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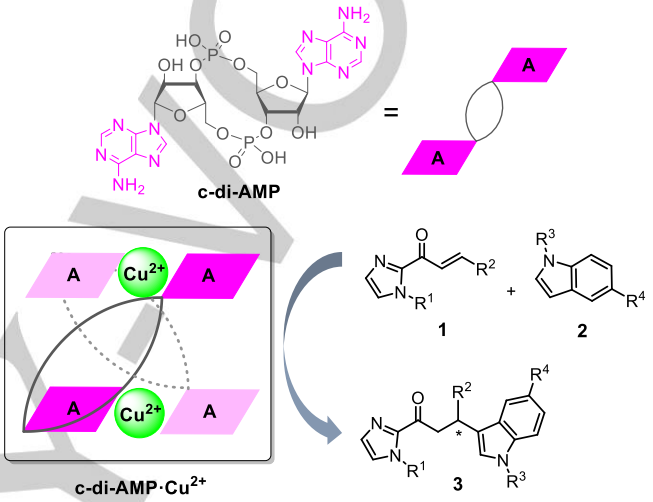
Highly Efficient Cyclic Dinucleotide Based Artificial Metalloribozymes for Enantioselective Friedel-Crafts Reactions in Water

Changhao Wang[+],* Min Hao[+], Qianqian Qi, Jingshuang Dang, Xingchen Dong, Shuting Lv, Ling Xiong, Huanhuan Gao, Guoqing Jia, Yashao Chen,* Jörg S. Hartig, and Can Li

Abstract: The diverse secondary structures of nucleic acids are emerging as attractive chiral scaffolds to construct artificial metalloenzymes (ArMs) for enantioselective catalysis. DNA-based ArMs using duplex and G-quadruplex scaffolds have been widely investigated, yet RNA-based ArMs are scarce. Here we report that a cyclic dinucleotide of c-di-AMP and Cu^{2+} ions assemble into an artificial metalloribozyme (c-di-AMP·Cu^{2+}) that enables catalysis of enantioselective Friedel-Crafts reactions in aqueous media with high reactivities and excellent enantioselectivities up to 97% *ee*. The assembly of c-di-AMP·Cu^{2+} gives rise to a 20-fold rate acceleration compared to Cu^{2+} ions. Based on various biophysical techniques and density function theory (DFT) calculations, a fine coordination structure of c-di-AMP·Cu^{2+} metalloribozyme is suggested where two c-di-AMP form a dimer scaffold and the Cu^{2+} ion locates in the center of an adenine-adenine plane via binding to two N7 and one phosphate-oxygen.

With ever-increasing interest for developing new-to-nature biocatalysts, much attention has been attracted to rationally designed artificial metalloenzymes (ArMs) that are merging the features of enzymatic catalysis and homogeneous catalysis.[1] ArMs are originating from incorporating metallo-cofactors into biomolecular scaffolds, which are used to expand the reaction reservoir and explore the novel functions of biomolecules.[2] Beside the extensive studies of proteins as chiral scaffolds for ArMs, nucleic acids have recently raised much interest to construct ArMs because of their diverse tertiary structures, chemical stability and easy synthetic access. In 2005, Roelfes and Feringa pioneered the DNA-based asymmetric catalysis using duplex DNA as scaffold to embed achiral copper(II) complexes to achieve an enantioselective Diels-Alder reaction.[3] This concept of DNA-based ArMs has been successively applied to many enantioselective transformations[4] and in some cases the presence of DNA could accelerate the reaction rates.[4g, 5]



Scheme 1. Schematic representation of enantioselective Friedel-Crafts reactions of *α,β*-unsaturated 2-acyl imidazoles (**1**) and indoles (**2**) by a cyclic dinucleotide based artificial metalloribozyme of c-di-AMP·Cu^{2+}.

