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Urea-Functionalized Fe$_4$L$_6$ Cages for Supramolecular Gold Catalyst Encapsulation to Control Substrate Activation Modes

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Abstract: The excellent catalytic performances of enzymes in terms of activity and selectivity are an inspiration for synthetic chemists and this has resulted in the development of synthetic containers for supramolecular catalysis. In such containers the local environment and pre-organization of catalysts and substrates leads to control of the activity and selectivity of the catalyst. Herein we report a supramolecular strategy to encapsulate single catalysts in a urea-functionalized Fe$_4$L$_6$ cage, which can co-encapsulate a functionalized urea substrate through hydrogen bonding. Distinguished selectivity is obtained, imposed by the cage as site isolation only allows catalysis through π activation of the substrate and as a result the selectivity is independent of catalyst concentration. The encapsulated catalyst is more active than the free analogue, an effect that can be ascribed to transition state stabilization rather than substrate pre-organization, as revealed by the MM kinetic data. The simple strategy reported here is expected to be of general use in many reactions, for which the catalyst can be functionalized with a sulfonate group required for encapsulation.

Introduction

Enzymes provide a blueprint for the design of sophisticated artificial catalysts as they typically display sub-cell catalytic performance due to their unique microenvironment around the active site.[1] To echo the concept of the enzymatic catalysis, the implementation of supramolecular strategies by employing self-assembled metal-organic cages to create such microenvironments has been explored over the past decades.[2] The artificial microenvironments in self-assembled cages lead to pre-organization of substrates and stabilization of reactive intermediates, and thereby to enhanced reactivity and selectivity in comparison to the catalysts in bulk solution.[3]

Supramolecular metal-organic cages are accessible by complexation of metal ions and multidentate ligands,[4] and the structure can easily be varied by small modifications to these ligands. As they are synthetically accessible they are frequently explored for guest encapsulation and for catalytic reactions.[5] The accommodating of guests is typically based on non-covalent interactions such as hydrophobic effect, π-π stacking, hydrogen bonding, ionic and dipolar interactions.[6] As hydrogen bonding is specific and directional, applications of cages with functional groups for hydrogen bonding are frequently used.[7] The cage itself can act as a catalyst, but it can also serve as host for a metal complex that acts as the catalytic center. Recently the Reek group has explored the use of M$_2$L$_{12}$ nanocages, which can bind multiple catalysts and substrates by hydrogen bonding to guanidinium binding sites that reside at the inside. This resulted to high local concentrations of catalysts and substrates which in turn provided efficient catalysis.[8] These examples nicely demonstrated the effect of high local concentrations of multiple catalysts and reagents in cavity leading to enhanced reactivity and selectivity compared to the monomeric catalysts for a variety of reactions. For gold catalyzed reactions such increase in local concentration resulted in rate enhancements of a factor up to 40. We were interested if cages could be designed that bind only one catalytic site using similar hydrogen bonding interactions.

We herein report a new tetrahedral Fe$_4$L$_6$ metallocage (Fe-cage) containing three urea groups at each corner as hydrogen binding sites, based on the subcomponent assembly strategy pioneered by Nitschke.[9] The Fe-cage encapsulates one gold complex that is functionalized with a sulfonated phosphine ligand via hydrogen bonding and urea functionalized substrates can be co-encapsulated (Scheme 1). We demonstrate that the pre-organization of the catalyst in the cage leads to increased reactivity in the challenging gold-catalyzed hydroamination of 1-(o-Ethynylphenyl)-3-ethylurea, forming quinazoline heterocycles in high selectivity by controlling the substrate reaction modes and reaction pathways.

Results and Discussion

Synthesis and characterization of ligand and Fe-cage

The bis(urea-aniline) ligand required to generate the Fe$_4$L$_6$-tetrahedral cage (Scheme S1) was prepared in two steps.

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bis(4-aminophenyl)pyrene and p-nitrophenylisocyanate were dissolved in THF and refluxed and the product was isolated as dark yellow solid (64 %) by just filtration of the precipitate after the reaction. The nitro functionalities were subsequently reduced by utilizing hydrazine monohydrate in precipitate after the reaction. The nitro functionalities were complicated. The NMR spectra of the cage were confirmed by NMR spectroscopy, and mass analysis (Figures S6–S13). Both the different binding sites per cage and possible small changes in binding of the different diastereomers, it is clear from these experiments that the binding is rather strong (estimated at 2×10^6 M^-1), (Figures S38 and S39).

