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Combined Computational and Experimental Studies on the Asymmetric Michael Addition of α-Aminomaleimides to β-Nitrostyrenes Using an Organocatalyst Derived from *Cinchona* Alkaloid

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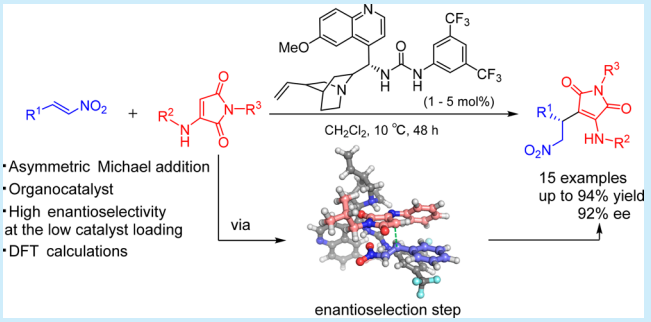
ABSTRACT: Maleimides are often used as electrophiles in conventional reactions; however, their application as nucleophiles is limited to only a few reactions, and reactions utilizing α-aminomaleimides as asymmetric Michael donors have not been reported to date. Thus, in this work, asymmetric Michael addition of α-aminomaleimides as Michael donors to β-nitrostyrenes was conducted for the first time using an organocatalyst derived from a *Cinchona* alkaloid. Density functional theory investigations were crucial to improve the enantioselectivity of the adduct.



The application of organocatalysts in highly enantioselective reactions has been extensively investigated in recent decades[1] because of their various advantages, such as low toxicity, requirement of mild reaction conditions, low cost, easy manipulation, and excellent enantiomeric excess (ee). Therefore, the development of more efficient reactions employing organocatalysts is essential. Particularly, organocatalysts derived from *Cinchona* alkaloids are applied in various asymmetric reactions, including Michael addition,[2] Mannich,[3] aldol,[4] Morita–Baylis–Hillman,[5] and dihydroxylation[6] reactions. The quinuclidine moiety of these organocatalysts plays a significant role as an activator of nucleophiles.

Maleimide is a promising framework because its derivatives have remarkable physical[7] and biological[8] properties (Scheme 1a). Furthermore, asymmetric Michael addition of maleimides has been extensively investigated because maleimides act as suitable Michael acceptors.[9] However, the products obtained by Michael addition to maleimides as Michael acceptors are converted to succinimides. In a few reactions, maleimides have been utilized as nucleophilic agents[10] for the highly effective construction of maleimide-containing compounds via direct introduction of the maleimide moiety (Scheme 1b). Although maleimides are often employed as electrophiles, their application as nucleophiles is limited to only a few reactions, and reactions utilizing α-aminomaleimides as asymmetric Michael donors have not been reported to date. Therefore, in this work, we conducted the asymmetric Michael addition of α-aminomaleimides as Michael donors to β-nitrostyrenes using a bifunctional organocatalyst derived from a *Cinchona* alkaloid. To the best of our knowledge, this is the first report of asymmetric Michael addition using α-aminomaleimides as nucleophiles.

Initially, we examined β-nitrostyrene (**1a**)[1f,11] as a Michael acceptor to optimize the organocatalyst (Table 1). Unexpectedly, when unmodified natural quinine and cinchonidine were used as organocatalysts, the Michael adduct **3aa** was acquired in moderate to good yields with moderate ee's (entries 1 and 2, respectively). In contrast, when benzoyl-protected quinine and cinchonidine were used as organocatalysts, **3aa** was obtained only in a trace amount or in 15% yield with low enantioselectivity, respectively. As β-nitrostyrene is well-controlled by urea-type organocatalysts,[1d] urea and thiourea were introduced to improve the enantioselectivity (entries 5–10). Consequently, **3aa** was formed in 81% yield with 73% ee using catalyst **J** derived from quinine containing a 3,5-bis(trifluoromethyl)phenyl moiety; thus, **J** was selected as an appropriate catalyst. However, the ee's acquired using **J** were not satisfactory. Therefore, we performed density functional theory (DFT) calculations to improve the enantioselectivity of the adduct.

