpropiolate, 1-octyne and phenylacetylene, showing a similar behavior than aromatic amines (Figure 1, **1i**, **1j-1j'** and **1k**).

3.2. Synthesis of Amines by Reduction of the Corresponding Imines

In general, imines can be hydrolyzed in acidic media, making no possible the purification by chromatographic methods using common stationary phases (silica gel or alumina). However, imines from HA reaction can be reduced to the corresponding amines with a simple method in the presence

of sodium cyanoborohydride, as described in the experimental section, giving the corresponding amines which are also of great interest for multiple applications (Scheme 3). For this purpose, some selected examples were tested reducing the corresponding imines by treatment with NaBH_3CN in the presence of *p*-toluenesulphonic acid, maintaining an acidic pH for about 2–4 h. The amines shown in Figure 4, obtained by reduction of the corresponding imines, were then purified by column chromatography giving in all cases very good to quantitative yields.



Scheme 3. Imine reduction to amine under NaBH_3CN treatment.

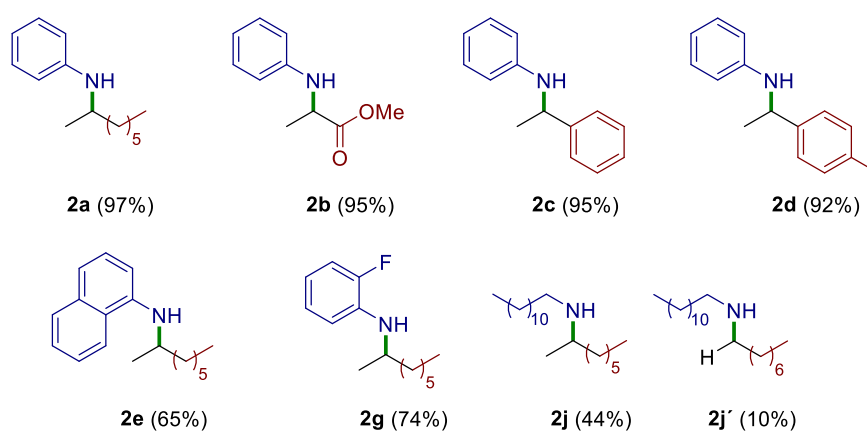


Figure 4. Amine products from HA imine reduction. In parentheses isolated yield after chromatographic purification.

3.3. Recyclability of $\text{CuNPs}/\text{MK10}$ Catalyst

In order to check the recyclability of the catalyst two model reactions were chosen. On one side, HA reaction was carried out under the optimized conditions, by using aniline and 1-octyne as reagents, and aniline and phenylacetylene by the other side (Figure 5). After each cycle of reaction, an aliquot was analyzed by GC-MS, and the catalyst was recovered by centrifugation, and washed several times with toluene, THF and EtOH as described in the experimental section. Then, the recovered solid was dried and weighted and used in another reaction cycle without any additional treatment. Similar behavior was observed in both model reactions tested, proving that the catalyst is reusable regardless of the starting reagents. Conversion of aniline to imine **1a** (Figure 5, blue) and **1c** (Figure 5, dark-red) shows very good activity of the catalyst at least after four cycles. The regioselectivity of the reaction was also maintained optimal, giving in all cases the Markovnikov adduct, with no presence of the anti-Markovnikov product.

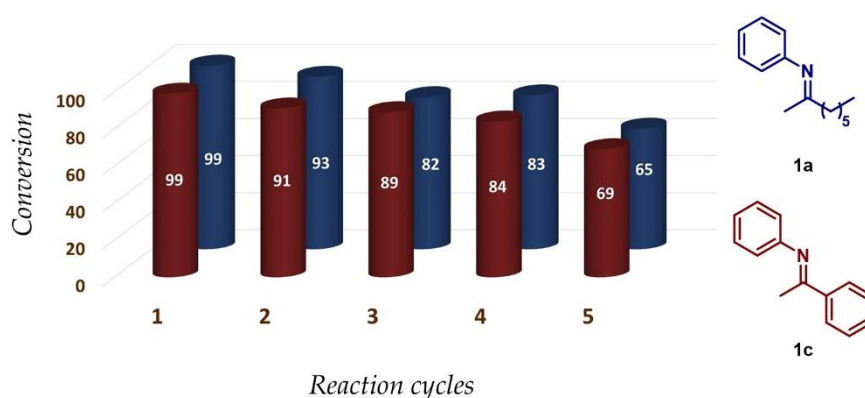


Figure 5. Representation of aniline conversion vs. reaction cycles for HA reaction under CuNPs/MK10 catalysis. Conversion of each cycle in the reaction to obtain imine **1a** shown in blue. In dark-red, the conversions of the same process for the synthesis of imine **1c**.

4. Conclusions

Different imines were synthesized by HA reaction under copper nanoparticles catalysis. CuNPs/MK10 shown to be very efficient for this reaction, leading to very good conversions of the starting amine into the HA products. The regioselectivity of the process was also controlled, affording in most cases, exclusively the Markovnikov adduct. Finally, it was possible to reuse the catalyst for at least four cycles with no decreasing conversion or regioselectivity of the reaction.

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Conflicts of Interest: The authors declare no conflict of interest.

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