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Introduction

Installing directing groups (DGs) is a versatile and reliable strategy for selective C-H functionalization.¹ Generally, directing groups are installed onto aromatic rings or other systems to ensure reactivity and regioselectivity by their coordination with metal and they are structurally left unchanged after the corresponding reactions (eqn (a-1) in Scheme 1).¹ In some cases, directing groups could also serve as internal oxidants or participate in the reaction directly to generate cyclic^{2,3} and acyclic⁴ compounds (eqn (a-2) and (a-3) in Scheme 1). With continuous interest on C-H functionalization with allenes,^{5,6} we wish to report here the first example of dual functions of the directing group in the rhodium(m)-catalyzed C-H functionalization of indoles with 4-aryl-2,3-allenyl carbonates generating unexpected thermodynamically unstable 2-(1(*Z*)-aryl-1,3-dienyl) indoles dictated by the aryl group and the directing group *via* π – π stacking (Scheme 1b).

Results and discussion

After some trial and error, it was observed that the $[Cp*RhCl_2]_2$ catalyzed reaction of indole **1a** and 4-phenyl-2,3-allenyl carbonate **2a**⁷ in the presence of AgSbF₆ and PivOH produced 2-(1(*Z*),3-

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Stereoselective rhodium-catalyzed 2-C–H 1,3dienylation of indoles: dual functions of the directing group†

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A rhodium-catalyzed intermolecular highly stereoselective 1,3-dienylation at the 2-position of indoles with nonterminal allenyl carbonates has been developed by using 2-pyrimidinyl or pyridinyl as the directing group. The reaction tolerates many functional groups affording the products in decent yields under mild conditions. In addition to C-H bond activation, the directing group also played a vital role in the determination of *Z*stereoselectivity for the C-H functionalization reaction with 4-aryl-2,3-allenyl carbonates, which is confirmed by the *E*-selectivity observed with 4-alkyl-2,3-allenyl carbonates. DFT calculations have been conducted to reveal that $\pi - \pi$ stacking involving the directing 2-pyrimidinyl or pyridinyl group is the origin of the observed stereoselectivity. Various synthetic transformations have also been demonstrated.

> dienyl)indole **3aa** in toluene at room temperature in 80% yield with an unexpected Z-selectivity of 96 : 4 (Table 1, entry 1), which is very different from what was observed by Shi and his coworkers with alkylidenecyclopropanes affording a 1 : 1 E/Z mixture of 1,3-dienes.^{8a} The reaction in dioxane afforded the product in a much lower yield (Table 1, entry 2) while no expected product was formed in CH₃CN with 75% recovery of **1a** (Table 1, entry 3). When AgBF₄ was used instead of AgSbF₆, the reaction was much slower (Table 1, entry 4). The control experiment showed that no product was generated in the absence of AgSbF₆ (Table 1, entry 5).



 $\label{eq:scheme1} \begin{array}{l} \mbox{Scheme 1} & \mbox{Novel function of directing groups in C-H functionalization reactions.} \end{array}$



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[†] Electronic supplementary information (ESI) available: Experimental procedures and characterization of all new compounds, DFT calculations, NMR spectra of substrates and products. CCDC [2014026]. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc02167b

Table 1 Optimization of reaction conditions for the reaction of 1a with $2a^{a}$



Entry	Variation from the standard conditions	NMR recovery of $1a^{b}$ (%)	NMR yield of 3aa ^b (%)	<i>Z</i> / <i>E</i> of 3aa ^{<i>c</i>}
1	None	_	80	96/4
2	Dioxane as solvent	_	62	96/4
3	CH ₃ CN as solvent	75	_	_
4	$AgBF_4$ replacing $AgSbF_6$	60	20	96/4
5	No [Ag]	78	_	—

^a The reactions were carried out using 0.2 mmol of 1a, 1.1 equiv. of 2a, 2.5 mol% of [Cp*RhCl₂]₂, 30 mol% of [Ag], and 1 equiv. of PivOH in 1 mL of solvent at room temperature. ^b Determined by ¹H NMR analysis using CH_3NO_2 as an internal standard. ^c The ratio of Z/E was determined by ¹H NMR analysis of the crude reaction mixture before chromatographic separation.

