

Ligand Design

Water and Air Stable Copper(I) Complexes of Tetracationic Catenane Ligands for Oxidative C–C Cross-Coupling

Man Pang Tang⁺, Lihui Zhu⁺, Yulin Deng⁺, Yi-Xiang Shi, Samuel Kin-Man Lai, Xiaoyong Mo, Xin-Yu Pang, Chunyu Liu, Wei Jiang[#], Edmund Chun Ming Tse, and Ho Yu Au-Yeung*

Abstract: Aqueous soluble and stable Cu(I) molecular catalysts featuring a catenane ligand composed of two dicationic, mutually repelling but mechanically interlocked macrocycles are reported. The ligand interlocking not only fine-tunes the coordination sphere and kinetically stabilizes the Cu(I) against air oxidation and disproportionation, but also buries the hydrophobic portions of the ligands and prevents their dissociation which are necessary for their good water solubility and a sustained activity. These catenane Cu(I) complexes can catalyze the oxidative C–C coupling of indoles and tetrahydroisoquinolines in water, using H₂O₂ as a green oxidant with a good substrate scope. The successful use of catenane ligands in exploiting aqueous Cu(I) catalysis thus highlights the many unexplored potential of mechanical bond as a design element for exploring transition metal catalysis under challenging conditions.

The strategic use of mechanical interlocking to obtain otherwise unstable cationic copper(I) complexes for exploring aqueous phase cross-coupling catalysis is reported. Although copper is earth-abundant and its rich coordination and redox chemistry are very attractive for catalyst development,^[1–5] Cu(I) is well-known for its prone air oxidation and disproportionation in water ($\log K_{\text{disp}} \approx 6$),^[6–10] and as such, developing well-defined Cu(I) molecular catalysts that are stable against disproportionation and oxidation in water, but are also active at the same time for aqueous-phase catalysis is not trivial.^[11] The relatively fast ligand exchange around copper ions in water may also render the active catalytic species difficult to be characterized for mechanistic understanding and further improvement,^[12–14] not to mention their susceptibility towards solvent attack and other side-reactions that may compromise the catalyst lifetime, durability and activity.

In this regard, although the “catenand effect” from catenane-derived ligands is well-known to kinetically stabilize Cu(I), applying catenane-coordinated Cu(I) complexes for aqueous catalysis applications remains unexplored (Figure 1).^[15–18] As the interlocked ligands could not completely dissociate but reorganize around the metal, a catalyst that is not only coordinatively saturated in its resting state, but also with an accessible coordination sphere can thus be obtained.^[19] New catalytic activity and selectivity could also be resulted from the spatial restrictions imposed by the interlocking.^[20–22] While a large number of transition metal complexes supported by catenane ligands have been reported as products from metal-templated synthesis,^[23–27] how the coordination features and chemical reactivity of the metal are affected by mechanical interlocking, and how these different coordination features are to be translated to favorable attributes in transition metal catalysis are yet to be investigated.

Herein, new tetracationic catenane ligands are designed to obtain water and air stable Cu(I) complexes, and their catalytic activity in the oxidative C–C cross-coupling of indoles and tetrahydroisoquinolines (THIQ) in water are described. The complex [Cu(**C8c**)I]₅ was obtained in 85 % yield from a one-step quaternization of the four secondary amines in [Cu(**C8**)I] using CH₃I (Scheme S1).^[28] UV/Vis spectrum of [Cu(**C8c**)I]₅ in DMSO shows intense absorptions at 279 nm ($\epsilon = 53000 \text{ M}^{-1} \text{ cm}^{-1}$) and 471 nm ($\epsilon = 6600 \text{ M}^{-1} \text{ cm}^{-1}$), which are characteristics ligand-centered

[*] M. P. Tang,⁺ Dr. L. Zhu,⁺ Y. Deng,⁺ Dr. Y.-X. Shi, Dr. S. Kin-Man Lai, Dr. X. Mo, Prof. E. C. M. Tse, Prof. H. Y. Au-Yeung
 Department of Chemistry, The University of Hong Kong
 Pokfulam Road, Hong Kong, P. R. China
 E-mail: hoyuay@hku.hk

Dr. L. Zhu,⁺ Prof. H. Y. Au-Yeung
 State Key Laboratory of Synthetic Chemistry,
 The University of Hong Kong,
 Pokfulam Road, Hong Kong, P. R. China

Prof. E. C. M. Tse, Prof. H. Y. Au-Yeung
 CAS-HKU Joint Laboratory on New Materials,
 The University of Hong Kong,
 Pokfulam Road, Hong Kong, P. R. China

X.-Y. Pang, Prof. W. Jiang[#]
 Department of Chemistry,
 South University of Science and Technology of China,
 Xueyuan Blvd 1088, Shenzhen, 518055, P. R. China

C. Liu
 Key Laboratory of Eco-Textiles, Ministry of Education,
 Jiangnan University, Wuxi, 100083, P. R. China

[⁺] These authors contributed equally.

