Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2021, **12**, 11330

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 19th April 2021
Accepted 16th July 2021

DOI: 10.1039/d1sc02167b

rsc.li/chemical-science

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

Yizhan Zhai,[ab] Xue Zhang *[a] and Shengming Ma *[ac]

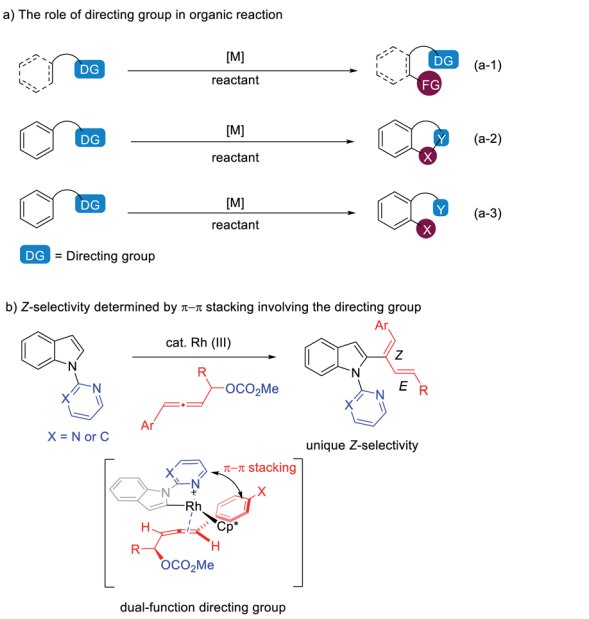
A rhodium-catalyzed intermolecular highly stereoselective 1,3-dienylation at the 2-position of indoles with non-terminal allenyl carbonates has been developed by using 2-pyrimidinyl or pyridinyl as the directing group. The reaction tolerates many functional groups affording the products in decent yields 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 π–π stacking involving the directing 2-pyrimidinyl or pyridinyl group is the origin of the observed stereoselectivity. Various synthetic transformations have also been demonstrated.

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 acyclic[4] 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(III)-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 $AgSbF_6$ and PivOH produced 2-(1(*Z*),3-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 CH_3CN with 75% recovery of **1a** (Table 1, entry 3). When $AgBF_4$ was used instead of $AgSbF_6$, the reaction was much slower (Table 1, entry 4). The control experiment showed that no product was generated in the absence of $AgSbF_6$ (Table 1, entry 5).



Scheme 1 Novel function of directing groups in C–H functionalization reactions.

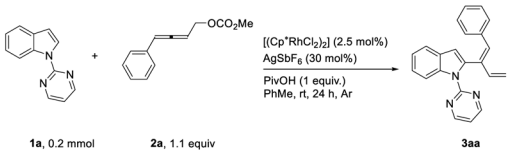
[a]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai, 200032, P. R. China. E-mail: masm@sioc.ac.cn*

[b]*University of Chinese Academy of Sciences, Beijing, 100049, P. R. China*

[c]*Research Center for Molecular Recognition and Synthesis, Department of Chemistry, Fudan University, 220 Handan Road, Shanghai, 200433, P. R. China*

† 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]

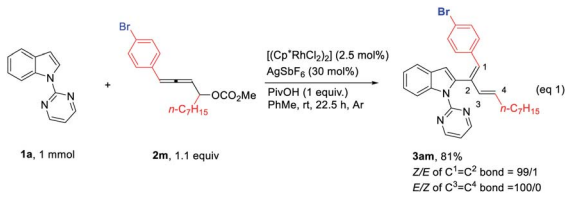


Entry	Variation from the standard conditions	NMR recovery of **1a**[b] (%)	NMR yield of **3aa**[b](%)	*Z*/*E* of **3aa**[c]
1	None	—	80	96/4
2	Dioxane as solvent	—	62	96/4
3	CH_3CN as solvent	75	—	—
4	$AgBF_4$ replacing $AgSbF_6$	60	20	96/4
5	No [Ag]	78	—	—

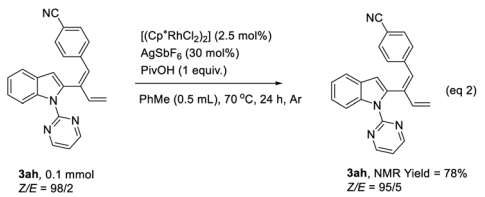
[a] The reactions were carried out using 0.2 mmol of **1a**, 1.1 equiv. of **2a**, 2.5 mol% of $[Cp^*RhCl_2]_2$, 30 mol% of [Ag], and 1 equiv. of PivOH in 1 mL of solvent at room temperature. [b] Determined by ^1H NMR analysis using CH_3NO_2 as an internal standard. [c] The ratio of *Z*/*E* was determined 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 electron-withdrawing synthetically versatile groups (4 F-, 4-Cl-, 4-Br-, 4-I-, 4-CN- and 4-CF_3-) (**3ad–3ai**) could react smoothly. 4-Naphthyl-2,3-butadienyl 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-CO_2Me 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)).