With the optimized reaction conditions in hand, we set out to examine the scope of the reaction (Table 2). Firstly, differently substituted 4-aryl-2,3-allenyl carbonates were applied with 1-(2-pyrimidinyl)indole 1a. Allenes with the 4-phenyl groups substituted with electron-donating (4-Me (3ab) and 4-MeO (3ac)) and electronwithdrawing synthetically versatile groups (4 F-, 4-Cl-, 4-Br-, 4-I-, 4-CN- and 4-CF₃-) (3ad-3ai) could react smoothly. 4-Naphthyl-2,3butadienyl carbonate also underwent the reaction although it should be conducted at 70 °C (3aj). The scope of indoles was demonstrated using 4-(p-bromophenyl)-2,3-butadienyl carbonate 2f: 5-Me, 5-MeO, 5-BnO, 5-Cl, 4-CO₂Me and 7-CHO could be tolerated, affording the corresponding 1,3-dienylation products 3bf-3gf in decent yields and an excellent stereoselectivity. The stereoselectivity of this reaction was further established by the X-ray diffraction study of compound 3cf. The functional groups highlighted in blue proved that this methodology tolerates many reactive functionalities and, thus, is very powerful for the syntheses of other indole derivatives. To further demonstrate the synthetic and medicinal potential of the reaction, allenyl carbonates derived from natural products or drug molecules were prepared via the ATA reaction of the corresponding aldehydes:7 Under standard conditions, a range of such allenyl carbonates derivatized from (L)-(-)-borneol (4) and adapalene (6) could be effectively applied affording the related products with an excellent stereoselectivity (3ak-3al).

In addition to primary 4-aryl-2,3-butadienyl carbonates, secondary 4-aryl-2,3-butadienyl carbonate 2m was also tested, affording 2-(1(Z),3(E)-dienyl) indole 3am with a Z-selectivity of 99 : 1 for the remaining double bond and complete E-selectivity for the newly formed double bond, respectively (eqn (1)).



In order to clarify the role of directing groups, some control experiments were carried out (Table 3). When the 2-pyrimidinyl group was replaced with Me (1h), no product was generated under standard conditions (Table 3, entry 1). Furthermore, directing groups such as Piv (1i)^{9a} and t-Bu₂P (1j)^{9b} failed to afford the corresponding products (Table 3, entries 2 and 3). When this directing group was replaced with the pyridinyl group (1k), the reaction still worked, indicating the importance of the nitrogen-containing directing group (Table 3, entry 4). On the other hand, in order to figure out the reason for the observed poor stereoselectivity of compound 3ah, some control experiments were also conducted. The Z/E-selectivity of 3ah remained almost unchanged regardless of lowering the reaction temperature, shortening the reaction time, or running the reaction in the absence of light (Table 3, entries 5-7). In addition, when compound **3ah** with a Z/E ratio of 98/2 obtained by preparative HPLC was treated under the standard condition at 70 °C, the ratio of Z/E slightly decreased (eqn (2)). These experimental results could rule out the possibility of isomerization from Z-3ah to E-3ah. The reason for the relatively lower stereoselectivity of 3ah remained unclear.



DFT calculations have been performed to investigate the mechanism of this rhodium-catalyzed 1,3-dienylation of indoles. Fig. 1 presents the energetic profile for the most favorable pathway of the reaction of indole 1a and 4-phenyl-2,3allenyl carbonate 2a. The pivalate-ligated species Cp*Rh(OPiv)₂ is generally regarded as the active catalyst, which may be generated via Rh dimer dissociation and ligand exchange starting from [Cp*RhCl₂]₂ and PivOH.^{2k} Cp*Rh(OPiv)₂ firstly dissociates one pivalate ligand and coordinates with the N atom of the pyrimidine moiety in 1a, resulting in the formation of the complex INT1, which is selected as the free energy reference. Subsequent indole 2-position C-H activation is realized via

