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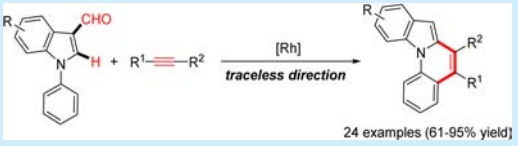
Aldehyde as a Traceless Directing Group for Rh(III)-Catalyzed C−H Activation: A Facile Access to Diverse Indolo[1,2-*a*]quinolines

Xingyan Liu,[†] Xiaoyu Li,[†] Hu Liu,[†] Qiang Guo,[†] Jingbo Lan,*[,†] Ruilin Wang,[‡] and Jingsong You*[,†]

[†]Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, and State Key Laboratory of Biotherapy, West China Medical School, and [‡]College of Materials Science and Engineering, Sichuan University, 29 Wangjiang Road, Chengdu 610064, China

Supporting Information

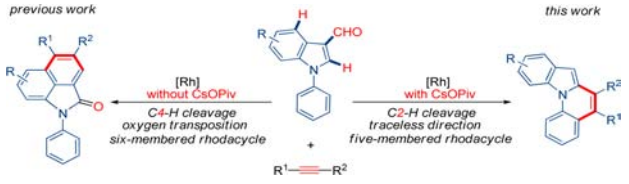
ABSTRACT: The aldehyde group has been developed for the first time as a traceless directing group to promote regioselective Rh(III)-catalyzed C−H activation/cyclization of indolyl aldehydes with alkynes. This protocol streamlines access to a variety of appealing indolo[1,2-*a*]quinoline structures. As illustrative examples, a concise three-step synthesis of indolo[1,2-*a*]quinoline-based sensitizers is accomplished that exhibits the potential of C−H activation in the construction of organic optoelectronic materials.



Transition-metal-catalyzed C−H bond activation has emerged as an increasingly important synthetic approach for construction of carbon−carbon and carbon−heteroatom bonds.[1] The use of chelation-assisted strategy enables wide substrate scope, good regioselectivity, structural diversity of products, and application to total synthesis.[2] The traceless directing C−H activation strategy, in which the C−H bond functionalization of substrate and the removal of directing group can be operated in one pot, not only avoids extra steps to remove the undesired directing group from products but also offers unusual regioselectivity of transformations such as a formal *meta*-selectivity of direct C−H arylation and thus has emerged as a greatly appealing synthetic protocol in the construction of organic functional molecules and natural products.[3−5] However, the functional groups that can be employed as the traceless directing groups remain relatively rare.[3] Due to the easy occurrence of decarboxylation under transition-metal-mediated conditions, the carboxylic acid has been developed as a traceless directing group for various decarboxylative C−H functionalizations.[4] In addition, *N*-oxide, silanol, and (pinacolato)boron (Bpin) have also been employed as traceless directing groups to promote direct C−H olefination and borylation of arenes.[5] Although the aldehyde group is removable under suitable reaction conditions,[6] transition-metal-catalyzed C−H activation reactions by utilizing the aldehyde group as a traceless directing group still remain unprecedented.

Aldehydes are prevalent in natural and synthetic products and are also versatile synthetic building blocks. However, the aldehyde group is rarely used as the directing group for transition-metal-catalyzed C−H functionalization reactions due to its weak coordinative affinity and facile oxidation under strongly oxidizing conditions.[7] Recently, we have disclosed Rh(III)-catalyzed aldehyde-directed regioselective C4−H activation/cyclization of indolyl aldehydes with alkynes to forge benzo-fused oxindoles through a probable six-membered metallocyclic intermediate.[8] During the mechanistic investigation process, we unexpectedly obtained indolo[1,2-*a*]quinoline derivatives as the products of C2−H activation/cyclization of indolyl aldehydes with alkynes. Notably, cesium pivalate (CsOPiv) is a critical additive in the control of selective activation between C2−H and C4−H of indoles (Scheme 1).