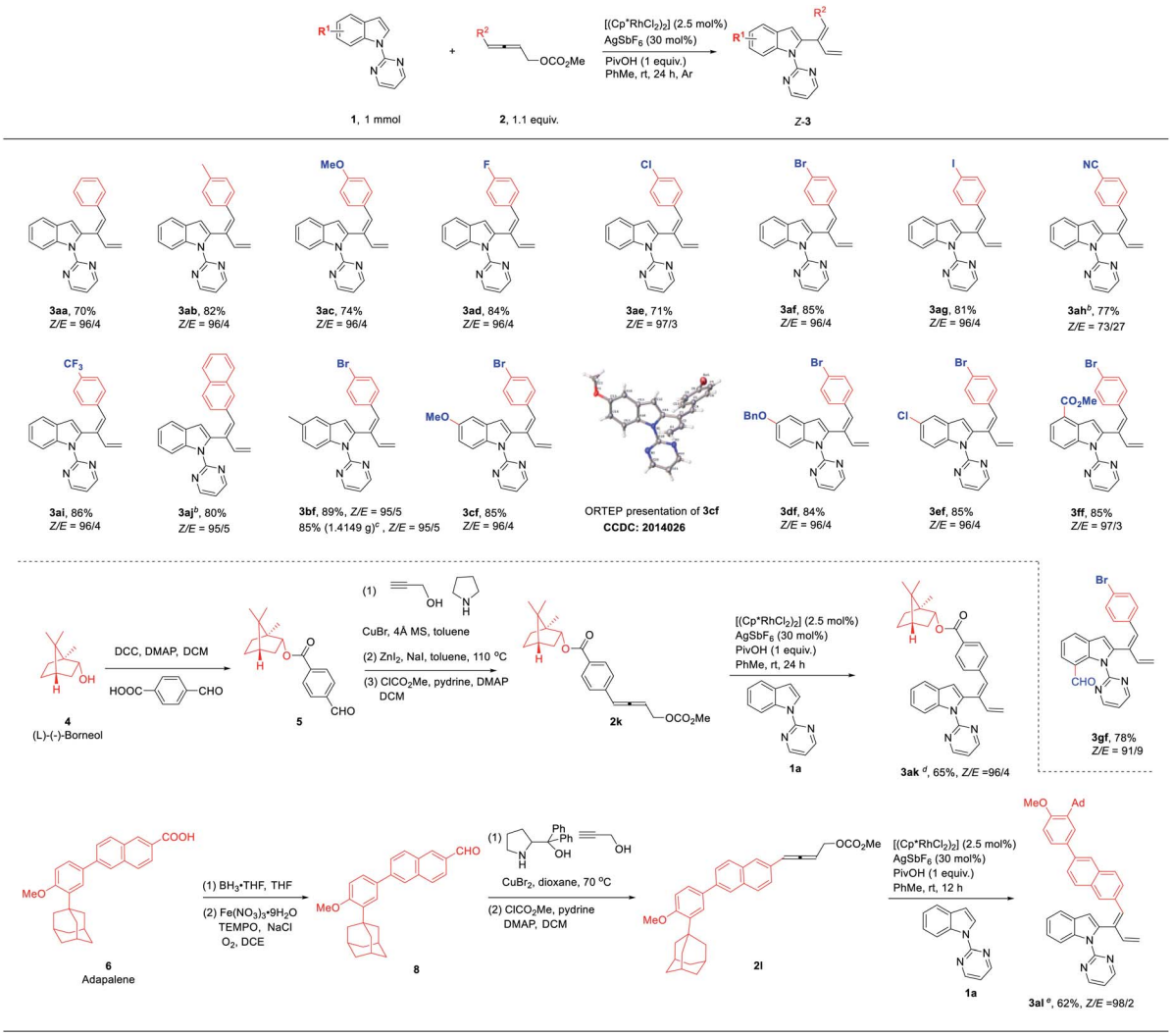


In order to clarify the role of directing groups, some control experiments were carried out (Table 3). When the 2-pyrimidinyl group was replaced with Me (**1h**), no product was generated under standard conditions (Table 3, entry 1). Furthermore, directing groups such as Piv (**1i**)[9a] and *t*-Bu_2P (**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-2,3-allenyl 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 $[Cp^*RhCl_2]_2$ 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]

