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Communication

Hypoiodite-Catalyzed Oxidative Umpolung of Indoles for Enantioselective Dearomatization

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Cite This: J. Am. Chem. Soc. 2022, 144, 5756−5761
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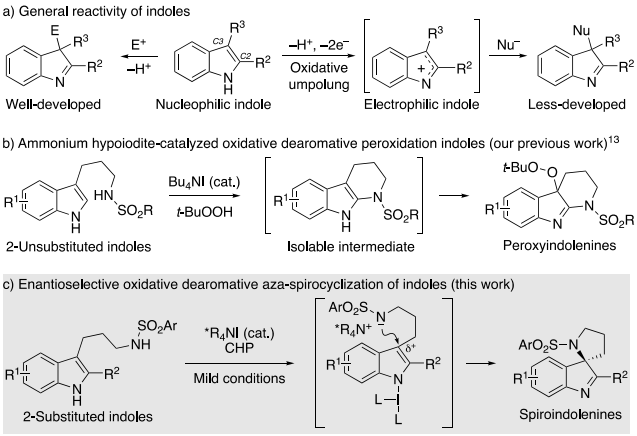
ABSTRACT: Here we report the oxidative umpolung of 2,3-disubstituted indoles toward enantioselective dearomative aza-spirocyclization to give the corresponding spiroindolenines using chiral quaternary ammonium hypoiodite catalysis. Mechanistic studies revealed the umpolung reactivity of C3 of indoles by iodination of the indole nitrogen atom. Moreover, the introduction of pyrazole as an electron-withdrawing auxiliary group at C2 suppressed a competitive dissociative racemic pathway, and enantioselective spirocyclization proceeded to give not only spiropyrrolidines but also four-membered spiroazetidines that are otherwise difficult to access.

Indole-derived alkaloids are the largest group of nitrogen-containing secondary metabolites.[1] Because of their wide range of biological and pharmacological activities, a tremendous amount of research has been devoted to the development of efficient methods for the synthesis of indole alkaloids in synthetic organic chemistry, especially for drug discovery.[1c,2] From this perspective, dearomatization of structurally planar indoles into enantioenriched three-dimensional indoline or indolenine structures has emerged as a powerful tool for the asymmetric synthesis of indole-derived alkaloids.[3] Because of the inherent nucleophilicity of indoles, especially at C3 due to enamine-like reactivity, dearomatization reactions often proceed by addition of electrophiles at C3 (Scheme 1a, left).[3c,d,4]

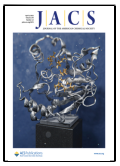
Conventionally, the incorporation of strong electron-withdrawing substituents[5b,6] or leaving groups[7] on the indole nucleus is often required for inversion of the polarity (umpolung)[8] of nucleophilic indoles to give electrophilic indoles. Recently, several asymmetric transformations of indole derivatives based on the C3 umpolung reactivity of 2-indolylmethanols have been achieved using chiral Brønsted acid catalysis.[7b−e] On the other hand, methods for direct umpolung without preactivation would open a new avenue for the dearomative functionalization of indoles (Scheme 1a, right).[5a] However, only a few examples of oxidative umpolung of indoles have been reported.[9−11] Recently, new methods, namely electro-[10] and photochemical[11] oxidation of indoles, have been developed. Enantioselective dearomative coupling of indoles has also been achieved in combination with chiral phosphate or phosphoric acid catalysts under photooxidation conditions. However, these methods have relied on the use of transition metal chromophores as photocatalyst as well as preoxidized nucleophiles such as nitroxyl radicals or hydroxylamine derivatives.[11a,b]

We recently reported the quaternary ammonium hypoiodite-catalyzed[12] oxidative C2-cyclization/peroxidation of homotryptamine derivatives (Scheme 1b).[13] We envisioned that the introduction of a substituent at C2 of homotryptamines might sterically suppress cyclization or 1,2-migration[14] at C2, allowing spirocyclization to proceed at C3 to form five-membered rings. Dearomative spirocyclization of homotryptamine derivatives to form aza-spiroindolenines has been reported.[15] However, preinstallation of an O-based leaving group on an electrophilic nitrogen tether[15a−c] or stoichiometric amounts of an organoiodine(III) as an oxidant[15d] were required. In addition, enantioselective dearomative aza-spirocyclization remains elusive. Here we report the oxidative umpolung of 2,3-disubstituted indoles toward enantioselective