Scheme 1. Rh(III)-Catalyzed Aldehyde-Assisted Site-Selective (Hetero)aromatic C−H Activation/Cyclization



The aldehyde group herein could act as a traceless directing group to promote Rh(III)-catalyzed *ortho*-C−H activation through a possible five-membered rhodacycle intermediate. To the best of our knowledge, the aldehyde group has not been disclosed as a traceless directing group for C−H activation reactions.

Indolo[1,2-*a*]quinoline derivatives are a class of privileged polycyclic heteroaromatic scaffolds frequently found in bioactive natural products, pharmaceuticals, and organic functional materials (Scheme 2).[9] The development of a new, efficient method to streamline the synthesis of these scaffolds is highly desirable.[10] Herein, we report the construction of diverse indolo[1,2-*a*]quinolines through a Rh(III)-catalyzed C−H activation/cyclization of indolyl aldehydes with alkynes by taking advantage of the aldehyde group as a traceless directing group.

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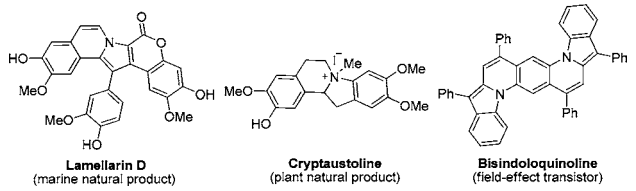
Scheme 2. Selected Natural Products and Organic Functional Molecules



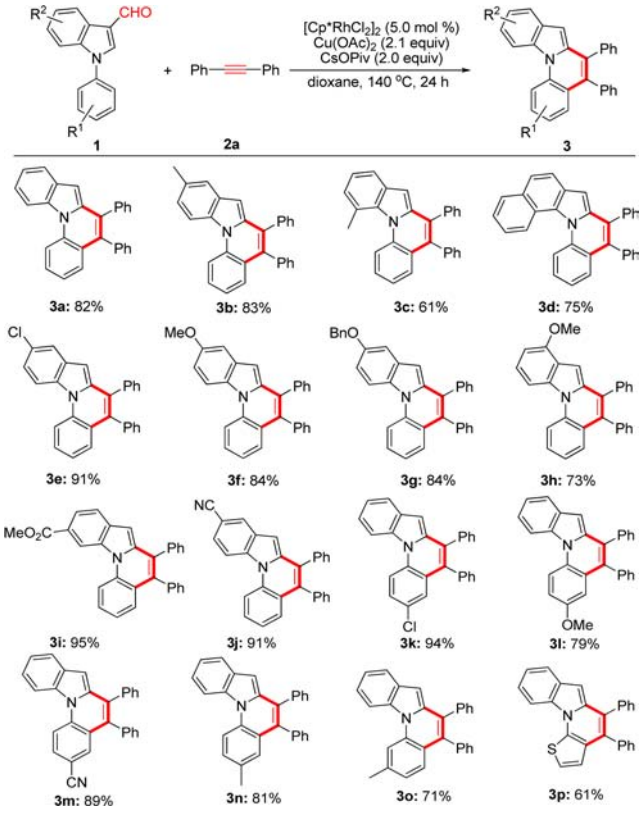
In an initial attempt, the C2−H activation product **3a** was formed in 26% yield when 1-phenyl-1*H*-indole-3-carbaldehyde (**1a**) reacted with 1,2-diphenylacetylene (**2a**) in the presence of $[Cp^*RhCl_2]_2$ (Cp* = pentamethyl cyclopentadienyl, 5.0 mol %)/$AgSbF_6$ (20 mol %) as catalyst, Ag_2CO_3 (2.1 equiv) as oxidant, and CsOPiv (2.0 equiv) as additive in toluene (2 mL) at 120 °C under N_2 for 24 h (Table S1, entry 1). The structure of **3a** was confirmed by ^1H and ^{13}C NMR spectra, mass spectrometry data, and single-crystal X-ray diffraction analysis (Figure S3). In the absence of CsOPiv, benzo-fused oxindole as the C4−H activation product of indolyl aldehyde was obtained.[8] Further optimization demonstrated that the reaction could also occur in a slightly better yield without $AgSbF_6$ (Table S1, entry 2). Other additives such as CsF, Cs_2CO_3, and CsOAc were found to be less effective than CsOPiv (Table S1, entries 6−8). After screening a variety of oxidants, $Cu(OAc)_2$ turned out to be more effective than others (Table S1, entries 9−11). The yield was improved to 68% when the temperature was raised to 140 °C (Table S1, entry 12). Among the solvents investigated, dioxane was the best choice, affording **3a** in 82% yield (Table S1, entry 14). Decreasing the catalyst loading would lead to a lower yield of **3a** (Table S1, entry 17). Overall, the optimized conditions consisted of $[Cp^*RhCl_2]_2$ (5.0 mol %), $Cu(OAc)_2$ (2.1 equiv), and CsOPiv (2.0 equiv) in dioxane at 140 °C under N_2 for 24 h.