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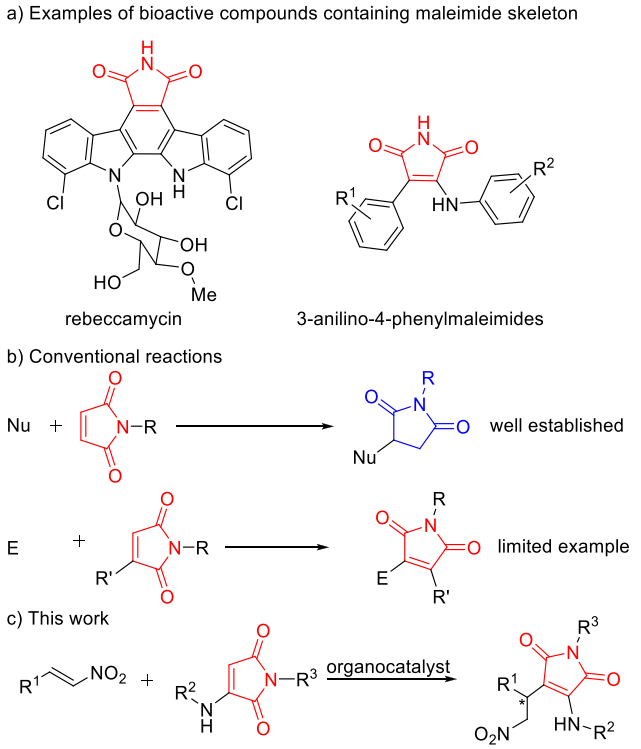
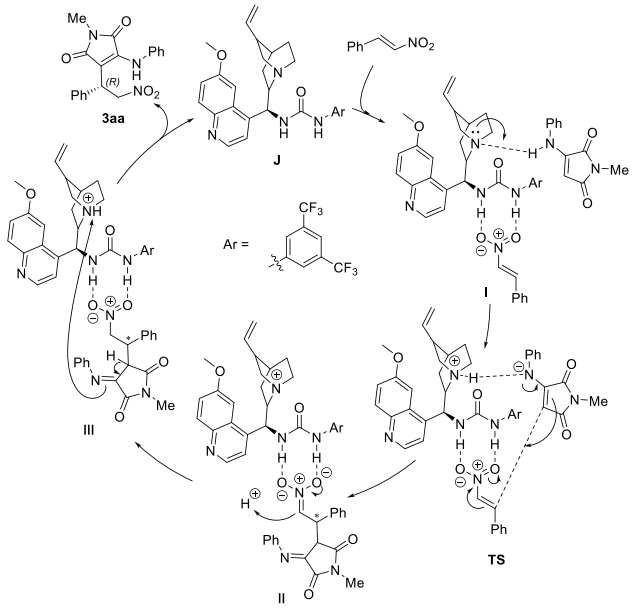
Scheme 1. Asymmetric Michael Addition Reactions



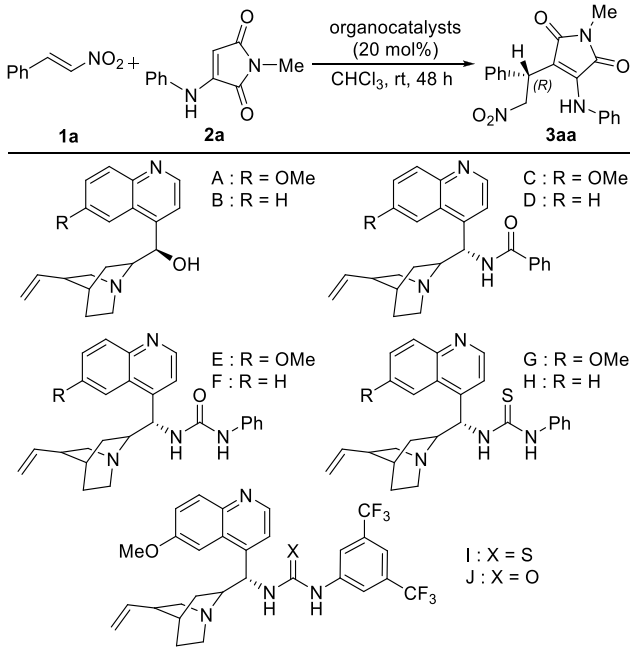
We proposed a plausible catalytic cycle (Scheme 2). Coordination of **1a** to **J** leads to urea−nitro group complex **I**.