Scheme 1. Oxidative Umpolung of Indoles for Dearomative Coupling Reactions



Received: February 17, 2022
Published: March 23, 2022

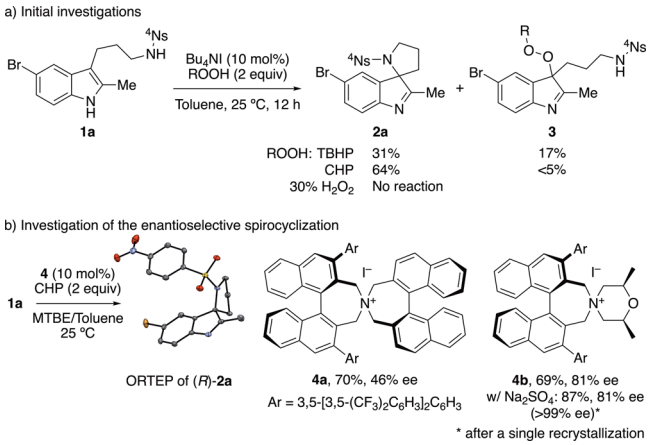


https://doi.org/10.1021/jacs.2c01852
J. Am. Chem. Soc. 2022, 144, 5756−5761

dearomatizative spirocyclization of not only homotryptamines but also tryptamines to afford the corresponding spiroindolenines using quaternary ammonium hypoiodite catalysis[12a,16] (Scheme 1c). Mechanistic studies revealed the umpolung reactivity of indole by iodination at N1.

We began our investigation by examining the oxidative spirocyclization of *C*2-methyl substituted homotryptamine derivative **1a** using *tert*-butyl hydroperoxide (TBHP) as an oxidant in the presence of 10 mol % *n*-tetrabutylammonium iodide (Bu_4NI) (Scheme 2a). Although the desired spiroindolenine **2a** was obtained in 31% yield, intermolecular coupling with TBHP also proceeded to give peroxyindolenine **3** as a byproduct. To suppress this side reaction, we used cumene hydroperoxide (CHP) as a more sterically hindered oxidant instead of TBHP, and to our delight, a cleaner reaction was observed to give **2a** in 67% yield.[17]

Scheme 2. Investigation of Reaction Conditions and Chiral Catalysts

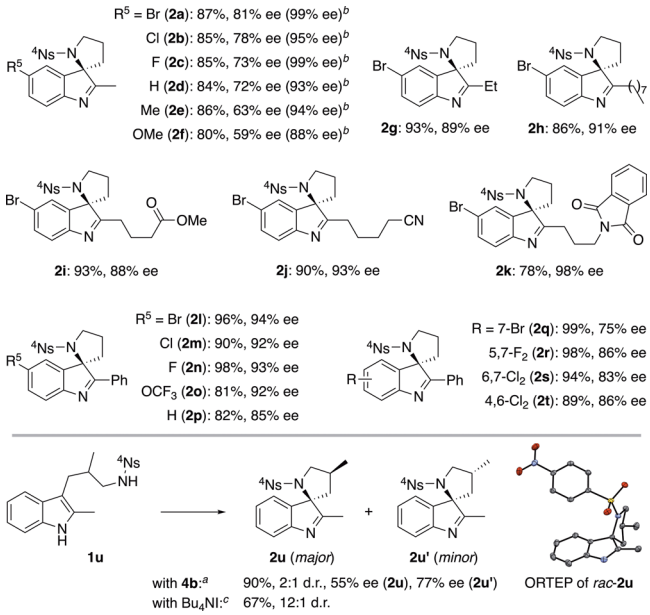


Next, we investigated enantioselective spirocyclization using bis(binaphthyl)-based chiral quaternary ammonium iodide **4a**, (Scheme 2b).[12a,16,18] After optimization of the reaction conditions (Table S1),[19] **2a** was obtained in 70% yield with 46% ee in a methyl *tert*-butyl ether (MTBE)/toluene mixed solvent. Toluene and MTBE were found to be effective as solvents to enhance the reactivity and enantioselectivity, respectively.