With the optimized conditions in hand, we next examined the scope of indolyl aldehyde substrates. As depicted in Scheme 3, a series of indolyl aldehydes reacted smoothly with 1,2-diphenylacetylene to give the corresponding products in good to excellent yields. Indolyl aldehydes with both electron-withdrawing and electron-donating groups were suitable substrates for this transformation. Various functional groups such as alkoxy, cyano, and ester on both the fused phenyl and *N*-aryl of indole were well tolerated (**3e−m**). However, the more reactive bromo, iodo, aldehyde, and alcohol functionalities were incompatible with the current catalytic system. In addition, indole aldehyde bearing a *N*-heteroaromatic substituent could also react with diphenylacetylene to give the desired product **3p** in 61% yield.

Next, the scope of the annulation reaction was further extended to various substituted acetylenes (Scheme 4). It was found that diverse diarylacetylenes with functional groups such as fluoro, chloro, and alkoxy smoothly gave 5,6-diarylindolo-[1,2-*a*]quinolines in good yields (**4c−e**). Gratifyingly, dialkylalkynes could enable the desired reaction in good to excellent yields (**4f,g**). The unsymmetrical alkyne could also go through the current transformation in a good yield but with a low regioselectivity (**4h**).

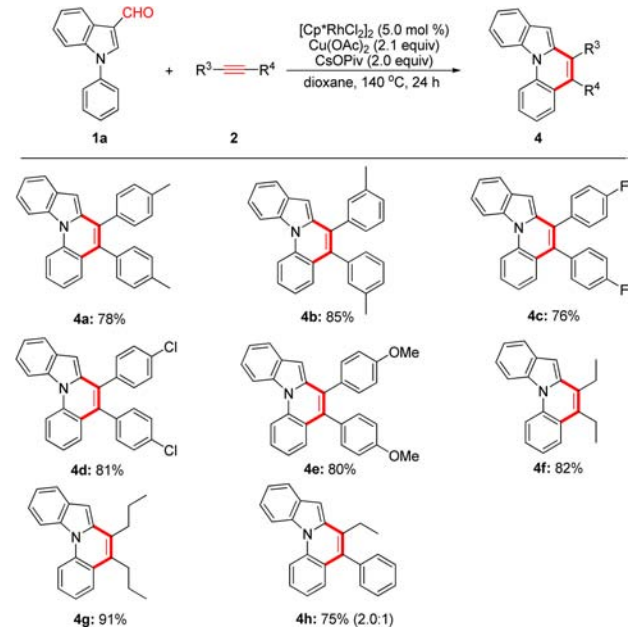
Although the product **3a** was obtained in 59% yield with 1-phenyl-1*H*-indole-3-carboxylic acid as the starting material, 1-phenyl-1*H*-indole-3-carboxylic acid was not detected with 1-phenyl-1*H*-indole-3-carbaldehyde as the starting material in the current catalyst system, and only a trace amount of 1-phenyl-

Scheme 3. Scope of Indole 3-Aldehydes[a]



[a]Reactions were performed in the presence of indole 3-aldehyde **1** (0.375 mmol), alkyne **2a** (0.25 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), $Cu(OAc)_2$ (2.1 equiv), CsOPiv (2.0 equiv), and dioxane (2.0 mL) at 140 °C for 24 h.