Scheme 2. Plausible Mechanism of the Asymmetric Michael Addition Reaction



Then the maleimide hydrogen is activated by the quinuclidine in **I**, and Michael addition occurs via a transition state (**TS**) to give **II**. This C−C bond formation step is the enantioselectivity-determining step. Thereafter, proton transfer to the nitrostyrene moiety takes place to regenerate the maleimide moiety and **J**. Initially, we employed *S* and *R* conformations of **TS**, which resulted in *S* and *R* enantiomers

Table 1. Optimization of the Organocatalyst[a]



entry	organocatalyst	yield (%)[b]	ee (%)[c]
1	**A**	78	−55[d]
2	**B**	74	−72[d]
3	**C**	trace	–
4	**D**	15	−13[d]
5	**E**	63	67
6	**F**	58	68
7	**G**	43	55
8	**H**	36	59
9	**I**	57	73
10	**J**	81	73

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), catalyst (20 mol %), $CHCl_3$ (0.5 mL), room temperature, 48 h, open air. [b]Isolated yields. [c]Determined by HPLC with a chiral IA column. [d]Negative ee values indicate that the *S* enantiomer of **3aa** was formed preferentially.

of **3aa**, respectively. The lowest-energy *R* conformation (*R*-$\mathbf{TS_{Me}6}$) and *S* conformation (*S*-$\mathbf{TS_{Me}1}$) at the B3LYP+D3BJ/6-311++G**(SMD)//M06-2X/6-31G**(SMD) level are shown in Scheme 3a. By comparing the two TSs, we obtained a $\Delta\Delta G^{\ddagger}$ (the Gibbs free energy of the most stable TS leading to the *S* product relative to the most stable TS leading to the *R* product) of 6.7 kJ mol^{-1} and a $\Delta\Delta H^{\ddagger}$ (the enthalpy of the most stable TS leading to the *S* product relative to the most stable TS leading to the *R* product) of 16.9 kJ mol^{-1} at 298.15 K between *R*-$\mathbf{TS_{Me}6}$ and *S*-$\mathbf{TS_{Me}1}$ via thermal corrections. On the basis of these results, we speculated that $\Delta\Delta S^{\ddagger}$ between these TSs was a dominant factor in $\Delta\Delta G^{\ddagger}$. To achieve a significantly smaller $\Delta\Delta S^{\ddagger}$, we increased the size of the N substituent of the maleimide, which demonstrated high flexibility in the TS. Among *N*-substituted maleimides, the *N*-isobutylmaleimide acts as a potential inhibitor of *Leishmania donovani*.[8c] Therefore, we analyzed the TS achieved by substituting the *N*-Me group of the *α*-aminomaleimide with an *N*-^{i}Bu group (Scheme 3b). Consequently, $\Delta\Delta G^{\ddagger}$ between the lowest-energy *R* conformation of *N*-^{i}Bu (*R*-$\mathbf{TS_{iBu}6}$) and the lowest *S* conformation of *N*-^{i}Bu (*S*-$\mathbf{TS_{iBu}2}$) was 15.9 kJ mol^{-1} and $\Delta\Delta H^{\ddagger}$