Owing to the tunable structures, G-quadruplex DNA-based ArMs have been developed and the enantioselective catalytic performances are largely dependent on the G-quadruplex structures.[6] In addition, an assembly of G-triplex DNA and Cu^{2+} ions was built to modestly promote a Diels-Alder reaction.[7] Since RNA is comparably less stable than DNA, few examples of RNA-based enantioselective catalysis were described. Jäschke and coworkers reported the selection of a ribozyme that achieves a Diels-Alder reaction with over 90% *ee*.[8] Smietana and Arseniyadis constructed double-stranded RNA hybrid catalysts for Friedel-Crafts (F-C) reactions with modest enantioselectivities.[9] The Hennecke group discussed the results that DNA is superior to RNA as scaffold in nucleic acid based enantioselective catalysis.[10] Although nucleic acid based ArMs successfully transfer the chirality from nucleic acids to the aimed products and achieve some challenging synthetic reactions, yet there are still many concerns to be solved e.g. lack of RNA-based ArMs, unclear fine structures and few explorations on reaction mechanisms. In particular, the current nucleic acid based ArMs contain several tens to several hundreds of oligonucleotides to form the second coordination sphere on a macroscale, thus the insight of the precise chiral microenvironment for targeting the metal cofactors is insufficient. Herein, we report an artificial metalloribozyme resulting from incorporation of Cu^{2+} ions into the scaffold of a cyclic dinucleotide of c-di-AMP that could effectively catalyze the enantioselective F-C reactions in aqueous media (Scheme 1).

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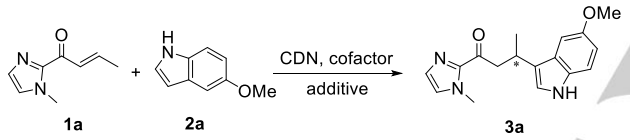
Cyclic dinucleotides (CDNs) are natural cyclic RNA molecules containing two ribonucleotide units and a 12-membered ring structure. So far, four canonical 3'-5' linked CDNs of c-di-GMP, c-di-AMP, c-AMP-GMP, c-AMP-UMP and one non-canonical CDN of 2',3'-c-GAMP have been discovered in nature[11] and identified as important second messengers in transduction of biological signals and regulation of many cellular processes.[12] These naturally occurring CDNs are easily produced by their specific cyclases and the canonical CDNs are readily synthesized in large scale using a one-pot chemical strategy.[13] Moreover, CDNs are able to form three-dimensional structures. C-di-GMP could fold into diverse structures in the presence of alkaline metal ions or aromatic planar intercalators.[14] Xi and Plavec reported that the monomeric CDNs are stable in U-type structures and prone to form dimer and tetramer.[15] The Hartig group proved that some of the formerly unknown CDNs form higher order structures.[13b] In addition, a heme analogue was embedded into a c-di-GMP octameric scaffold that mimicked the G-quadruplex DNA peroxidase.[16] Hence, the multiple structures of CDNs raise our interest to employ them as chiral scaffolds to construct RNA-based hybrid catalysts.

Table 1: Enantioselective Friedel-Crafts reaction catalyzed by CDN-based hybrid catalysts.[a]



1a **2a** **3a**

Entry	CDN	Cofactor[b]	Additive	Conversion [%]	*ee* [%]
1	c-di-GMP	none	KCl	20	4
2	c-di-GMP	$Cu(OTf)_2$	KCl	96	2
3	c-AMP-GMP	$Cu(OTf)_2$	KCl	93	10
4	c-di-AMP	$Cu(OTf)_2$	KCl	>99	72
5	c-di-AMP	$Cu(OTf)_2$	NaCl	>99	71
6	c-di-AMP	$Cu(OTf)_2$	$MgCl_2$	>99	55
7	c-di-AMP	$Cu(OTf)_2$	none	>99	85
8	c-di-AMP	$Cu(bpy)(NO_3)_2$	none	>99	45
9	c-di-AMP	$Cu(dmbpy)(NO_3)_2$	none	>99	55
10	c-di-AMP	$Cu(phen)(NO_3)_2$	none	>99	59
11[c]	c-di-AMP	$Cu(OTf)_2$	none	>99	90
12[d]	c-di-AMP	$Cu(OTf)_2$	none	>99	60
13[e]	c-di-AMP	$Cu(OTf)_2$	none	>99	87