Scheme 4. Scope for Alkynes[a]



[a]Reactions were performed in the presence of indole 3-aldehyde **1a** (0.375 mmol), alkyne **2** (0.25 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), $Cu(OAc)_2$ (2.1 equiv), CsOPiv (2.0 equiv), and dioxane (2.0 mL) at 140 °C for 24 h.

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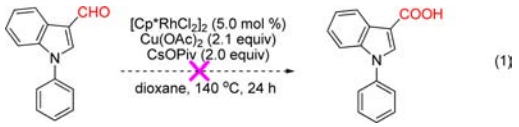
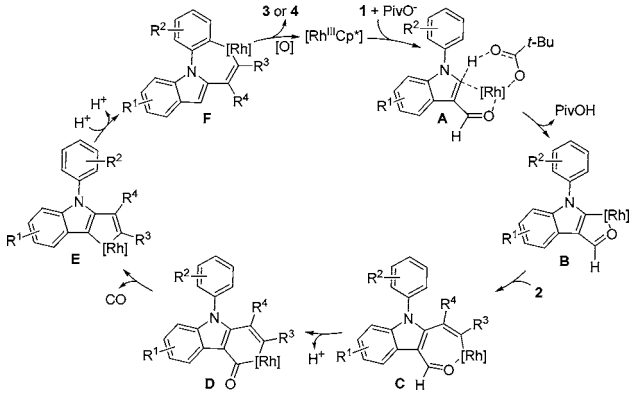
1*H*-indole was observed. Furthermore, the indolecarboxylic acid was not yet detected in the absence of alkynes except for the recovery of indole 3-aldehyde (eq 1). Thus, we speculated



(1)

that the annulation reaction could undergo a decarbonylative process. In addition, a small amount of C3-deuterated product was observed with the deuterated aldehyde (CDO) as a substrate. The parallel reactions were performed by using indole 3-aldehyde and 2-deuterioindole 3-aldehyde under the optimized conditions. A primary kinetic isotopic effect (KIE) of 1.13 was observed, which revealed that the C2−H bond cleavage of indole might not be involved in the rate-determining step.[14] Accordingly, a plausible mechanism for annulation is depicted in Scheme 5. First, the coordination of

Scheme 5. Plausible Catalytic Cycle

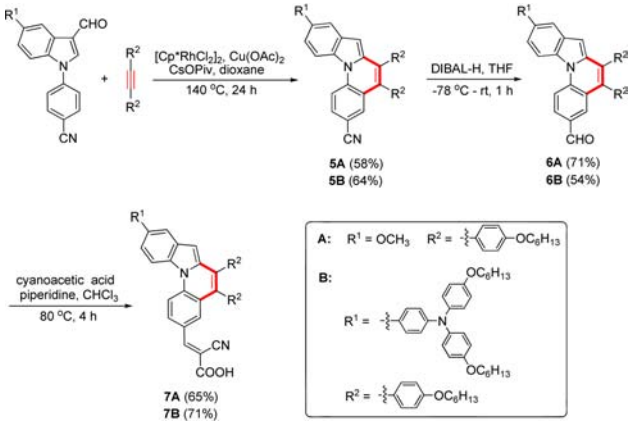


the carbonyl oxygen atom to Rh(III) and sequential pivalate-assisted C2−H bond activation form a five-membered rhodacycle **B**.[11,12] Insertion of alkyne to the Rh−C bond generates a seven-membered rhodacycle **C**. Cleavage of the aldehyde C−H bond and subsequent rearrangement generate a six-membered rhodacycle **D**.[13] The decarbonylation next occurs to reproduce a five-membered rhodacycle **E**.[6] Subsequent protonolysis of the Rh−C bond of indole and recyclorhodation with the phenyl ring afford a seven-membered rhodacycle **F**, which undergoes reductive elimination to afford the final product and regenerate the active Rh(III) species.