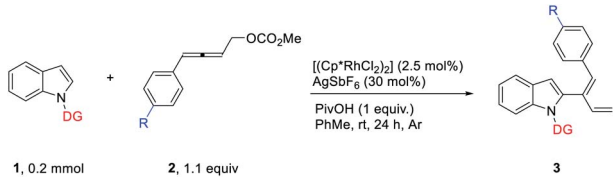


[a] The reactions were carried out using 1 mmol of **1**, 1.1 equiv. of **2**, 2.5 mol% of $[Cp^*RhCl_2]_2$, 30 mol% of $AgSbF_6$, and 1 equiv. of PivOH in 5 mL of toluene at room temperature. Yields of isolated products were given. The ratio of *Z*/*E* was determined by ^1H NMR analysis. [b] The reaction 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(III) 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(III) 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**

Table 3 Control experiments[a]



Entry	DG	*R*	NMR recovery of **1**[b] (%)	NMR yield of **3**[b] (%)	*Z*/*E* of **3**
1	Me (**1h**)	H (**2a**)	83	—	—
2	Piv (**1i**)	(**2a**)	76	—	—
3	*t*-Bu$_2$P (**1j**)	(**2a**)	85	—	—
4[c]	2-pyridinyl (**1k**)	(**2a**)	—	**3ka** 60(52[d])	90/10[e]
5[f]	2-pyrimidinyl (**1a**)	CN (**2h**)	25	**3ah** 60	75/25
6[g,h]	(**1a**)	(**2h**)	28	**3ah** 57	74/26
7[h,i]	(**1a**)	(**2h**)	—	**3ah** 66	73/27

[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 CH_3NO_2 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.

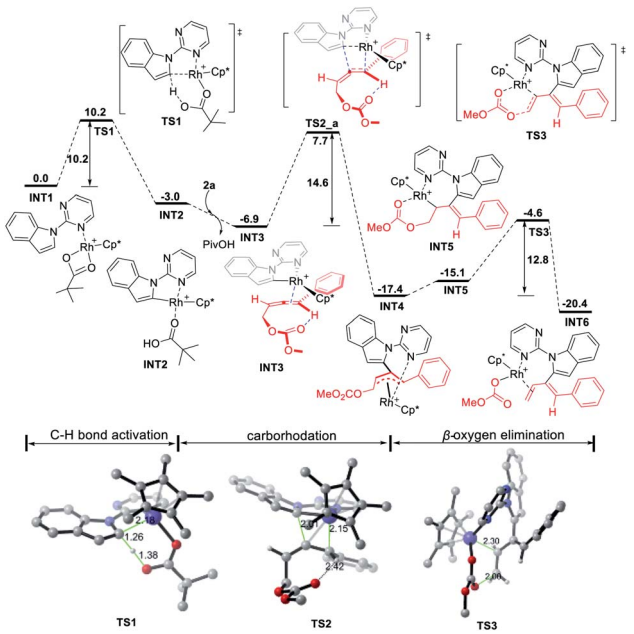


Fig. 1 Free energy profile (kcal mol^{-1}) for the most favorable pathway of the reaction of indole **1a** with 4-phenyl-2,3-allenyl carbonate **2a**. Bond lengths are given in angstroms.

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 non-covalent interaction (NCI) analysis (performed by Multiwfn[12] and VMD[13] 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 4-cyclohexyl-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.