[[#]] Deceased 25 December 2022

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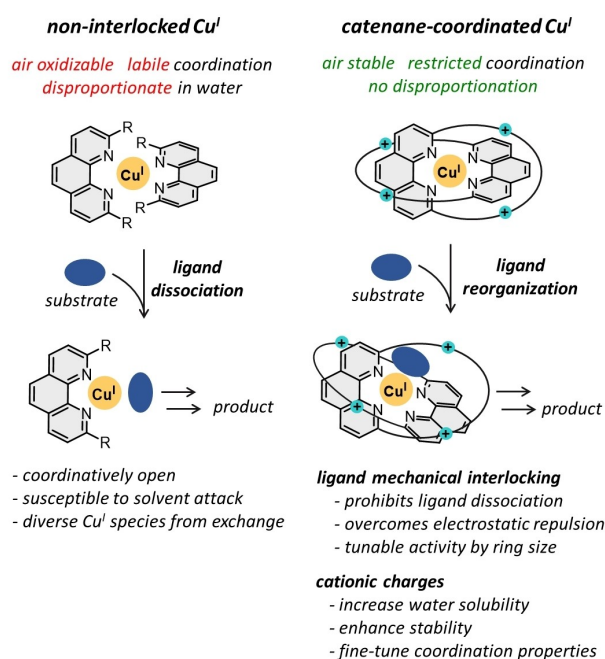


Figure 1. Comparison between Cu(I) molecular catalysts supported by non-interlocked and catenane ligands.

(LC) and MLCT transitions of Cu(I)-phenanthroline complexes (Figure 2).^[15,29,30] While similar LC absorption was also observed for [Cu(C8)]⁺ (λ_{\max} = 278 nm, ϵ = 49000 M⁻¹cm⁻¹) and the non-interlocked [Cu(L4)₂]⁺ (λ_{\max} = 278 nm, ϵ = 72000 M⁻¹cm⁻¹), the MLCT absorption of [Cu(C8c)]⁵⁺ is more red-shifted than that of [Cu(C8)]⁺ (λ_{\max} = 465 nm, ϵ = 5300 M⁻¹cm⁻¹) and the non-interlocked [Cu(L4)₂]⁺ (λ_{\max} = 453 nm, ϵ = 6700 M⁻¹cm⁻¹). The cationic catenane ligand in [Cu(C8c)]⁵⁺ also raises both the oxidation (E_{pa}) and reduction (E_{pc}) potentials of the Cu^{II/I} redox couple by respectively 0.135 V and 0.112 V when compared to that of [Cu(C8)]⁺ as measured by CV, showing that the energy level and electronic structure of the Cu(I) can be fine-tuned by the catenane ligands despite a highly similar primary coordination.

¹H NMR spectrum (500 MHz, *d*₆-DMSO, 298 K) of [Cu(C8c)]₅ showed the three phen protons are slightly more downfield than those of [Cu(C8)]I by 0.09–0.16 ppm. More significant downfield shifts by 0.32 ppm and 0.42 ppm were also observed for H_{Ar} in the phenyl linkers in [Cu(C8c)]⁵⁺ when compared to that of [Cu(C8)]⁺, which is consistent to a more expanded conformation of the macrocycles due to the mutual repulsion between the ammoniums. X-ray crystal structure of [Cu(C8c)]₅ (Figure 3)^[31] is also compared with that of the previously reported [Cu(C8)]-(PF₆)₂^[20] and comparable Cu–N distances are found in both complexes, suggesting that the cationic charges may not have a strong influence on the Cu–N bond strength