Since investigation of the substituents at the 3- and 3′-positions of bis(binaphthyl)ammonium cation **4** failed to improve the enantioselectivity, we explored the use of mono(binaphthyl)-based catalysts **4**[18] (Table S3). The use of morpholine-derived mono(binaphthyl)ammonium iodides improved the enantioselectivity, and the best result (81% ee) was obtained with *cis*-2,6-dimethylmorpholine-derived **4b** (Scheme 2b). To further improve the chemoselectivity, we used Na_2SO_4 as a desiccant to give **2a** in 87% yield with 81% ee (Table S4). The absolute stereochemistry of **2a** was assigned to be *R* by X-ray analysis of an enantiomerically pure sample that was obtained after a single recrystallization.

We examined the enantioselective dearomative aza-spirocyclization of several *N*-(4-nosyl)homotryptamines **1** under the optimized conditions (Scheme 3). 2-Methylindole derivatives **1a**−**f** bearing electron-donating or -withdrawing substituents at C5 gave the corresponding spiroindolenines **2a**−**f** in high yields with good to moderate enantioselectivities (59−81% ee). The optical purity of **2a**−**f** could be improved to 88−99% ee after a single recrystallization. Good to excellent enantioselectivities (75−98% ee) were achieved for the reaction of 2-alkyl (larger than methyl)- or 2-phenyl-substituted indoles bearing electron-withdrawing substituents (**1g**−**o**, **1q**−**t**) or no substituent (**1p**) on the indole nucleus. Interestingly, while the reaction of *rac*-**1u** using Bu_4NI gave high diastereoselectivity (12:1), the use of chiral catalyst **4b** afforded a 2:1 mixture of **2u** and **2u′** with higher enantioselectivity for the minor diastereomer **2u′**.

Scheme 3. Enantioselective Oxidative Aza-spirocyclization to Give Spiropyrrolidines 2 Under the Optimized Conditions[a]



[a]Reaction conditions: **4b** (10 mol %), CHP (2 equiv), Na_2SO_4, MTBE/toluene, 25 °C, 10−24 h. [b]After a single recrystallization. [c]Reaction conditions: Bu_4NI (10 mol %), CHP (2 equiv), toluene, 25 °C, 10 h.

Control experiments revealed that the ammonium hypoiodite species might be the catalytically active species for the oxidative dearomative spirocyclization of **1** and that a free radical pathway might be unlikely (Table S7).

To gain further insight into the reaction mechanism, we performed kinetic studies using the oxidative dearomatization of **1v**, a *p*-(trifluoromethyl)benzenesulfonyl-protected analogue of **1a**, as a model reaction (Figures S1−S4).[20] The reaction rate was found to have a zeroth-order dependence on the concentration of substrate **1v** and a first-order dependence on the concentrations of both CHP and **4b**. However, a difference in the initial reaction rates was observed depending on the substituent of **1**, suggesting that oxidation of a catalyst−substrate complex might be the rate-determining step.[21] To further evaluate the mechanism, we performed a Hammett analysis with a series of *N*-4-(trifluoromethyl)benzenesulfonyl homotryptamines **1v**−**y** and *N*-sulfonyl 5-bromohomotryptamines **1z**−**ab** to probe the electronic effects of the para substituents on the indole and sulfonamide nitrogens, respectively, on the reaction rate (Scheme 4a and Figures S5−S8). As a result, a linear correlation with a negative slope (ρ = −0.98) was observed from the corresponding plot of the σ_{para} constants versus $\log(k_R/k_H)$ for indole substituents (R^5). On the other hand, a poor correlation was observed from the