[a] Reaction conditions: **1a** (1 mM), **2a** (5 mM), CDN (100 μM), cofactor (50 μM), additive (100 mM), MOPS buffer (1 mL, 20 mM, pH 6.5), 4 °C, 24 h. The conversion and *ee* were determined from the crude product by HPLC analysis on a chiral stationary phase. All data were averaged by at least duplicated experiments with the reproducibility of ±5%. [b] OTf = trifluoromethanesulfonate, bpy = 2,2'-bipyridine, dmbpy = 4,4'-dimethyl-2,2'-bipyridyl, phen = 1,10-phenathroline. [c] c-di-AMP (250 μM) and $Cu(OTf)_2$ (50 μM). [d] Reaction at 37 °C. [e] MES buffer (20 mM, pH 5.5).

To investigate the enantioselective catalytic functions of CDNs, an enantioselective F-C reaction of (*E*)-1-(1-methyl-1*H*-imidazol-2-yl)but-2-en-1-one (**1a**) and 5-methoxy-1*H*-indole (**2a**) was selected as a probe reaction. We initially tested c-di-GMP that could form G-quadruplex structure in the presence K^+ ions (Figure S1). However, the sole c-di-GMP showed low activity and nearly racemic products of **3a** were obtained using either c-di-GMP or c-di-GMP·Cu^{2+} (Table 1, entries 1-2). Since different CDNs displayed distinct profiles in circular dichroism (CD) spectra (Figure S2), we examined c-AMP-GMP and c-di-AMP hybrid catalysts. In K^+-containing media, c-AMP-GMP·Cu^{2+} provided **3a** with 93% conversion and 10% *ee* (Table 1, entry 3). Surprisingly, c-di-AMP·Cu^{2+} in the presence of K^+ ions achieved the F-C reaction with a quantitative conversion and a good enantioselectivity of 72% *ee* (Table 1, entry 4), suggesting that c-di-AMP and Cu^{2+} ions are effectively interacting in order to function as a potent hybrid catalyst. Furthermore, we investigated the reaction conditions for c-di-AMP·Cu^{2+} catalyzed F-C reaction by varying additives, cofactors, temperatures and buffers. Different alkaline metal ions and alkaline earth metal ions as additives caused negative effects to the enantioselectivities and the highest 85% *ee* was obtained with no additives (Table 1, entries 4-7, Tables S1 and S2). This phenomenon is different from Na^+ or K^+ promoted G-quadruplex DNA-based enantioselective catalysis.[6b, 6c, 17] For the cofactors in the c-di-AMP hybrid catalysts, Cu^{2+} ion served as the best cofactor to assist c-di-AMP to achieve the enantioselectivity regardless of the used counter anions (Table S3). However, the introduction of achiral ligands to c-di-AMP·Cu^{2+} resulted in decreased *ee* values (Table 1, entries 8-10). With increasing the ratio of c-di-AMP/Cu^{2+}, the enantioselectivity was gradually increasing up to 90% *ee* using c-di-AMP·Cu^{2+} (5:1) yet further increasing the c-di-AMP/Cu^{2+} ratio caused no significant changes (Table 1, entry 11, Table S4). When increasing the reaction temperature, a reduced *ee* was obtained (Table 1, entry 12). For the buffers of either 4-morpholinepropanesulfonic acid (MOPS) or 4-morpholineethanesulfonic acid (MES), MES (pH 5.5) was selected as the optimal buffer for the following studies (Table 1, entry 13, Table S5).