**Host-guest study**

We next evaluated the binding of the anionic sulfonated guest ([TPPMSAuCl]-(tetra(n-butyl) ammonium)(TBA)⁻) in the Fe-cage (see the Supporting Information) via UV/Vis titrations (Figure S36) in acetonitrile at 298 K. The job plot (Figure S37) based on UV/Vis titrations, reveals the dominant formation of a 1:1 complex between the Fe-cage and (TPPMSAuCl)⁻(TBA)²⁻, indicating that one ([TPPMSAuCl]⁻(TBA)²⁻) is located within the cavity. Several different titrations were performed and monitored by UV/Vis, and fitted to various models (1:1 and 1:2) (Figures S38–S40). Although these binding curves were not fitting optimally with the various models (Figure S40), likely due to the different binding sites per cage and possible small changes in binding of the different diastereoisomers, it is clear from these experiments that the binding is rather strong (estimated at 2×10⁶ M⁻¹, (Figures S38 and S39)).
The formation of host-guest complex was further supported by NMR and CSI-MS (Figures S41–S49). Upon addition of the \((\text{TPPMSAuCl}(\text{TBA}^+))\) guest, the signals of urea-protons of the cage in shifted 0.01 to 0.05 ppm upfield in the \(^1\text{H}\) NMR spectra, in line with binding of the guest by hydrogen bonding (Figures, S9, S41, S42). The aromatic signals of the bound guest \((\text{TPPMSAuCl}(\text{TBA}^+))\) can not be distinguished from the aromatic signals of the \(\text{Fe-cage}\) in \(^1\text{H}\) NMR (Figure S41). However, \(^1\text{H}-^1\text{H}\) COSY of the host-guest complex (Figure S42) presents a new signal at 8.29 ppm with respect to the \(^1\text{H}-^1\text{H}\) COSY of the \(\text{Fe-cage}\) (Figures S8 and S9) and \((\text{TPPMSAuCl}(\text{TBA}^+))\) (Figure S43), which is attributed to the encapsulated gold species. This signal shows a downfield shift of 0.34 ppm in comparison with the free \((\text{TPPMSAuCl}(\text{TBA}^+))\) complex (Figure S43), in line with the anticipated shielding effect of the aromatic walls of the cage. The signals of the countercation \(\text{TBA}^-\) from \((\text{TPPMSAuCl}(\text{TBA}^+))\) are not shifted in the \(^1\text{H}\) NMR spectra with respect to the free gold complex, suggesting that these cations are not enclosed in the cationic cage (Figure S42). Diffusion ordered spectroscopy (DOSY) (Figure S44) of the host-guest complex shows that all the aromatic signals are in a single band (log \(D = -9.38, 2r \approx 3.14\) nm), whereas the free gold complex \((\text{TPPMSAuCl}(\text{TBA}^+))\) has a much higher diffusion (log \(D = -8.73, 2r \approx 0.70\) nm), in agreement with the full encapsulation of the guest. The \(^{31}\text{P}\) NMR spectra of the host-guest complex in \(\text{CD}_3\text{CN}\) at 233 K (Figure S45), displays a broadened signal with a downfield shift of 0.64 ppm compared to the free \((\text{TPPMSAuCl}(\text{TBA}^+))\), as a result of shielding effects imposed by the aromatic walls of the cage. A shift of 0.18 ppm of \((\text{TPPMSAu}^+)@\text{Fe-cage}(\delta = -80.03\) ppm) is obtained in comparison with \(\text{TPPMSAu}^+\) \((\delta = -80.21\) ppm) in \(^{19}\text{F}\) NMR (Figure S46), suggesting that the counterion may be partly in the cage.

Cold spray ionization mass spectrometry (CSI-MS) provides final evidence for formation of gold encapsulated of \(\text{Fe-cage}\) system, as a set of highly charged species were observed that correspond to the elemental composition of \((\text{TPPMSAuCl}(\text{TBA}^+))\) (Figures S47 and S48). Further analysis of the MS data shows that only very minor peaks are visible for the 1 : 2 complex (1058.9404 for 6\(^+\) and 1326.5024 for 5\(^+\)) (Figures S49), indicating again that the binding is dominated by the formation of a 1 : 1 complex.