 Table 2
 Reaction scope^a



^{*a*} The reactions were carried out using 1 mmol of **1**, 1.1 equiv. of **2**, 2.5 mol% of $[Cp*RhCl_2]_2$, 30 mol% of $AgSbF_6$, and 1 equiv. of PivOH in 5 mL of toluene at room temperature. Yields of isolated products were given. The ratio of Z/E was determined by ¹H NMR analysis. ^{*b*} The reaction was carried out at 70 °C. ^{*c*} The reaction was carried out on a 4 mmol scale. ^{*d*} The reaction was carried out on a 0.2 mmol scale. ^{*e*} The reaction was carried out on a 0.4 mmol scale.

a six-membered cyclic transition state TS1, in which the resting pivalate ligand acts as the base to deprotonate the ortho aromatic proton to form the Rh-C bond simultaneously. This concerted metalation-deprotonation (CMD)^{10,11} process requires an energy barrier of 10.2 kcal mol^{-1} to afford the five-membered rhodacycle INT2. Subsequently, the dissociation of the PivOH molecule from the Rh(III) center and the coordination of the allene moiety of 2a provides INT3. Then the coordinated allenic C=C double bond connected with the aryl group in 2a undergoes an insertion into the Rh-C bond via TS2_a to provide the π -allyl Rh(m) complex INT4, which may easily isomerize to the η^1 -allyl Rh(III) complex **INT5** with the help of the coordination of the carbonate carbonyl group. This cyclic carborhodation step is computed to be exergonic (ΔG_{sol} = -10.5 kcal mol⁻¹) requiring an activation barrier of 14.6 kcal mol⁻¹ (**TS2**, Fig. 1). Subsequent β -oxygen elimination

of **INT5** needs to overcome an energy barrier of 12.8 kcal mol⁻¹ (**TS3**), providing the final product and regenerating the Rh(m) catalyst. Overall, the current reaction is found to occur irreversibly, as the energy of the final product **INT6** is about 20 kcal mol⁻¹ below the energy of the starting materials, and the carborhodation step is not only the rate-limiting but also the selectivity-determining step.

The stereoselectivity of the reaction of indole 1a with 4-phenyl-2,3-allenyl carbonate 2a was further explored by DFT calculations. Due to the possibility of the participation of both C=C bonds of allenyl carbonates 2a, there are totally eight competing transition states referring to the stereoselectivity of the carborhodation step (TS2_a-d and TS2_a'-d' Fig. 2). Nevertheless, in order to avoid the severe steric interactions, the Rh–C bond would prefer to approach from the opposite side of the larger substituents (the methyl carbonate or the phenyl group) and, thus, TS2_a/TS2_b



^{*a*} The reactions were carried out using 0.2 mmol of **1**, 1.1 equiv. of **2**, 2.5 mol% of $[Cp*RhCl_2]_2$, 30 mol% of $AgSbF_6$, and 1 equiv. of PivOH in 1 mL of toluene at room temperature. ^{*b*} Determined by ¹H NMR analysis using CH₃NO₂ as an internal standard. ^{*c*} 0.5 mmol scale. ^{*d*} Isolated yield. ^{*e*} The ratio of *Z/E* was determined by ¹H NMR analysis. ^{*f*} At 50 °C. ^{*g*} 1 mmol scale for 7 h. ^{*h*} At 70 °C. ^{*i*} The reaction was run in the absence of light.



Fig. 1 Free energy profile (kcal mol⁻¹) for the most favorable pathway of the reaction of indole **1a** with 4-phenyl-2,3-allenyl carbonate **2a**. Bond lengths are given in angstroms.