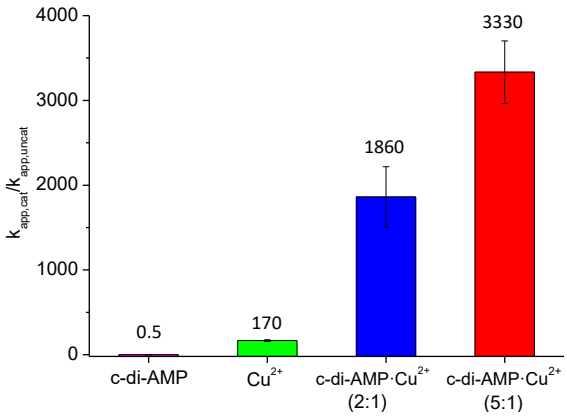
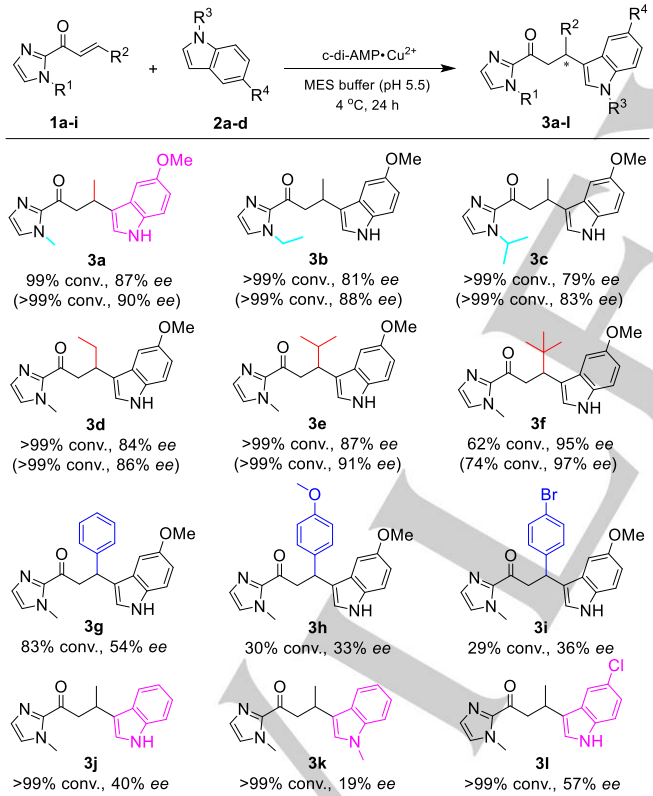


Figure 1. The rate acceleration effect ($k_{app,cat}/k_{app,uncat}$) for c-di-AMP, Cu^{2+}, and c-di-AMP·Cu^{2+}. The apparent second-order rate constant (k_{app}) was estimated from the initial rate of the F-C reaction with **1a** (0.8 mM) and **2a** (5 mM) in MES buffer (1 mL, 20 mM, pH 5.5) at 4 °C without catalyst ($k_{app,uncat}$) and with catalysts of c-di-AMP (100 μM), Cu^{2+} (50 μM), c-di-AMP·Cu^{2+} (2:1, 100 μM c-di-AMP and 50 μM Cu^{2+}), and c-di-AMP·Cu^{2+} (5:1, 250 μM c-di-AMP and 50 μM Cu^{2+}), respectively.