As crystals could not be obtained, the geometry of the host-guest complex \((\text{TPPMSAu}^+)@\text{Fe-cage}\) was studied by modeling using GFN2-xTB \(^1\) by utilizing the isomer 1\(-S^4\) as the host. The structure with minimum energy shows that every oxygen atom of the sulfonated functional group of the guest hydrogen bonds to two urea-protons of the cage wall at the corner of \(\text{Fe-cage}\) (Figure S66). Importantly, the gold center of the encapsulated species points towards the cavity.
To study if the substrate can be co-encapsulated, that is next of the urea substrate (1-(o-Ethynylphenyl)-3-ethylurea), we explored the binding behavior within the confined space of the Fe-cage. The shifts of the urea-protons are difficult to probe in NMR (Figure S55), as there are multiple urea signals present in excess and will not displace the catalyst. The binding constant is as high as $K = 8.33 \, \mu M$. [b] The reactions were monitored by $^1H$ NMR spectroscopy and calculated with 1,3,5-trimethoxybenzene as an internal standard.

(Figure S66), which allows catalytic reactions taking place within the confined space of the Fe-cage.

After having established that the Fe-cage can bind a molecular gold complex, we explored the binding behavior of the urea substrate (1-(o-Ethynylphenyl)-3-ethylurea). To study if the substrate can be co-encapsulated, that is next to the bound gold catalysts, we evaluated substrate binding in (TPPMSAuCl)$_2$ Fe-cage. The job plot analysis based on UV/Vis titrations (Figures S50 and S51) exhibits a 1 : 1 ratio of (TPPMSAuCl)$_2$ Fe-cage and substrate 1, indicating that the Fe-cage preferably co-encapsulates substrate 1 next to the gold catalyst. The binding constant is as high as $K = 2.25 \times 10^5 \, \text{M}^{-1}$ (Figures S52 and S53), suggesting that multiple hydrogen bonds between the urea groups from the substrate and the cage corner are involved. Based on these titration data, it is clear that the anionic catalyst binds an order of magnitude stronger, and therefore the substrate can be present in excess and will not displace the catalyst. The encapsulation of substrate 1 is also supported by $^1H$ NMR spectroscopy, since its alkyne proton is shifted upfield from 3.79 ppm (free state) to 3.15 ppm (encapsulated state) (Figure S55). The shifts of the urea-protons are difficult to probe in NMR (Figure S55), as there are multiple urea signals from the cage and the substrate, both in the bound and the free state. DOSY NMR spectroscopy (Figure S54) shows a clear single band in aromatic region were both the signals of the guest and the host are found, further supporting the co-encapsulation of the substrate next to the catalyst in the cavity.

**Cage controlled catalysis**

The catalytic properties of the supramolecular catalytic system (TPPMSAuCl)$_2$ Fe-cage were assessed in the gold-catalyzed hydroamination of 1-(o-Ethynylphenyl)-3-ethylurea 1 (Tables 1 and S1). Gimeno and co-authors reported the selective synthesis of the 6-exo-dig or 5-endo-dig product by conventional catalyst optimization demonstrating that steric factors imposed by the ligand play an important role. We selected this catalytic reaction as a benchmark reaction because the urea substrate 1 not only contains a hydrogen motif for binding at the corner of the cavity, but it also has two activation modes providing alternative reaction pathways leading to different products.[13,14] In principle, the hydroamination of substrate 1 can proceed either mono-gold ($\pi$ activation mode) or dual gold ($\sigma,\pi$ activation mode) activation modes, leading to 6-exo-dig or 5-endo-dig cyclization respectively.[13,14] Alkynylurea compounds have three potential nucleophiles and two electrophilic carbon atoms in the molecular framework.[13] As a result, the hydroamination of substrate 1 can lead to at least 4 different products forming 4-ylidene-3,4-dihydroquinazolin-2-ones (via N-3 attack) or their constitutional isomers 4-ylidene-benzoxazin-2-ylideneanilines (O attack) (path A), indoles (N-1 attack) (path B), and benzodiazepin-2-ones (N-3 attack) (path C) (Figure 2), as previously reported.[13]