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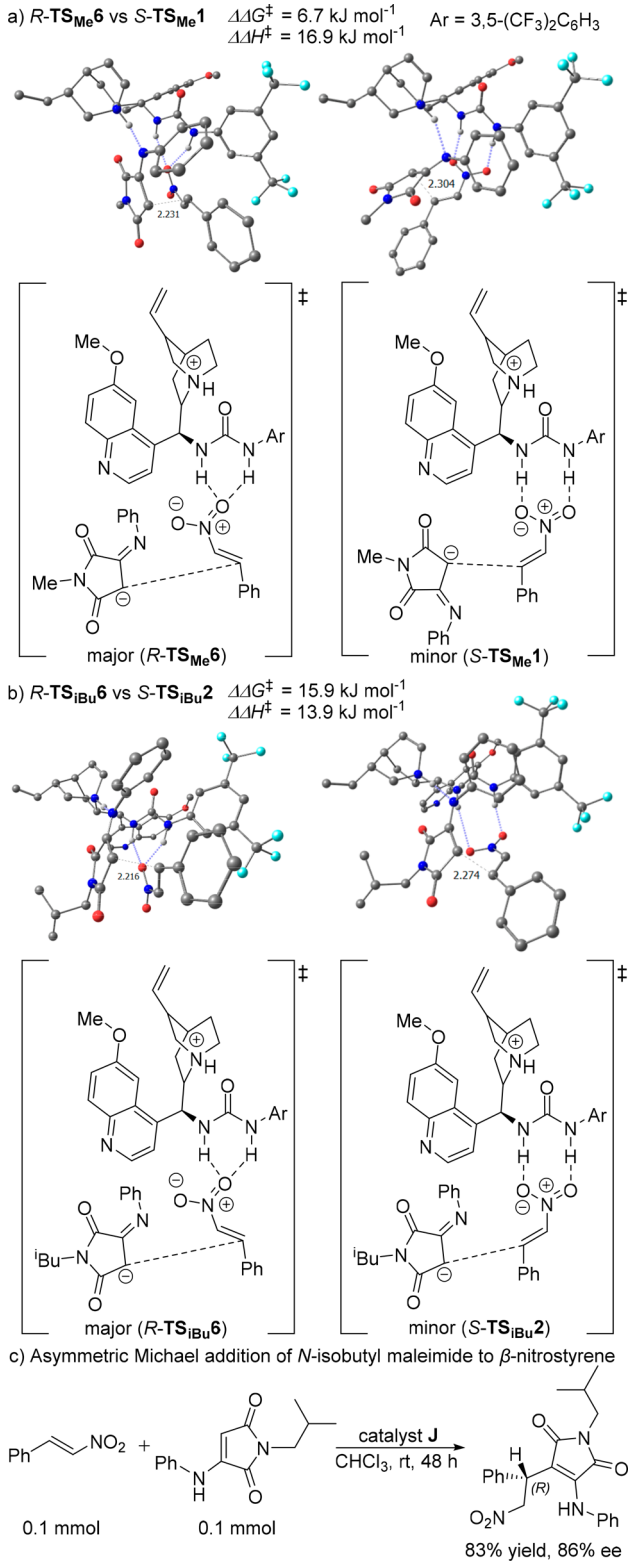
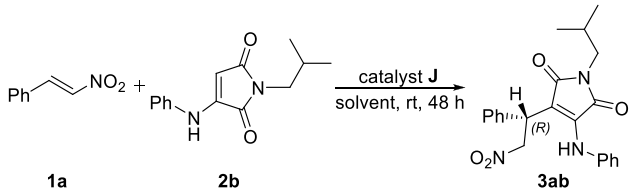
Scheme 3. Comparison of Transition States in the Enantioselection Step



was 13.9 kJ mol^{-1}, as expected. Using these theoretical results, we conducted the asymmetric Michael addition of *N*-isobutyl-*α*-aminomaleimide **2b** to *β*-nitrostyrene, and the result is shown in Scheme 3c. When **2b** was used instead of **2a** as the Michael donor, the ee increased from 73% to 86%. We also performed DFT calculations for the *N*-Bn-substituted Michael adduct to verify the validity of the above-mentioned results (see the Supporting Information). Furthermore, we conducted intrinsic reaction coordinate (IRC) analysis of *R*-**TS$_{iBu}$6** to confirm the reaction mechanism along with energy decomposition analysis (EDA) and non-covalent interaction (NCI) analysis to understand the enantioselectivity. The electronic circular dichroism (ECD) spectrum of **3ab** was measured and computed by time-dependent DFT calculations to determine the stereochemistry of **3ab** (see the Supporting Information).

Next, using **J** and **2b**, we tested the effect of the solvent on the yield and ee of **3ab** (Table 2). When a polar protic solvent (methanol) and an aprotic solvent (dimethyl sulfoxide) were used, **3ab** was obtained in only 15% and 24% yield with 34% and −3% ee, respectively (entries 5 and 6). In contrast, when a halogenic solvent or an ether was employed, **3ab** was obtained with high enantioselectivity (entries 1−4, 7, and 8), possibly because of the high solubility of the substrate in the solvent. Consequently, we chose dichloromethane as an optimal solvent because it provided **3ab** in 85% yield with 88% ee (entry 2).