In order to evaluate the catalytic roles of c-di-AMP and Cu^{2+} in c-di-AMP·Cu^{2+}, we determined the apparent second-order rate constant (k_{app}) for the F-C reaction as previously described.[5d] Compared to the uncatalyzed reaction ($k_{app,uncat}$), c-di-AMP slightly inhibited the reaction with $k_{app,c\text{-}di\text{-}AMP}/k_{app,uncat}$ = 0.5 ± 0.1, while Cu^{2+} ions remarkably accelerated the reaction with $k_{app,Cu2+}/k_{app,uncat}$ = (1.7 ± 0.1) × 10^2 (Figure 1 and Table S6). Once the c-di-AMP and Cu^{2+} were assembled with the molar ratio of 5:1, the c-di-AMP·Cu^{2+} (5:1) gave rise to a rate enhancement of 3330-fold compared to the uncatalyzed reaction and 20-fold compared to Cu^{2+} ions (Figure 1 and Table S6). Compared to c-di-AMP·Cu^{2+} (5:1), c-di-AMP·Cu^{2+} (2:1) caused a bit lower rate acceleration effect (Figure 1). These results suggest that c-di-AMP and Cu^{2+} are assembling into a CDN-based artificial metalloribozyme where Cu^{2+} ions are the main catalytic species and the c-di-AMP provides a chiral second coordination sphere. This phenomenon is similar to the descriptions of duplex DNA and G-quadruplex DNA metalloenzymes.[3, 6b]

With c-di-AMP·Cu^{2+} metalloribozyme in hand, we tested different *α,β*-unsaturated 2-acyl imidazoles (**1a-i**) and indoles (**2a-d**) for the enantioselective F-C reactions (Scheme 2).



Scheme 2. Substrate scope of the c-di-AMP·Cu^{2+} catalyzed F-C reactions. Reaction conditions: **1** (1 mM), **2** (5 mM), c-di-AMP (100 μM), $Cu(OTf)_2$ (50 μM), MES buffer (1 mL, 20 mM, pH 5.5), 4 °C, 24 h. The conversion (conv.) of **3a** was calculated by HPLC and the conversions of **3b-l** were estimated by ^{1}H NMR from the crude products. The *ee* values were determined from the crude products on a chiral HPLC. The data in parentheses represented the corresponding F-C reactions using c-di-AMP·Cu^{2+} (5:1) with 250 μM c-di-AMP and 50 μM Cu^{2+} ions. All data were averaged by two independent experiments with the reproducibility of conversions at ±5% and *ee* values at ±3%.

Compared to **1a** bearing R^1 = methyl reacted with **2a**, the substrates **1b** and **1c** with larger R^1 groups (ethyl, *iso*-propyl) provided decreased *ee* values (**3a** vs. **3b**-**c**). Once changing c-di-AMP·Cu^{2+} (2:1) to c-di-AMP·Cu^{2+} (5:1), the corresponding enantioselectivities of **3a**-**c** slightly increased. For tuning the R^2 group in *α,β*-unsaturated 2-acyl imidazoles of methyl, ethyl and *iso*-propyl, no significant differences for the enantioselectivities were obtained (**3a**,**3d**-**e**) using either c-di-AMP·Cu^{2+} (2:1) and c-di-AMP·Cu^{2+} (5:1). Surprisingly, once the R^2 group of **1f** was substituted by a *tert*-butyl moiety, the corresponding F-C reactions showed modest conversions but excellent enantioselectivities of **3f** at 95% *ee* and 97% *ee* by c-di-AMP·Cu^{2+} (2:1) and c-di-AMP·Cu^{2+} (5:1), respectively. When the R^2 groups in the substrates were substituted by aromatic moieties, both reactivities and enantioselectivities were obviously suppressed (**3g-i**). Furthermore, different indoles (**2a-d**) were examined to react with **1a** and varied enantioselectivities were obtained (**3j-l**). To examine the synthetic potential of c-di-AMP·Cu^{2+}, we conducted the benchmark reaction on a large scale (**1a**, 75 mg) using c-di-AMP·Cu^{2+} (2:1) of 2 mol%. After gel column chromatography, we obtained **3a** at 80% isolated yield and 85% *ee*, indicating that c-di-AMP·Cu^{2+} is potentially applied for practical synthesis.