referring to the upper-face insertion of the $C^2=C^3$ bond and TS2_c/TS2_d referring to the front-face insertion of the $C^1==C^2$ bond are relatively more favorable. Due to the steric hinderace, the other four transition structures (TS2_a'-d') are all disfavorable. TS2_a, which leads to the formation of the *Z*-isomer, was found to be the most stable, thus, accounting for the domination of the *Z* products in the reaction with 4-aryl-2,3-allenyl carbonates. TS2_a and TS2_b associated with the upper-face insertion of the Rh–C bond into the phenyl substituted $C^2=C^3$ bond are more favorable than the other two (TS2_c/TS2_d). Meanwhile, the intramolecular hydrogen bond, formed between

the carbonyl oxygen with the sp^2 hydrogen stabilized both structures of TS2_a and TS2_b. The π - π stacking interaction between the phenyl substituent of 2a with the pyrimidine group further increases the stability of TS2_a, which is also proven by the noncovalent interaction (NCI) analysis (performed by Multiwfn12 and VMD¹³ software). However, the structure of TS2_b suffers from unfavorable steric repulsions between the phenyl group and Cp* ligand and also between the methyl carbonate and the indole group. Thus, both factors account for the preference of TS2_a over TS2_b by 4.1 kcal mol⁻¹. Furthermore, no hydrogen bonds exist in TS2_c and TS2_d associated with the front-face insertion of the Rh-C bond into the $C^1 = C^2$ bond. Without the hydrogen bond and the obvious hindrance, TS2_c presents similar stability to **TS2** b (18.7 and 18.9 kcal mol^{-1}). However, severe steric interactions between the methyl carbonate and the Cp* ligand destabilize **TS2 d**, making it even more unfavorable (6.5 kcal mol^{-1} higher than that of TS2_a). Therefore, not only the steric effect but also the π - π stacking interaction are operative in the control of the Z-stereoselectivity.

A further question is how about the selectivity of the 4-alkyl-2,3-allenyl carbonates without the π - π stacking interaction. Similar calculations were then conducted on the reaction of 4cyclohexyl-2,3-allenyl carbonates 2n. The four competing transition structures TS2_a1-d1, associated with 2n participating in the carborhodation step, are listed in Fig. 3 (below) together with the corresponding transition structures of the 2a system (above) for comparison. Due to the lack of the π - π stacking interaction, TS2 a1 suffers from the steric interactions between the cyclohexyl substituent of 2n with the pyrimidine group, leading to the decrease of the stability of TS2_a1. Moreover, unfavorable steric repulsions in TS2_b1 and TS2_d1 destabilize both structures. With no obvious hindrance, TS2 c1 becomes the most favorable one among the four transition structures. Thus, the reactions of alkyl-substituted allenyl carbonates should present different stereoselectivity as compared to the aryl-substituted allenyl carbonates to yield the major E products.



Fig. 2 Origin of the Z-stereoselectivity for the reaction of 1a with 4-phenyl-2,3-allenyl carbonate 2a. Free energies are given in kcal mol⁻¹ with respect of INT3.



Fig. 3 Origin of the different stereoselectivity for the reaction of 4-phenyl- and 4-cyclohexyl-2,3-allenyl carbonates (2a and 2n). Free energies are given in kcal mol⁻¹ with respect to INT3 or INT3_1.



Fig. 4 LUMOs calculated for (R_a)-2a and (R_a)-2n (R enantiomer is selected as the example). The orbital energies are given in eV.

In order to further investigate the factors controlling the stereoselectivity, we also analyzed the frontier molecular orbitals for the carborhodation step, which mainly involve a nucleophilic attack of the C-Rh σ bond on the coordinated C=C bond. The C-Rh σ bond orbital in **INT3** corresponds to the HOMO, while the π^* orbital of the coordinated C=C double bond of allenyl carbonate 2 corresponds to the LUMO. Fig. 4 shows the spatial plots and the orbital energies for the LUMOs of 4-phenyl-2,3-allenyl carbonate 2a and 4-cyclohexyl-2,3-allenyl carbonate 2n. The LUMO of 2a is mainly the π^* orbital of the phenyl substituted $C^2 = C^3$ bond, suggesting the preference of the $C^2 = C^3$ bond over the other $C^2 =$ C¹ bond in the carborhodation step. Nevertheless, in the LUMO of 2n, the π^* orbital of the C²=C¹ bond contributes significantly, indicating that 2n and 2a prefer to participate in the carborhodation with different C=C bonds, which has already been proven by the results shown in Fig. 2 and 3. Further examination

Table 4 Reaction scope⁴

reveals that a conjugative effect between the phenyl substituent and the $C^2 = C^3$ bond stabilizes the LUMO of 2a, making the orbital energy of the LUMO in 2a lower than that in 2n, and thus 2a would be more favourable to participate in the carborhodation reaction.