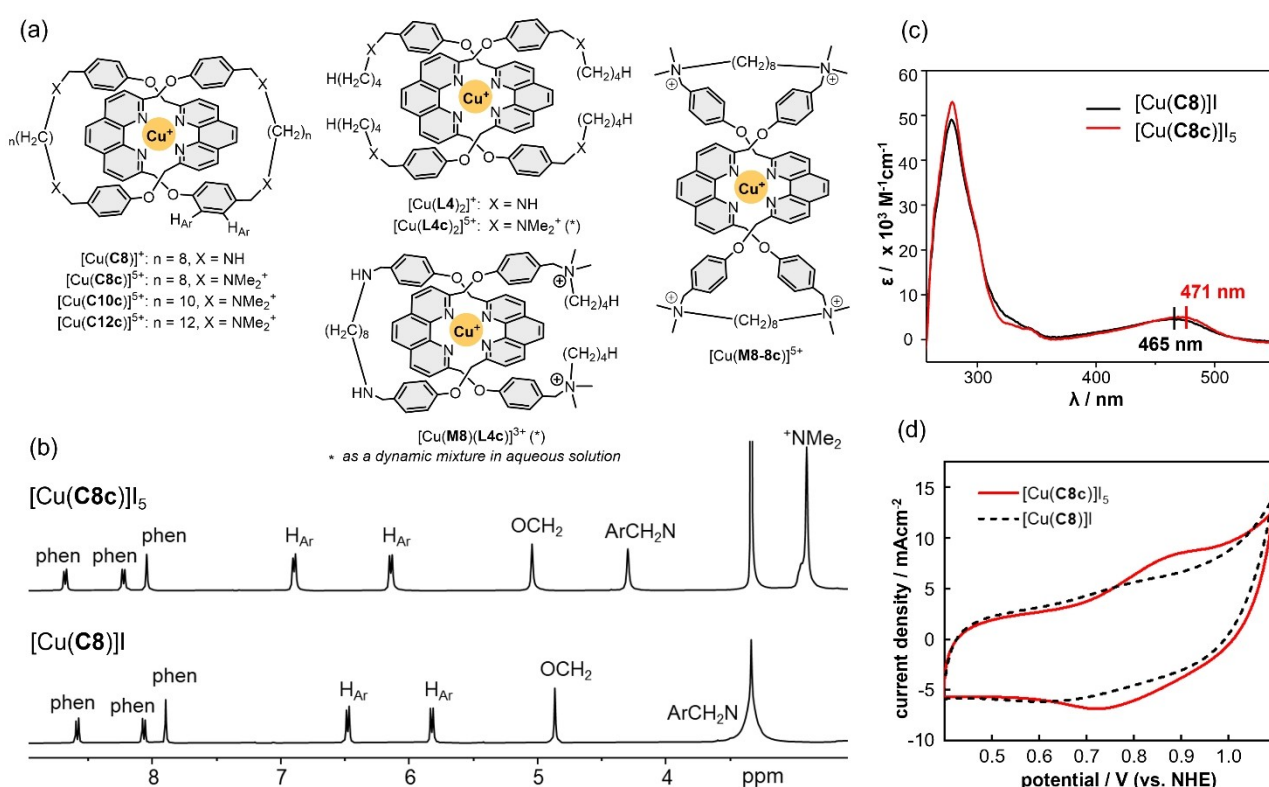


Figure 2. (a) Structures of the Cu(I) catenane and control complexes; (b) ¹H NMR (500 MHz, *d*₆-DMSO, 298 K) spectra; (c) UV/Vis spectra; and (d) cyclic voltammograms of [Cu(C8c)]₅ and [Cu(C8)]I.

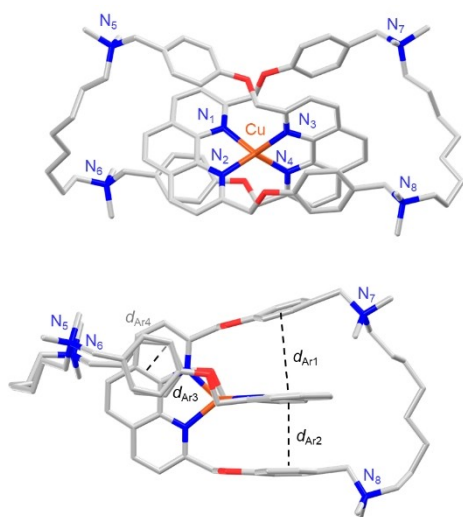


Figure 3. (a) X-ray crystal structure of $[\text{Cu}(\text{C8c})]^{5+}$. Solvent molecules, counter iodide and hydrogen atoms are omitted for clarity (orange: Cu; blue: N; red: O; grey: C).