Table 2. Examination of the Solvent Effect[a]



entry	solvent	yield (%)[b]	ee (%)[c]
1	$CHCl_3$	83	86
2	CH_2Cl_2	85	88
3	$(CH_2Cl)_2$	84	87
4	chlorobenzene	73	87
5	MeOH	15	34
6	DMSO	24	−3[d]
7	THF	53	84
8	Et_2O	63	85

[a]Reaction conditions: **1a** (0.1 mmol), **2b** (0.1 mmol), catalyst **J** (20 mol %), solvent (0.5 mL), room temperature, 48 h, open air. [b]Isolated yields. [c]Determined by HPLC with a chiral IA column. [d]The negative ee value indicates that the *S* enantiomer of **3ab** was formed preferentially.

Moreover, the reaction conditions were optimized (Table 3). The concentration of reactant did not affect the ee of **3ab** (entries 1−3). Satisfactorily, **3ab** with 88% ee was obtained even when the amount of the catalyst was reduced to 1 mol % (entries 3−6). When the reaction temperature was changed to 10 °C, **3ab** was obtained in 86% yield with 90% ee (entry 8). When the reaction temperature was lowered further, the solubility of the substrate and hence the product yield were reduced. Thus, the optimal reaction conditions were as follows: 0.1 mmol of *β*-nitrostyrene and 0.1 mmol of *α*-aminomaleimide in 0.3 mL of dichloromethane with a catalyst loading of 1 mol % at 10 °C.

With the optimized reaction conditions in hand, we investigated the substrate scope of *β*-nitrostyrene derivatives (Scheme 4). When the phenyl moiety of *β*-nitrostyrene was substituted with an electron-withdrawing group, the resulting Michael adduct decomposed, and *p*-NO_2-, *p*-COOMe-, and

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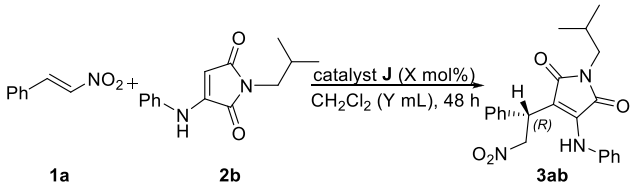
Table 3. Optimization of the Reaction Conditions[a]