https://doi.org/10.1021/jacs.2c01852
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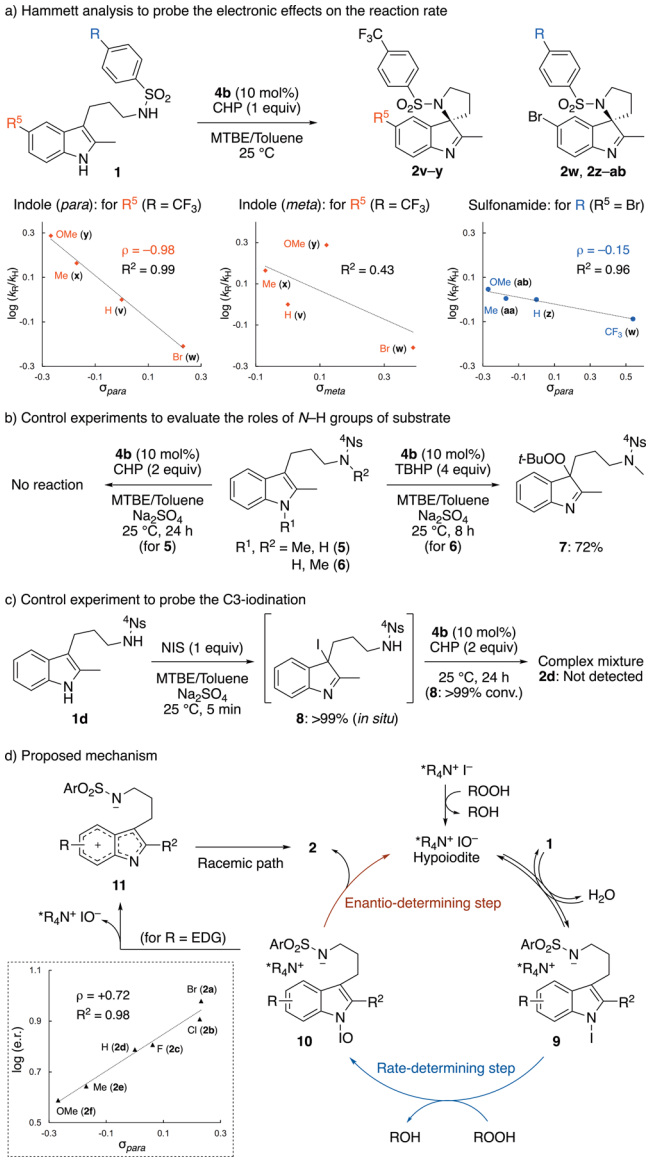
Scheme 4. Mechanistic Studies



corresponding plot of the σ_{meta} constants, suggesting the accumulation of positive charge on the indole nitrogen rather than C3 in the rate-determining transition state.[22,23] Although a linear correlation was also obtained for sulfonamide substituents (R), the reaction constant was much smaller (ρ = −0.15), suggesting that accumulation of positive charge on the sulfonamide nitrogen might be unlikely.

Next, to evaluate the roles of the *N*−H groups of the indole and sulfonamide units for the oxidation reactions, *N*-methylindole **5** and *N*-methylsulfonamide **6** were prepared and examined under the standard conditions (Scheme 4b). While most of the starting material was recovered from the reaction of **5**, the dearomatization of **6** proceeded smoothly to give peroxide adduct **7** in good yield. Consistent with the results of the Hammett analysis, these results indicated that umpolung of the indole moiety through the generation of an *N*−I indole intermediate might be crucial for the oxidative dearomatization reaction. On the other hand, the smooth reaction of **1d** using *N*-iodosuccinimide as a stoichiometric I^+ reagent under neutral conditions gave C3-iodine adduct **8** (Scheme 4c). C3 iodination was not observed under our catalytic conditions (Figure S9), and exposure of **8** to our conditions gave a complex mixture of several unidentified products; **2d** was not observed, suggesting that spirocyclization via iodination of indole C3 might be unlikely.