(Table 1). Yet, a larger deviation from a tetrahedral geometry was observed for $[\text{Cu}(\text{C8c})]^{5+}$, with a dihedral angle α of 74.8° between the planes of the two phen and a phen(centroid)-Cu-phen(centroid) angle β of 174.5° when compared to $[\text{Cu}(\text{C8})]^+$ ($\alpha = 87.3^\circ$ and $\beta = 177.5^\circ$). While the phen units in $[\text{Cu}(\text{C8})]^+$ were found to π -stack between the two phenyl rings at similar distances ($d_{\text{Ar}} = 3.565\text{--}3.694 \text{ \AA}$), the phen units in $[\text{Cu}(\text{C8c})]^{5+}$ were closer to one of the phenyl rings with a less symmetrical arrangement ($d_{\text{Ar}} = 3.922 \text{ \AA}$ and 3.348 \AA). These differences are likely due to the Coulombic repulsion between the ammoniums in $[\text{Cu}(\text{C8c})]^{5+}$ that enforces a more expanded macrocycle con-

Table 1: Comparison of selected structural parameters of $[\text{Cu}(\text{C8c})]^{5+}$ and $[\text{Cu}(\text{C8})]^+$.^[20]

	$[\text{Cu}(\text{C8c})]^{5+}$	$[\text{Cu}(\text{C8})]^+$
$d_{\text{Cu-N1}}, d_{\text{Cu-N2}}/\text{\AA}$	2.014, 2.026	2.016, 2.027
$d_{\text{Cu-N3}}, d_{\text{Cu-N4}}/\text{\AA}$	2.014, 2.026	2.016, 2.032
α/deg	74.8	87.3
β/deg	174.5	177.5
$d_{\text{Ar1}}, d_{\text{Ar2}}/\text{\AA}$	3.922, 3.348	3.565, 3.694
$d_{\text{Ar3}}, d_{\text{Ar4}}/\text{\AA}$	3.922, 3.348	3.579, 3.688
$\text{N}(sp^3)\text{--N}(sp^3)/\text{\AA}$		
$d_{\text{N5-N6}}, d_{\text{N7-N8}}$ (same ring)	8.534, 8.534	7.299, 8.783
$d_{\text{N5-N7}}, d_{\text{N6-N8}}$ (different rings)	15.692, 15.692	14.585, 14.701
$d_{\text{N5-N8}}, d_{\text{N7-N6}}$ (different rings)	13.717, 15.928	14.264, 14.500

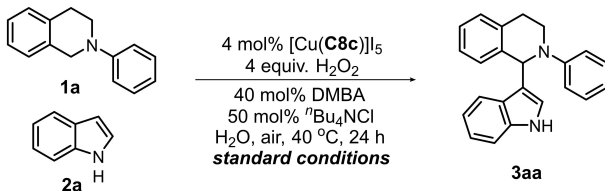
formation. Indeed, the two ammonium nitrogen atoms within the same macrocycle in $[\text{Cu}(\text{C8c})]^{5+}$ are further away from each other, with an averaged distance of 8.534 \AA when compared to that of 8.041 \AA in $[\text{Cu}(\text{C8})]^+$. Together with the UV/Vis, CV and NMR data, these findings hence suggest that the chemical environment in both the primary and secondary coordination sphere of the Cu(I) are influenced by the cationic ammoniums on the catenane ligand.