As we have established the formation of a mononuclear gold catalyst in a well-defined Fe-cage via hydrogen bonding, we hypothesized that the encapsulated catalyst would follow the pathway via $\pi$ activation, thus leading to selective formation of the 6-exo-dig product. Initial catalysis was probed by subjecting substrate 1 to a catalytic amount of 2.5% in deuterated acetonitrile at 60°C for 24 h (Table 1, Entries 1 and 2). When TPPMSAu$^+$ (after in situ halide abstraction) was applied as catalyst for the cyclization
reaction, it afforded a mixture of four products (1a/1b/1c/1d in a ratio of 2.27:1.24:1) and the reaction resulted in a moderate conversion of 51.77% (Table 1, Entry 1). In line with the hypothesis, the employment of (TPPMSAu\(^{+}\))@Fe-cage as a catalyst led to the mainly formation of the 6-exo-dig ring (1b) and also a higher conversion was observed (76.37%). Only small amounts of the 5-endo-dig ring (1a) were produced (Table 1, Entry 2), in line with substrate activation via only \(\pi\) activation, as a result of the site isolated mononuclear gold complex in confined space.

In the control experiment with the free gold catalyst in solution, four different products are obtained (Table 1, Entry 1), consistent with the previously reported results.\(^{[13]}\) The caged catalyst not only changes the 1a/1b product ratio, but also prevents the formation of 1c and 1d as byproducts, thus leading to the selective formation of heterocycle 1b (Table 1, Entry 2). The products 1a and 1b result from \(\sigma\pi\) (N-1 attack) and \(\pi\) (N-3 attack) activation modes, respectively. The product benzooxazine 6-exo-dig 1c can be obtained via nucleophilic attack of the urea oxygen and is reported to be a kinetic product.\(^{[14]}\) We were wondering if product 1d is also a kinetic intermediate as reported for product 1c. If 1c and 1d are both kinetic products, they may disappear at higher conversion or when the catalysis is operated at an elevated temperature. As such, we explored the catalytic reaction with the free TPPMSAu\(^{+}\) and (TPPMSAu\(^{+}\))@Fe-cage at 80°C (Table 1, Entries 3 and 4), and indeed under these conditions higher conversions were obtained and product 1c and 1d could not be observed. Importantly, the (TPPMSAu\(^{+}\))@Fe-cage still exhibits an excellent selectivity for producing 1b in comparison to the free catalyst TPPMSAu\(^{+}\).

To further demonstrate that 1c and 1d are both kinetic products, a reaction was carried out in two stages at different temperatures (60°C, 80°C), and the process was monitored by \(^1\)H NMR (Figures S56–S58). The reaction was carried out using substrate 1 (20 \(\mu\)mol) with a catalytic amount of 2.5% of TPPMSAu\(^{+}\) in deuterated acetonitrile at 60°C in a NMR tube. After 24 h the ratio of 1a/1b/1c/1d was 2.25/1.125/1 (Figure S56). Subsequently, this tube was placed in an oil bath at 80°C for 5 h, and the mixtures were analyzed again, showing that 1c and 1d were present in smaller amounts gradually transformed into 1b (1a/1b/1c/1d = 2.25/2.25/0.5/0.375) (Figure S56). After heated at 80°C for another 13 h, 1c and 1d totally disappeared and they were transformed into 1b as the integration of 1b was the sum of 1b, 1c and 1d present at the initial stage (Figure S56). These experiments confirm that 1c and 1d are kinetic products.