On the basis of these experimental results and previous works,[13a,16] a proposed catalytic reaction mechanism is depicted in Scheme 4d. Ammonium hypoiodite could be generated in situ as an active species from the oxidation of ammonium iodide with an oxidant. *N*-Iodo intermediate **9** might be produced by a reversible reaction of hypoiodite with the indole *N*−H directly or by iodination of the sulfonamide *N*−H followed by intramolecular iodo transfer.[24] To enhance the electrophilicity[21] of indole, *N*-iodine(III) intermediate **10** might be generated by rate-determining oxidation of **9**. The accumulation of positive charge on the indole nitrogen in the rate-determining transition state with the generation of a highly electron-deficient iodine(III) species is also in agreement with the results of the Hammett analysis. Finally, reductive elimination of ammonium hypoiodite might proceed via intramolecular capture of highly electrophilic intermediate **10** by the chiral ammonium sulfonamide as the enantiodetermining step to give aza-spiroindolenine **2**.

Given the high nucleofugality of hypervalent iodines,[25] we considered that zwitterionic intermediate **11** might be generated by the competitive dissociation of ammonium hypoiodite prior to spirocyclization,[26] which would render asymmetric induction difficult (Scheme 4d). A dissociative racemic pathway might preferentially proceed for the oxidation of electron-rich indoles (e. g., **1e** and **1f**) as a result of stabilization of cationic intermediate **11** by electron-donating substituents to give moderate enantioselectivity (Scheme 3). In addition, plotting log(e.r.)[27] of products **2a**−**f** against the corresponding σ_{para} constants gave a linear correlation with a positive slope (Scheme 4d, inset), which might also support the existence of a dissociative pathway during umpolung of indole.

We envisioned that the introduction of an electron-deficient substituent at C2 might suppress the dissociative pathway by destabilization of cationic intermediate **11**. In addition, an electron-deficient group at C2 would further reduce the LUMO energy at C3, which might enhance the rate of the spirocyclization step and further improve the chemoselectivity. Moreover, if an electron-deficient auxiliary could be used as a leaving group, the synthetic utility of the products would be enhanced. With these assumptions in mind, we focused on pyrazole as an electron-deficient auxiliary because it can be easily introduced[28] and removed via nucleophilic acyl substitution.[29] To our delight, spiroindolenines **2ac**−**ae** were obtained after smooth reaction of the corresponding 2-pyrazol-1-ylhomotryptamine derivatives **1ac**−**ae** (Scheme 5a). Most importantly, in sharp contrast to those for 2-methylindole analogues **2a**, **2d**, and **2f**, good enantioselectivities (81−86% ee) were achieved regardless of the electron-donating or -withdrawing substituents at C5. A gram-scale oxidation of **1ac** was also achieved with the use of 5 mol % **4b** to give **2ac** in enantiomerically pure form after recrystallization. In addition, an additive robustness screen analysis[30] revealed that a wide range of functional groups were tolerated under our mild conditions, including carbonyls, amines, alkyne, and heteroarenes (Table S5).

In sharp contrast to previous methods,[31] with the introduction of a pyrazole auxiliary at C2, site-selective spirocyclization of 2-pyrazol-1-yltryptamine **12** at C3 pro-

https://doi.org/10.1021/jacs.2c01852
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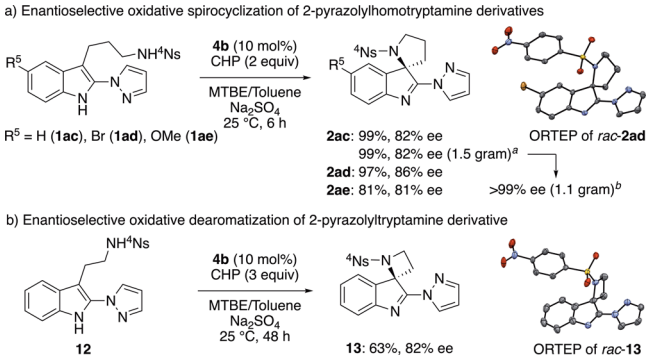
Scheme 5. Harnessing an Electrophilic Indole by Introducing a Pyrazolyl Auxiliary