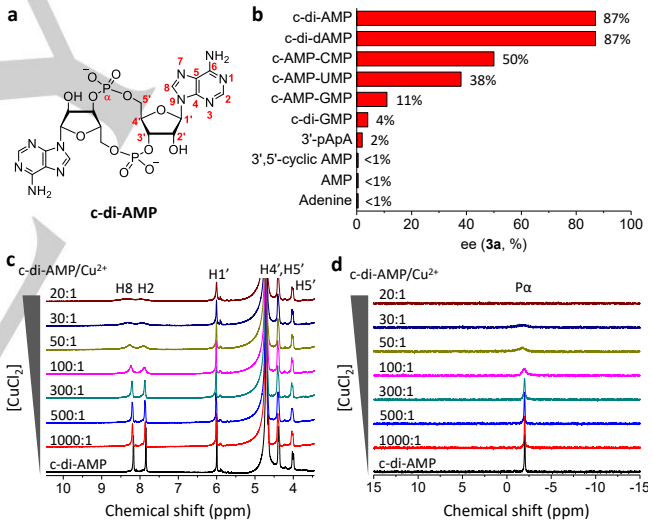


Figure 2. a) Chemical structure of c-di-AMP. b) Control experiments for the Cu^{2+}-catalyzed F-C reaction with different c-di-AMP analogues. Reaction conditions: **1a** (1 mM), **2a** (5 mM), c-di-AMP analogue (100 μM), $Cu(OTf)_2$ (50 μM), MES buffer (1 mL, 20 mM, pH 5.5), 4 °C, 24 h. All the control experiments were at conversions beyond 98%. c) ^{1}H NMR and d) ^{31}P NMR spectroscopic titrations of c-di-AMP (9.4 mM) by varying the concentration of $CuCl_2$ (9.4-470 μM) in D_2O.

For c-di-AMP (Figure 2a), the possible coordination sites for Cu^{2+} ions are N1, N3, N6, N7, O2' and phosphate oxygen atoms as described previously for copper/nucleic acid complexes.[18] In an attempt to probe the location of Cu^{2+} ion in c-di-AMP·Cu^{2+}, we conducted a series of control experiments for the benchmark F-C reaction with different c-di-AMP analogues (Figure 2b). Cyclic dideoxyribonucleotide (c-di-dAMP) instead of c-di-AMP resulted the similar enantioselectivity in Cu^{2+}-catalyzed F-C

reaction, indicating that O2' in c-di-AMP is not a primary binding site of Cu^{2+} ions. Compared to c-di-AMP, the CDNs containing one AMP moiety (c-AMP-CMP, c-AMP-UMP and c-AMP-GMP) based metalloribozymes yielded the decreased *ee* values and c-di-GMP provided a very low *ee*, showing that Cu^{2+} ions could be specifically targeted by adenine in CDNs. Moreover, the non-cyclic form of c-di-AMP (3'-pApA), 3',5'-cyclic AMP, AMP and adenine gave nearly racemic products in Cu^{2+}-catalyzed F-C reaction. The above results suggest that the 12-membered cyclic scaffold and two adenines are indispensable for CDN-based metalloribozymes to exert high enantioselective catalysis.

To investigate the interaction between c-di-AMP and Cu^{2+} ions, several biophysical techniques were employed. With increasing the amount of Cu^{2+} ions, UV-Vis and CD spectra of the c-di-AMP exhibited slight concentration-dependent behaviors (Figure S13), indicating that c-di-AMP and Cu^{2+} ions are indeed interacting. The binding affinity between c-di-AMP and Cu^{2+} ions was quantitatively analyzed with an apparent dissociation constant (K_d) of 646 ± 32 μM by UV titration experiments (Figure S16). Nuclear magnetic resonance (NMR) technique was also used although Cu^{2+} ions are paramagnetic species. Compared to ^{1}H NMR of c-di-AMP, the titration of Cu^{2+} ions broadened and shifted downfield the signals of H8 and H2, yet other protons remained almost unchanged (Figure 2c). These results suggest that the magnetic environment around H8 and H2 of c-di-AMP is disturbed upon the addition of Cu^{2+} ions, leading us to assume that N1, N3 and N7 are likely the binding sites of Cu^{2+} ions. Moreover, the addition of Cu^{2+} ions to c-di-AMP caused the broadening and a small shift downfield for the Pα signal (Figure 2d), indicating that phosphates in c-di-AMP are likely another binding site of Cu^{2+} ions. Taken together the c-di-AMP analogues experiments and biophysical characterizations, we conclude that Cu^{2+} ions are most likely interacting with N7, N3, N1 and phosphate in c-di-AMP to assemble a CDN-based metalloribozyme.