Electrostatic repulsion between two cationic ligands on the same metal would actually destabilize the metal complex.^[32] A simple estimation of the electrostatic potential between the ammonium ions in $[\text{Cu}(\text{C8c})]^{5+}$ (ca. 370 kJ mol^{-1} at $\sim 15 \text{ \AA}$) suggests the unfavorable repulsion may not be fully compensated by the Cu(I)-phen coordination (ca. -65 kJ mol^{-1} to -120 kJ mol^{-1} for $\log \beta \approx 11$ to 21).^[33,34] In fact, the Cu(I)-phen coordination in $[\text{Cu}(\text{C8c})]^{5+}$ ($\log \beta = 15.9$) is very stable, with a stability comparable to that of $[\text{Cu}(\text{C8})]^+$ ($\log \beta = 16.3$). Attempts to prepare the cationic, non-interlocked $[\text{Cu}(\text{L4c})_2]^{5+}$ from methylation of $[\text{Cu}(\text{L4})_2]^+$, or direct Cu^+ coordination using L4c^{2+} , led only to dynamic mixtures that contain $[\text{Cu}(\text{L4c})_2]^{5+}$, $[\text{Cu}(\text{L4c})]^{3+}$ and free L4c^{2+} as shown by ESI-MS analysis (Figures S1 and S2). Coordination of Cu^+ to a 1:1 mixture of L4c^{2+} and the charge-neutral phenanthroline macrocycle **M8** also resulted in a dynamic mixture containing the Cu(I)-pseudorotaxane $[\text{Cu}(\text{M8})(\text{L4c})]^{3+}$, $[\text{Cu}(\text{L4c})]^{3+}$ and free **M8** ligand (Figures S4 and S5). These findings thus demonstrate the importance of the mechanical bond in maintaining the structural integrity of the cationic Cu(I) complex, particularly when the strong ligand-ligand repulsion would result in an otherwise unstable species.^[35,36]

With the presence of four cationic ammoniums, $[\text{Cu}(\text{C8c})]_5$ displayed a good water solubility (2.6 mg/mL at 25°C), which can be further increased by exchanging the iodide counterion to chloride (25.9 mg/mL at 25°C). In fact, the efficient shielding of the ligand hydrophobic portions due to interlocking is also essential for the good aqueous solubility of $[\text{Cu}(\text{C8c})]_5$, and the isomeric $[\text{Cu}(\text{M8-8c})]_5$ is not really soluble in water ($< 0.1 \text{ mg/mL}$ at 25°C). Unlike many other Cu(I) species,^[5] aqueous solutions of $[\text{Cu}(\text{C8c})]_5$ are very stable against disproportionation and air oxidation due to the kinetic stabilization by the catenane. A sample of $[\text{Cu}(\text{C8c})]_5$ in D_2O has been stored under ambient conditions for 6 months, and the ^1H NMR spectrum obtained was found to show no observable difference as compared to that of a freshly prepared sample (Figure S6). Assuming a 5% uncertainty in the ^1H NMR peak integration, a $\log K_{\text{disp}}$ value of less than -3 is estimated for $[\text{Cu}(\text{C8c})]^{5+}$ in water, corresponding to a stabilization by about 9 orders of magnitude.^[6] Comparing $[\text{Cu}(\text{C8c})]_5$ and $[\text{Cu}(\text{C8})]_5$, the cationic ammoniums in the former complex also enhances the stability of the ligand scaffold against chemical decomposition under oxidizing conditions. While treatment of a 1 mM aqueous solution of $[\text{Cu}(\text{C8})]_5$ with 50 eq. of H_2O_2 at 80°C for 12 hours led to the decomposition of $\sim 80\%$ of the catenane to various oxidatively cleaved species, no observable degradation was found when $[\text{Cu}(\text{C8c})]_5$ was treated under the same conditions (Figures S8–S12).

The good aqueous stability and solubility of [Cu(**C8c**)]₅ prompted us to further study its catalytic activity in aqueous oxidative C–C coupling, which is of fundamental importance in constructing the molecular skeletons of pharmaceuticals, natural products, and many other valuable commodity chemicals.^[37–39] Initial screening showed that 4 mol % of [Cu(**C8c**)]₅ can catalyze the coupling of THIQ **1a** and indole **2a** in water with 4 equiv. of H₂O₂ as the oxidant at 40 °C to give **3aa** in 36 % yield (Table 2, entry 2). Further condition optimization showed that the presence of 2,5-dimethylbenzoic acid (DMBA) as an acid additive can increase the yield of **3aa** to 81 % (Table 2, entry 3),^[40] but a lower yield of **3aa** was observed when the coupling is conducted in organic solvents or aqueous organic mixtures (Table S5). Albeit of a lower yield, O₂ and ^tBuOOH were also found to be viable oxidants and gave **3aa** in 60 % and 68 % yields respectively (Table 2, entries 4 and 5). Using ^tBuOO^tBu as the oxidant gave no coupling product, which may be due to the large steric hindrance of the oxidant. Of note, ^tBuOOH is a more commonly used oxidant in other reported metal-catalyzed oxidations that are mostly conducted in organic medium.^[41,42] The possible use of aqueous H₂O₂ for the oxidative C–C coupling, with comparable or even better efficiency is therefore more attractive because of the lower cost, easier handling procedure, and generation of no carbon-containing by-products.^[43–45] Changing the counterion from iodide to chloride resulted in a slight decrease in the yield of **3aa**, which may suggest the possible interaction of the anion with the oxidant and/or intermediates,^[46] and further mechanistic investigation will be necessary to fully elucidate the effects of the anion (Table 2, entry 8). Finally, the yield of **3aa** can be further improved to 94 % by addition of ⁿBu₄Cl that likely increases the aqueous solubility of the organic substrates (Table S6).