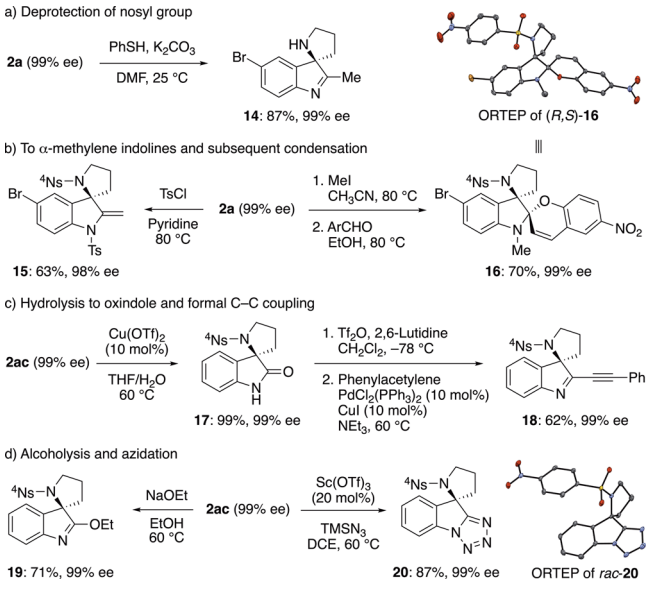


[a]**4b** (5 mol %). [b]After a single recrystallization.

ceeded to give the difficult-to-access four-membered spiroazetidine **13** with good enantioselectivity (Scheme 5b).[32]

Finally, we demonstrated the synthetic utility of enantioenriched spiroindolenines **2** (Scheme 6). First, the 4-nosyl group

Scheme 6. Transformations



of **2a** could be easily removed under standard deprotection conditions to give free amine **14** (Scheme 6a).[19] Deprotonation of **2a** triggered by N-tosylation gave 2-methyleneindoline **15** in good yield (Scheme 6b, left). Similarly, N-methylation of **2a** followed by condensation with salicylaldehyde afforded spiropyran **16**, a structure that is commonly found in photochromic compounds[33] (Scheme 6b, right). On the other hand, the pyrazole auxiliary of **2ac** could be easily removed by Lewis acid-catalyzed hydrolysis to give oxindole **17** quantitatively (Scheme 6c).[34] Formal nucleophilic substitution of pyrazole **2ac** with a carbon nucleophile was accomplished by triflation of **17** followed by a Sonogashira coupling reaction to give 2-alkynylspiroindoline **18**. In addition, ethanolysis[13a] of pyrazole **2ac** proceeded smoothly to give imino ester **19** in good yield (Scheme 6d, left). Moreover, we found that scandium-catalyzed nucleophilic substitution of pyrazole **2ac** by trimethylsilyl azide followed by intramolecular click cyclization gave tetrazoloindole **20** as a unique structure, which was confirmed by X-ray analysis (Scheme 6d, right). No loss of enantioselectivity was observed in any of these transformations.

In summary, we have developed an oxidative umpolung strategy for the chiral ammonium hypoiodite-catalyzed enantioselective dearomative aza-spirocyclization of homotryptamine derivatives to give the corresponding aza-spiroindolenines with good to excellent enantioselectivity. Mechanistic studies revealed the unusual umpolung reactivity at C3 of indoles by N1 iodination. Moreover, by the introduction of pyrazole as an electron-deficient auxiliary at C2, site-selective spirocyclization of a tryptamine derivative was also achieved to give the difficult-to-access spiroazetidine in an enantioselective manner. Furthermore, to demonstrate the synthetic utility of our dearomative spirocyclization, 2-alkyl- and 2-pyrazole-substituted spiroindolenines were readily converted to various useful and unique structures. These results demonstrate the high potential of hypoiodite catalysis for oxidative umpolung of indoles toward the synthesis of polycyclic indole-derived alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c01852.

Additional information, synthesis procedures, and spectral data (PDF)

Accession Codes

CCDC 2143581, 2143588−2143591, and 2159841 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this project was partially provided by JSPS KAKENHI (20K20559 to K.I., 21H01932 to M.U., and 18H01973 to M.U.), the Society of Iodine Science (to M.U.), and the Nagoya University Graduate Program of Trans-

formative Chem-Bio Research (GTR). This work is partially supported by Nagoya University Research Fund.

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https://doi.org/10.1021/jacs.2c01852
J. Am. Chem. Soc. 2022, 144, 5756−5761