As the (TPPMSAu\(^{+}\))@Fe-cage catalyst can only proceed via a mononuclear mechanism as a result of site isolation, we hypothesized that its selectivity should be independent of the catalyst concentration. In contrast, the free catalyst TPPMSAu\(^+\) can operate via mono and bi-nuclear activation, leading to different product ratio’s, and it is anticipated that this catalyst provides a 1a/1b ratio that depends on the catalyst concentration. We therefore investigate the effect of catalyst loading on the level of the regioselectivity of product 1b. A dilution analysis was performed by subjecting various catalyst concentration (0.417 \(\mu\)M, 0.833 \(\mu\)M, 1.667 \(\mu\)M, 3.333 \(\mu\)M) with substrate 1 (0.083 mM) in deuterated acetonitrile (0.6 mL) at 80°C for 24 h (Figure 3). In line with the hypothesis the high regioselectivity of product 1b obtained from the (TPPMSAu\(^{+}\))@Fe-cage is independent of the catalyst concentration. In contrast, the experiments with increasing concentrations of the TPPMSAu\(^+\) present a sharp drop in the selectivity of product 1b. These results exhibit highlight that catalyst isolation by supramolecular catalyst encapsulation effectively blocks reaction pathways via dinuclear mechanism, even at high catalyst concentrations, leading to excellent regioselectivity of product 1b.

Michaelis–Menten kinetics

The conversion of substrate 1 in the presence of (TPPMSAu\(^{+}\))@Fe-cage as catalyst exceeds that of the free TPPMSAu\(^+\) at both 60°C and 80°C (Table 1). To further investigate this, kinetic experiments were performed for both the encapsulated and the free catalysts at 60°C. As the proposed mechanism\(^{[13]}\) involves coordination of the substrate and subsequent rate determining cyclization/protode metallation the kinetic data can be fitted by Michaelis–Menten equations. The kinetic experiments were conducted by means of initial rates of gold-catalyzed hydroamination of substrate 1 in deuterated acetonitrile at 60°C by employment of (TPPMSAu\(^{+}\))@Fe-cage (Figures 4a and 4b, S59–S61) or free TPPMSAu\(^+\) (Figures 4c and 4d, S62–S64). As expected, the rate vs substrate concentrations shows a profile with substrate saturation behavior, which could be linearized by plotting the double reciprocal of concentration and rate. The Michaelis–Menten parameter \(K_m\) for (TPPMSAu\(^{+}\))@Fe-cage is provided to be 3.23×10\(^{-3}\) M, while the \(k_{cat}\) (Michaelis–Menten enzymatic rate constant) is afforded to be 2.75×10\(^{3}\) s\(^{-1}\) from the aforementioned Lineweaver–Burk plot (Figures 4a and 4b). These results are consistent with an overall Michaelis–Menten-type mechanism.

In line with the higher conversion, we observe that the encapsulated catalyst shows a higher \(k_{cat}\) (Figure 4). Interestingly, the encapsulated catalyst shows a larger \(K_m\) and a larger \(V_{max}\) (Figure 4). Whereas we anticipated that the preorganization of the catalyst and the substrate would lead to

\[ \text{Figure 3. Regioselectivity to 1b in dilution studies differs when in the presence of TPPMSAu\(^+\) and (TPPMSAu\(^{+}\))@Fe-cage, respectively. The selectivity of 1b is plotted against the catalyst concentration.} \]
higher rates, the data suggest that the substrate is more strongly bound to the free catalyst (in line with lower determined at different temperatures, for both further support for transition state stabilization by the cage higher rates, the data suggest that the substrate is more could be ascribed to the substrate pre-organization. during the catalytic process, the GFN2-xTB (ΔH lower for the caged catalyst compared to free gold catalyst with the higher rate. The barrier is much lower when the reaction is carried out in the transition state stabilization, that is the overall reaction Burk plot for TPPMSAu@Fe-cage. (c) Michaelis–Menten and (d) Lineweaver–Burk plot for TPPMSAu+. The axis C presents the varying concentrations of the substrate 1.

Figure 4. Kinetic studies on the hydroamination of substrate 1 at 60°C. (a) Michaelis–Menten and (b) Lineweaver–Burk plot for the (TPPMSAu+)@Fe-cage. (c) Michaelis–Menten and (d) Lineweaver–Burk plot for TPPMSAu+. The axis C presents the varying concentrations of the substrate 1.

Further support for transition state stabilization by the cage was sought via Eyring analysis of the reaction rates determined at different temperatures, for both (TPPMSAu+)@Fe-cage and TPPMSAu+ (Figure S65). The ΔG°‡ at 333 K for the caged catalyst is 1.16 kJ/mol lower, in line with the higher rate. The ΔH°‡ at 333 K (13.49 kJ/mol) was slightly lower for the caged catalyst compared to free gold catalyst (ΔH°‡ at 333 K (13.77 kJ/mol)), in line with the transition state stabilization effect of the cage. The caged catalyst also shows a lower entropy of activation ΔS°‡ at 333 K (−0.389 kJ/mol/K) in comparison to −0.393 kJ/mol/K for TPPMSAu+, which could be ascribed to the substrate pre-organization.