Table 2: Condition screening of the oxidative C–C coupling.



Entry	Variation from standard conditions	Yield ^[a]
1	none	94 % ^[b]
2	no DMBA and ⁿ Bu ₄ NCl	36 %
3	no ⁿ Bu ₄ NCl	81 %
4	O ₂ (balloon) as oxidant	60 %
5	^t BuOOH as oxidant	68 %
6	^t BuOO ^t Bu as oxidant	n.d.
7	[Cu(C8)] as catalyst	76 %
8	[Cu(C8c)]Cl ₅ as catalyst	84 %
9	[Cu(C10c)] ₅ as catalyst	88 %
10	[Cu(C12c)] ₅ as catalyst	80 %

Reaction was conducted with **1a** (0.1 mmol), **2a** (0.15 mmol), oxidant (4 equiv.), and additives in 1 mL H₂O at 40 °C for 24 hours. [a] Determined by ¹H NMR using CH₂Br₂ as an internal standard. [b] Isolated yield: 91 %.

To further understand the effects of the structure of the catenane ligand on the cross-coupling, the C₈ linkers in [Cu(**C8c**)]₅ were replaced by the longer C₁₀ and C₁₂ chains to give [Cu(**C10c**)]₅ and [Cu(**C12c**)]₅, which also displayed aqueous solubility and stability comparable to [Cu(**C8c**)]₅ (Table S2). Employing [Cu(**C10c**)]₅ and [Cu(**C12c**)]₅ as the catalyst under the optimized conditions resulted in a slightly lower yield of **3aa** in 88 % and 80 % respectively (Table 2, entry 9 and 10), which may be ascribed to the looser interlocking of the larger catenanes with a less efficient reorganization in response to changes in the coordination sphere during the catalytic cycle.^[20,47] Further loosening of the ligand entanglement and using [Cu(**C8**)(**L4c**)]³⁺ (as a dynamic mixture) as the catalyst resulted in **3aa** in 65 % yield, and a lactam side product due to THIQ oxidation was also observed in 31 % yield (Scheme S7). Of note, no product other than that from the C–C coupling was found when the catenane complexes were used as the catalyst, and these findings thus reinforce that the kinetically stabilized, well-defined coordination environment provided by the catenane that inhibits ligand exchange is of critical importance to the activity and selectivity of the Cu(I)-mediated catalysis.

The presence of the interlocked ligands around the metal coordination sphere, regardless of the stage of the catalysis, could also serve as a mean to differentiate substrate of different steric requirement. Indole substrates with varying size, i.e. H, Me, Et and ^tBu, at the 2-position were tested using the optimized conditions, and the corresponding C–C coupled products were formed in 91 %, 64 %, 56 % and 49 % respectively (Figure 4, **3aa–3ad**). Although previous study on related THIQ oxidative coupling has shown that 3-methylindole can be coupled at the 2-position,^[42] no coupling product was found in our hands under the optimized conditions, suggesting the catenane catalyst may be more sensitive to the environment around the reaction point of the substrate. Finally, the scope of the catalysis by [Cu(**C8c**)]₅ was investigated by using various THIQ and indole derivatives. Different indoles with alkyl or halogen substituents at the 4-, 5-, 6-, 7- and *N*-positions were successfully coupled with THIQ **1a** to give **3ae–3ao** in 89 % to 93 % yields. Coupling of dimethoxy substituted THIQ **1b** with different indoles resulted in **3ba–3bo** in 35 % to 92 % yields, and *N*-substituted THIQ derivatives with F, Cl, Br, CF₃ and ^tBu groups were also successfully coupled with indole **2a** to give **3ca–3ga** in 88 % to 91 % yields.