Encouraged by the above DFT calculation results, 4-alkyl-2,3allenyl carbonates were tested under standard conditions (Table 4). As expected, the stereoselectivity was reversed, affording 2-(1E,3-dienyl)indoles 3an-3ar smoothly in good yields and an Estereoselectivity of 90:10-93:7. The C=C configuration of compound 3ao was established by NOESY studies (see the ESI for details). Therefore, the experimental results were in line with DFT calculations. To illustrate the utility of this catalytic system, the scope could be extended to allenyl carbonates derived from natural products or drug molecules; 2s and 2t derived from citronellal (9) and cholesterol (10) could provide the corresponding products with an excellent stereoselectivity (3as-3at) under standard conditions. It is interesting to observe that the E-stereoselectivity for 3as and 3at has been greatly improved obviously due to the increased bulkiness of the R group.

The synthetic potential of the diene products has also been demonstrated (Scheme 2); compound 3bf could undergo the Diels-Alder reaction with N-methylmaleimide and diethyl acetylenedicarboxylate to yield corresponding compounds 14 and 15. The Suzuki coupling reaction with PhB(OH)2 generated compound 16.^{14a} The directing group 2-pyrimidinyl was further applied to execute subsequent C-H functionalization at C-7 of indole with methyl acrylate to afford compound 17.14b The directing group could be removed to generate corresponding indole 18 in the presence of NaOEt and DMSO at room temperature. Furthermore,



^a The reactions were carried out using 1 mmol of 1a, 1.0 equiv. of 2, 2.5 mol% of [Cp*RhCl₂]₂, 30 mol% of AgSbF₆, and 1 equiv. of PivOH in 5 mL of toluene at room temperature. Yields of isolated products were given. The ratio of Z/E was determined by ¹H NMR analysis. An unidentified unknown product was formed. ^b 1.1 equiv. of 2 was added. ^c The yield and ratio of Z/E were calculated based on *E*-3 and the Z/E mixture of 3 after column chromatography according to ¹H NMR analysis. ^d 0.5 mmol scale.



Scheme 2 Synthetic applications of 3bf, 3am, and E-3an.

the Diels–Alder reaction of **3am** with diethyl acetylenedicarboxylate under the catalysis of Sc(OTf)₃ at 100 °C afforded *cis*-**19** in 55% yield. Similarly, when cyclohexyl-substituted 2-(1*E*,3-dienyl)indole **3an** was treated with NaOEt and DMSO at 40 °C, corresponding indole *E*-**20** could be produced without isomerization.

Conclusions

In summary, we have developed a rhodium-catalyzed C–H functionalization of indoles with 4-aryl-2,3-allenol carbonates to access 2-(1,3-diene)-substituted indoles with the assistance of directing groups leading to unique thermodynamically unfavored *Z*-stereoselectivity. In the reaction, the directing group not only plays a vital role in showing basic directing effects, but also has distinctive π - π stacking interactions with the aromatic ring of allene substrates. DFT calculations rationalized the *Z* selectivity of the reaction for the aryl substrate and forecasted an *E* selectivity for the alkylsubstituted allene substrate, which was confirmed by the experimental results. The synthetic potential of the products has been demonstrated. Due to the importance of the indole derivatives, this method will be of high interest for organic and medicinal chemists. Further studies are ongoing in our laboratory.

Data availability

Crystallographic data for **3cf** has been deposited at the CCDC with the number of 2014026 and can be obtained from www.ccdc.cam.ac.uk. The ESI include experimental detail, analytical data, computational details, and all the spectra.

Author contributions

Y. Z. performed the experiments. X. Z. performed DFT calculations. S. M. directed the project. All authors contributed to the preparation of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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