To gain a deeper insight of the substrate binding mode during the catalytic process, the GFN2-xtB[11] was undertaken to optimize the geometry of the host guest complex (Fe-cage(TPPMSAu+)/substrate 1) (Figure S66, Table S3). We found that when the substrate 1 was encapsulated in cavity, it exhibited a lower energy than the case of being inlaid outside the cage windows.

Substituent effect on the selectivity

With a further attempt to validate the catalytic applicability of the caged catalyst in hydroaminations, we expanded the substrate scope and investigated the effect of various substituents on the selectivity and reactivity displayed by (TPPMSAu+)@Fe-cage and its free analogue TPPMSAu+. Substituted urea substrates with electronic donating (–CH3O) and withdrawing substituents (–CF3, –Cl) on aryl ring were synthesized and characterized (Scheme S3, Figures S14–S35). A set of catalytic reactions were performed to convert the various urea substrates (1–7) (20 μmol) with catalysts (2.5 %; caged or free) in deuterated acetonitrile at 80°C for 10 h (Figures 5 and S67–S109). In all examples studied here the cyclization in a 6-exo-dig fashion is dominant when using the encapsulated catalyst, while the free TPPMSAu+ catalyst produces predominantly the product that forms via 5-endo-dig cyclization (Figure 5b). It is noted that this selectivity is similar in comparison to results obtained at 80°C in Table 1. These results confirm that the distinguished selectivity resulting from the cavity can be obtained for a broader substrate scope and is relatively insensitive to the electronic, steric properties and substituent positions of the substitutions on aryl ring.

In line with the kinetic data we also found for substrates 1–7 that the encapsulated (TPPMSAu+)@Fe-cage catalyst is more efficient leading to higher conversions compared to the free TPPMSAu+ (Figures 5c, S110–S113). The electron-withdrawing or -donating groups on the para- or meta-substituted aryl ring do have an influence on the conversion, but in all these examples the encapsulated catalyst provides

Figure 5. Gold-catalyzed hydroaminations of substituted urea substrates (1–8) in pre-dried CD3CN at 80°C for 10 h in an Ar atmosphere. 1,3,5-trimethoxybenzene was used as an internal standard. The reactions were monitored by 1H NMR spectroscopy. (a) Substrate scope (1–8) and the yields of the 6-exo-dig ring (1b–8b) in gold-catalyzed hydroamination reactions with the (TPPMSAu+)@Fe-cage. (b) The regioselectivity to the 6-exo-dig ring and (c) the conversions of urea substrates (1–8) in hydroamination reactions.
higher conversion than the free analogue. It is worth mentioning that the reaction to cyclize substrate 7, which has electron-donating group (−OCH3) at meta-position, surpass the benchmark reaction (substrate 1) when utilizing (TPPMSAu+)@Fe-cage. For the free catalyst, however, the benchmark substrate 1, gave higher conversion, indicating that electronic effects have a different effect when the reaction is carried out in the cage.

Subsequently, the substituent effect on the urea group was also probed by changing from an ethyl group to an aryl group in substrate 8. Again the selectivity when the reaction was carried out in the cage by using (TPPMSAu+)@Fe-cage was very high, just like for the other substrates (Figure 5). Interestingly, in the reaction with the free catalyst higher conversion was obtained compared to the benchmark substrate 1, suggesting a higher inherent reactivity of the substrate. In contrast, when the reaction was carried out with (TPPMSAu+)@Fe-cage the conversion was slightly lower, suggesting that for this more bulky substrate steric hindrance come into play when the reaction is carried out in confined space.

Conclusion

In this contribution we report a new self-assembled cage by incorporating urea groups at each corner of the self-assembled structure. A gold catalyst that is functionalized with a sulfonate group can be bound strongly via hydrogen bonding with the urea groups at the corners of the cage by incorporating urea groups at each corner of the self-assembled structure. A gold catalyst that is functionalized with a sulfonate group.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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