In summary, tetracationic catenanes have been developed as an efficient coordination ligand to obtain molecular Cu(I) catalysts that are water soluble and stable against oxidation and disproportionation. The cationic, interlocked ligand structure improves the aqueous solubility and fine-tune the coordination environment around the metal, and their Coulombic repulsion that may otherwise promote ligand dissociation and destabilize the complex is overcome and prevented by the mechanical interlocking. The oxidative C–C coupling of THIQs and indoles catalyzed by [Cu(**C8c**)]₅ in water, using H₂O₂ as a green oxidant is efficient with a total of 33 examples. Although metal complexes featuring mechanically interlocked ligands are generally

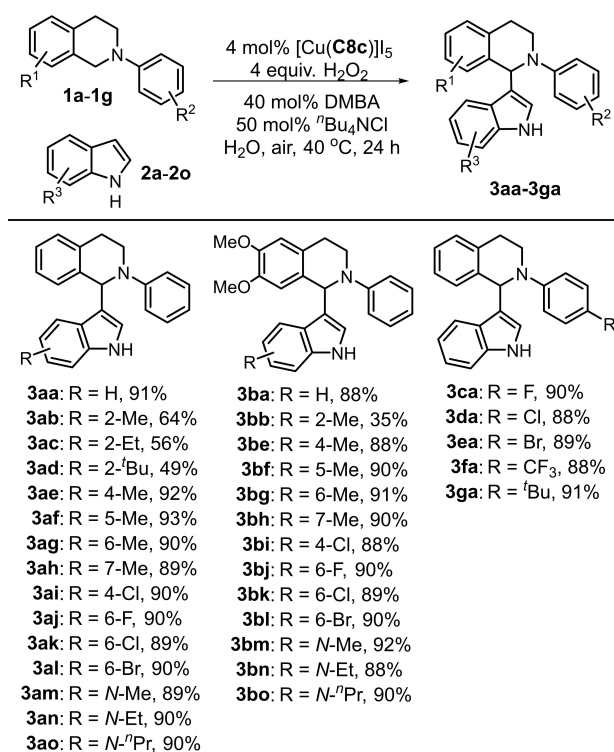


Figure 4. All reactions were conducted with THIQ **1a–1g** (0.1 mmol), indole **2a–2o** (0.15 mmol), [Cu(C8c)]₅ (0.004 mmol), H₂O₂ (0.4 mmol), DMBA (0.04 mmol) and TBAC (0.05 mmol) in 1 mL H₂O at 40 °C for 24 hours. All yields presented are isolated yields.

very stable, and reactivity of the coordinated metals are usually inhibited,^[48–52] our present work demonstrates that it is also possible to exploit their catalytic activity whilst enjoying the advantages due to their kinetic stability by an appropriate design of the interlocked ligands. Findings from this work thus not only demonstrate the potential of catenane ligands for developing new transition metal complexes for green and sustainable catalysis, but also highlight mechanical interlocking as a useful ligand design in exploring transition metal chemistry with coordination features that may not be easily achieved by non-interlocked analogues, especially when being applied under challenging conditions.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: catenane · cationic ligands · copper · mechanical interlocking · oxidative coupling

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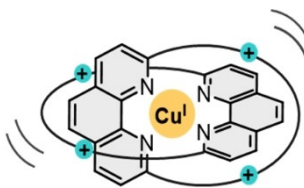
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Communications

Ligand Design

M. P. Tang, L. Zhu, Y. Deng, Y.-X. Shi,
S. Kin-Man Lai, X. Mo, X.-Y. Pang, C. Liu,
W. Jiang, E. C. M. Tse, H. Y. Au-
Yeung* [e202405971](#)

Water and Air Stable Copper(I) Complexes
of Tetracationic Catenane Ligands for Oxi-
dative C–C Cross-Coupling



- ⊘ *dissociative exchange*
- ⊙ *robust ligand, water solubility,
sustained activity, stable Cu(I),
green C-C coupling*

Copper(I) molecular catalysts that are water soluble and stable against oxidative degradation are obtained by the strategic use of multiply charged catenane ligands. By using the new catalysts, oxidative C–C cross-coupling is realized in water using H₂O₂ as a green and convenient oxidant, highlighting the potential of ligand interlocking in leveraging transition metal catalysis under challenging conditions.