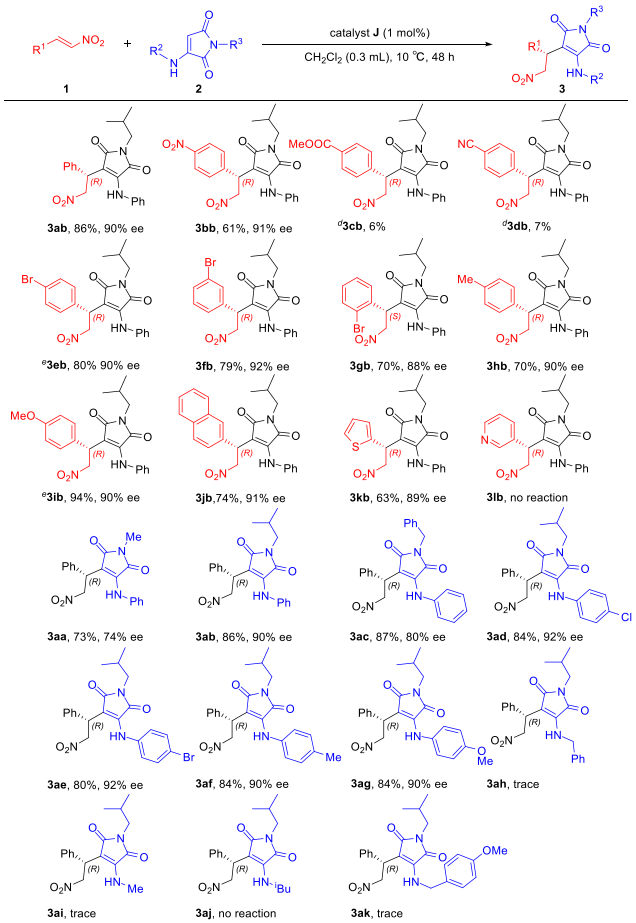


1a 2b 3ab

entry	X (mol %)	Y (mL)	temp. (°C)	yield (%)[b]	ee (%)[c]
1	20	1	rt	86	88
2	20	0.5	rt	85	88
3	20	0.3	rt	85	88
4	10	0.3	rt	85	88
5	5	0.3	rt	84	88
6	2.5	0.3	rt	85	89
7	1	0.3	rt	86	88
8	1	0.3	10	86	90
9	1	0.3	0	66	90
10	5	0.3	−10	79	91
11	20	0.3	−20	56	92

[a]Reaction conditions: **1a** (0.1 mmol), **2b** (0.1 mmol), 48 h, open air. [b]Isolated yields. [c]Determined by HPLC with a chiral IA column.

Scheme 4. Substrate Scope[a,b,c]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), catalyst **J** (1 mol %), CH_2Cl_2 (0.3 mL), 10 °C, 48 h, open air. [b]Isolated yields are shown. [c]The enantiomeric excess was determined by HPLC with a chiral IA column. [d]Decomposition of the Michael adduct. [e]The catalyst loading was 5 mol %.

p-CN-substituted maleimides were isolated in 61%, 6%, and 7% yield, respectively. *β*-Elimination possibly occurred at the chiral center. When *β*-nitrostyrenes with *o*-, *m*-, and *p*-bromo-substituted phenyl moieties were used, the corresponding Michael adducts were obtained in appropriate yields with high enantioselectivities (**3eb**−**gb**). However, when *β*-nitrostyrene with a *p*-bromo-substituted phenyl group was employed, the catalyst loading had to be increased from 1 to 5 mol % to execute the reaction (**3eb**). Furthermore, the reactivity of the *para* electron-donating group of *β*-nitrostyrene was lower than those of the other groups, and thus, a higher catalyst loading was required. The Michael adduct was obtained in 94% yield with 90% ee when the catalyst loading was increased from 1 to 5 mol % (**3ib**). Naphthyl and thienyl groups were appropriately tolerated, and the desired products **3jb** and **3kb** were obtained in moderate yields with high ee's. However, *β*-nitrostyrene with a pyridyl moiety did not react at all (**3ib**)

Finally, we examined the tolerance of *α*-aminomaleimides. *α*-Aminomaleimides with a halogen-substituted phenyl ring provided the corresponding Michael adducts in suitable yields with high enantioselectivities (**3ad** and **3ae**). When *α*-aminomaleimides with a phenyl group containing an electron-donating group were employed, the desired products were obtained in appropriate yields with high enantioselectivities (**3af** and **3ag**). Our attempt to synthesize *α*-aminomaleimides with electron-withdrawing groups, such as a *p*-nitro group, was unsuccessful. When *α*-aminomaleimides with an aliphatic moiety at the *α*-amino position were used, the desired Michael adducts were rarely obtained (**3ah**−**ak**).

In conclusion, we have performed the asymmetric Michael addition of *α*-aminomaleimides to *β*-nitrostyrenes using an organocatalyst derived from *Cinchona* alkaloid for the first time to afford chiral maleimides with up to 92% ee. This reaction provides a new route to various useful chiral maleimide derivatives. Furthermore, DFT results guided the improvement of the ee of the adduct and revealed the reaction mechanism, including the stereochemistry of the adduct.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01831.

General information, catalyst screening using *N*-^{i}Bu maleimide, experimental procedure, characterization data, fluorescence data, details and references of computational study, IRC analysis, EDA analysis, NCI analysis, ECD spectra, and copies of NMR and HPLC spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **2b**, **2d**−**k**, **3aa**−**ag**, **3bb**, and **3eb**−**kb** (ZIP)

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Author Contributions

M.K. and T.O. designed the project. N.S. conducted all of the experiments. N.S. and K.K. performed all of the calculations. N.S., S.M., and T.O. analyzed and discussed the data and wrote the manuscript.

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Notes

The authors declare no competing financial interest.

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