Considering that the indolo[1,2-*a*]quinoline skeleton has multiple substitution sites and an electron-rich π-system similar to ullazine,[15] we conceived that indolo[1,2-*a*]quinoline would be a good candidate for the construction of π-conjugated materials for dye-sensitized solar cells (DSSCs). To elucidate the usefulness of the method further, the concise synthesis of indolo[1,2-*a*]quinoline-based sensitizers **7A** and **7B** was performed by the sequential Rh(III)-catalyzed C−H activation/cyclization of indolyl aldehyde with alkyne, reduction of cyano, and Knoevenagel condensation with cyanoacetic acid (Scheme 6).

UV−vis absorption spectra of **7A** and **7B** in CH_2Cl_2 solution and on TiO_2 film exhibit broad absorption bands in the range of 300−550 nm (Figure S2). The molar extinction coefficients of both **7A** and **7B** in CH_2Cl_2 solution are quite high, exceeding 4.0×10^4 M^{-1} cm^{-1}, which suggests a good absorbance of

Scheme 6. Synthesis of Indolo[1,2-*a*]quinoline-Based Sensitizers



sunlight. The ground oxidation potentials of **7A** (E_{ox} = 0.94 V vs NHE) and **7B** (E_{ox} = 0.79 V vs NHE), estimated from cyclic voltammograms (CV), are more positive than the iodine/iodide redox potential value (0.42 V vs NHE), and the excited-state oxidation potentials of **7A** (E^*_{ox} = −1.33 V vs NHE) and **7B** (E^*_{ox} = −1.46 V vs NHE) are sufficiently negative in comparison with the conduction band energy level of TiO_2 (−0.5 V vs NHE) (Figure S1 and Table S2). The incident photon-to-current conversion efficiencies (IPCEs) of the DSSC devices based on **7A** and **7B** display a broad band in the region of 300−600 nm (Figure S2). Under simulated AM 1.5G irradiation, the photocurrent−voltage (*J*−*V*) plots exhibit an overall conversion efficiency (η) of 5.8% for the **7B**-based DSSC (J_{sc} = 11.64 mA cm^{-2}, V_{oc} = 0.765 V, and FF = 0.650) and 4.6% for the **7A**-based DSSC (J_{sc} = 9.51 mA cm^{-2}, V_{oc} = 0.717 V, and FF = 0.676), respectively (Figure S2 and Table S3), suggesting indolo[1,2-*a*]quinolines may be ideal π-conjugated skeletons for applications in DSSCs.

In summary, we have developed a regioselective Rh(III)-catalyzed C−H activation/cyclization of indolyl aldehydes with alkynes via the aldehyde group as a traceless directing group to construct diverse indolo[1,2-*a*]quinolines. This protocol is compatible with various functional groups such as fluoro, chloro, alkoxy, cyano, and ester, which are very useful for further synthetic transformations. To elucidate the usefulness of the method developed herein, a concise three-step synthesis of indolo[1,2-*a*]quinoline-based sensitizers is accomplished. The highly efficient path to polycyclic heteroaromatic scaffolds described here shows the potential of C−H activation in the construction of organic optoelectronic materials.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, X-ray crystal structure (CIF) of **3a** (CCDC 1055155), and copies of NMR. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01171.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: jsyou@scu.edu.cn.
*E-mail: jingbolan@scu.edu.cn.

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Notes

The authors declare no competing financial interest.

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