To clarify the structure of c-di-AMP·Cu^{2+} and explore the plausible reaction mechanism, density function theory (DFT) calculations were conducted. In experimental study, the absolute configuration of **3a** was confirmed in *R* type in c-di-AMP·Cu^{2+} catalyzed F-C reaction (Figure 3a and Figure S17) that corresponds to the literature reported.[19] In DFT calculations, c-di-AMP is stable in U-type scaffold with an intramolecular π-π stacking between two adenines (Figure 3b), which is consistent with the recent literature.[15] Once the Cu^{2+} ions are added, two possible c-di-AMP·Cu^{2+} monomers were obtained (Figure S18). The stable one shows that the Cu^{2+} ion binds to two oxygens from two phosphates, but this c-di-AMP·Cu^{2+} monomer interacting with **1a** provides an intermediate with no further chiral induction (Figure 3b). Another c-di-AMP·Cu^{2+} monomer is less stable and yields the product **3a** in *S* configuration that conflicts with the experimental result (Figure S18). Intriguingly, the stable c-di-AMP·Cu^{2+} monomer tends to reconstruct a more stable dimer with intermolecular π-π stacking of adenines (Figure 3b), which undergoes an exothermic process with a binding energy of -85.4 kcal/mol. In this c-di-AMP·Cu^{2+} dimer, two Cu^{2+} ions are locating equivalently in the center of two adenine-adenine planes and each Cu ion is trapped by two N7 atoms from different c-di-AMP and one nearby phosphate-oxygen (Figure 3b). Importantly, the addition of **1a** to the c-di-AMP·Cu^{2+} dimer

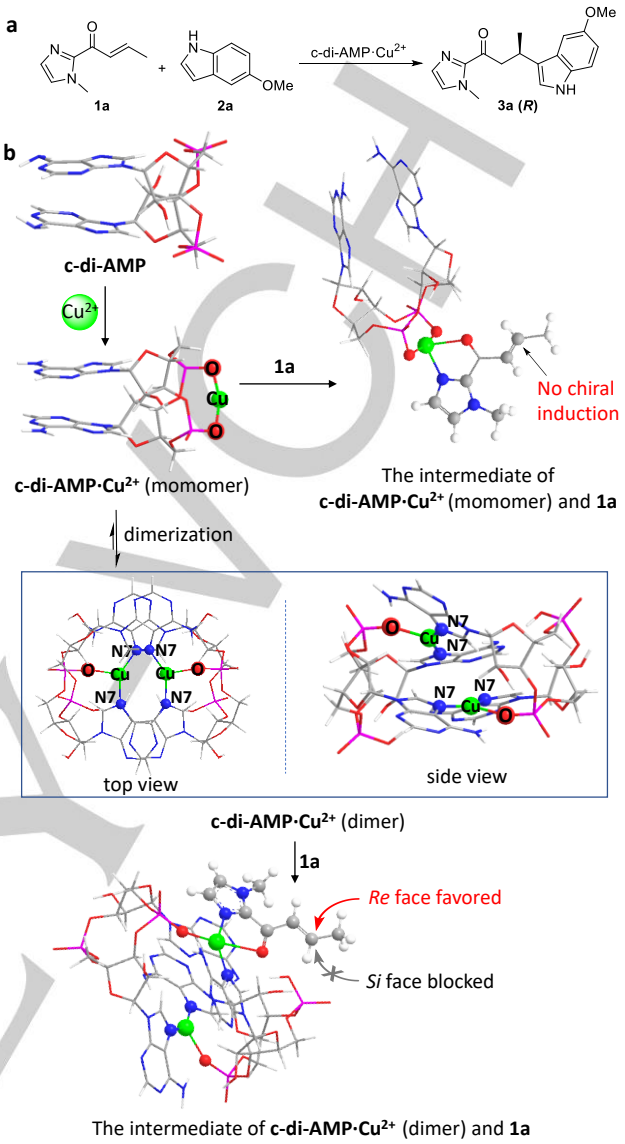


Figure 3. a) c-di-AMP·Cu^{2+} catalyzed F-C reaction of **1a** and **2a** to yield **3a** in *R* configuration. b) DFT calculations of the optimized conformations of c-di-AMP, c-di-AMP·Cu^{2+} and the intermediates of c-di-AMP·Cu^{2+} and **1a**.

forms an intermediate that allows **2a** to preferentially attack from the *Re* face rather than *Si* face (Figure 3b), leading to the product **3a** in *R* configuration which is in accordance with the experimental result. Taken together of the above experimental data and the DFT calculations, a plausible fine structure of c-di-AMP·Cu^{2+} metalloribozyme is depicted in dimeric form where the Cu^{2+} ion is located in the center of an A-A plane via binding to two N7 and one phosphate-oxygen.

In conclusion, we found that c-di-AMP and Cu^{2+} ions enable to assemble into a CDN-based artificial metalloribozyme that shows quantitative conversions and up to 97% *ee* in the enantioselective F-C reactions. The resulted c-di-AMP·Cu^{2+} provides a significant rate acceleration effect in comparison of Cu^{2+} ions. The enantioselective catalytic performance of c-di-AMP·Cu^{2+} is largely dependent on the 12-membered cyclic

scaffold and the two adenines moieties. Based on biophysical characterizations and DFT calculations, the structure of c-di-AMP·Cu^{2+} is proposed as a dimeric complex where the Cu^{2+} ion is likely locating in the A-A plane via coordinating with two N7 and one phosphate-oxygen. This study suggests that the CDNs serve as powerful scaffolds in order to construct artificial metalloribozymes and their (enantio)selective performances could be tuned by alteration of the nucleobases in CDNs. Given the ability to bind metal ions and catalyze the described reactions, we anticipate that cyclic dinucleotides could be able to catalyze other challenging organic transformations. In addition, we speculate that such small, naturally occurring cyclic RNAs could have been able to catalyze metabolic reactions in an early RNA world scenario.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: nucleic acid based catalysts • cyclic dinucleotide • c-di-AMP • artificial metalloribozyme • enantioselective catalysis

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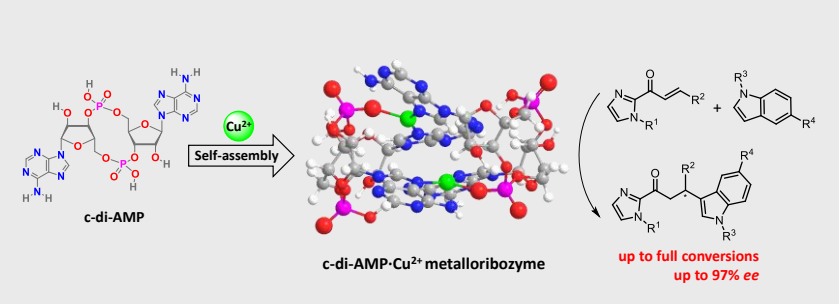

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Highly Efficient Cyclic Dinucleotide Based Artificial Metalloribozymes for Enantioselective Friedel-Crafts Reactions in Water

A cyclic dinucleotide based artificial metalloribozyme assembled by c-di-AMP and Cu^{2+} ions enables the catalysis of enantioselective Friedel-Crafts reactions with high reactivities and excellent enantioselectivities up to 97% *ee*.