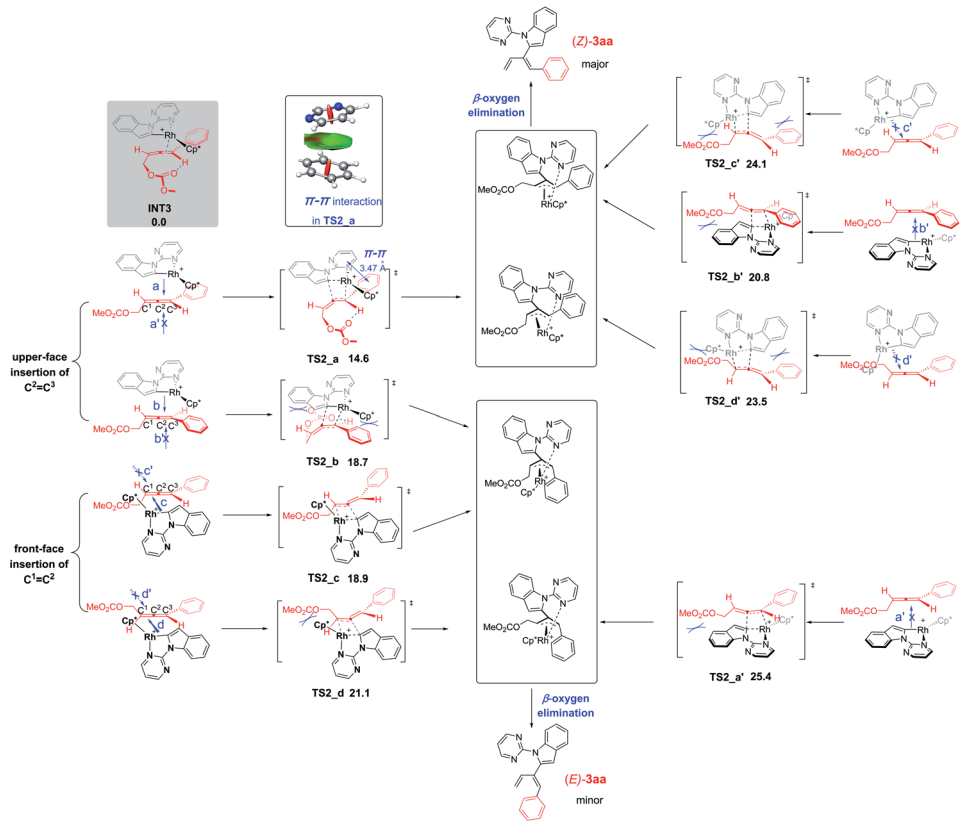


Fig. 2 Origin of the *Z*-stereoselectivity for the reaction of **1a** with 4-phenyl-2,3-allenyl carbonate **2a**. Free energies are given in kcal mol^{-1} with respect of **INT3**.

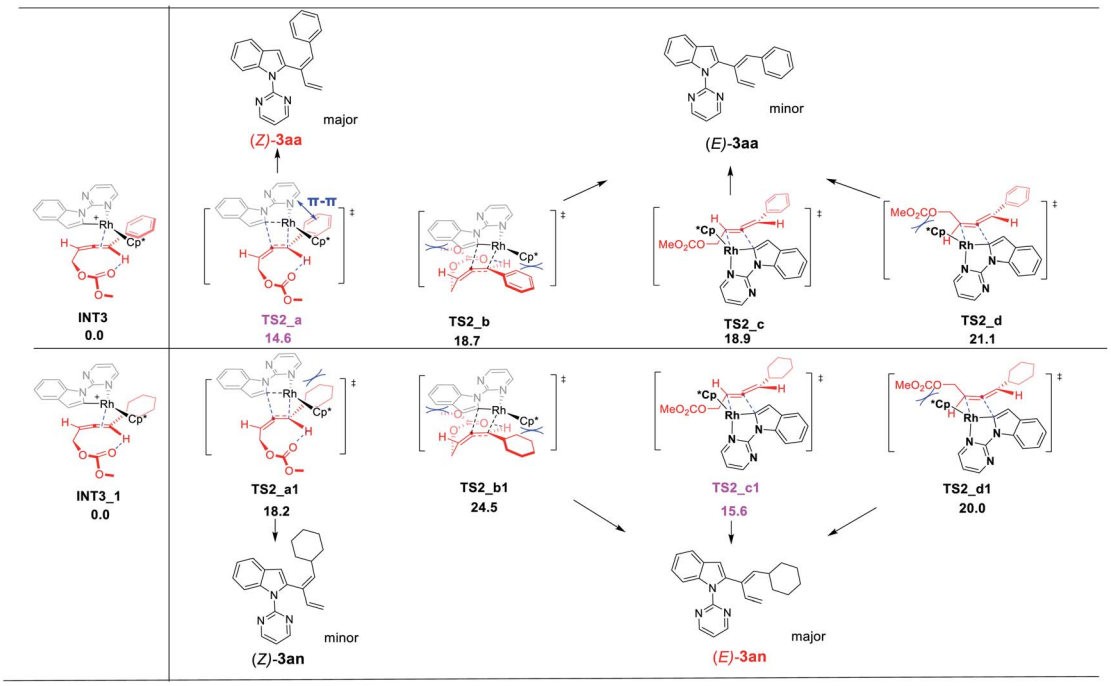


Fig. 3 Origin of the different stereoselectivity for the reaction of 4-phenyl- and 4-cyclohexyl-2,3-allenyl carbonates (**2a** and **2n**). Free energies are given in kcal mol^{-1} with respect to **INT3** or **INT3_1**.

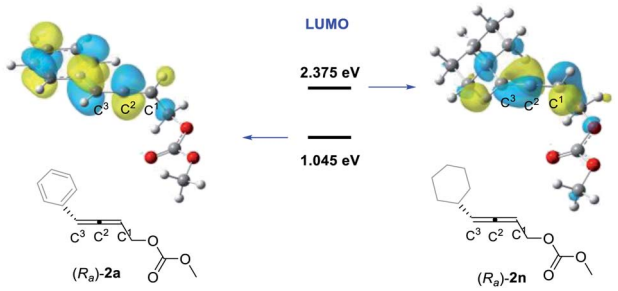


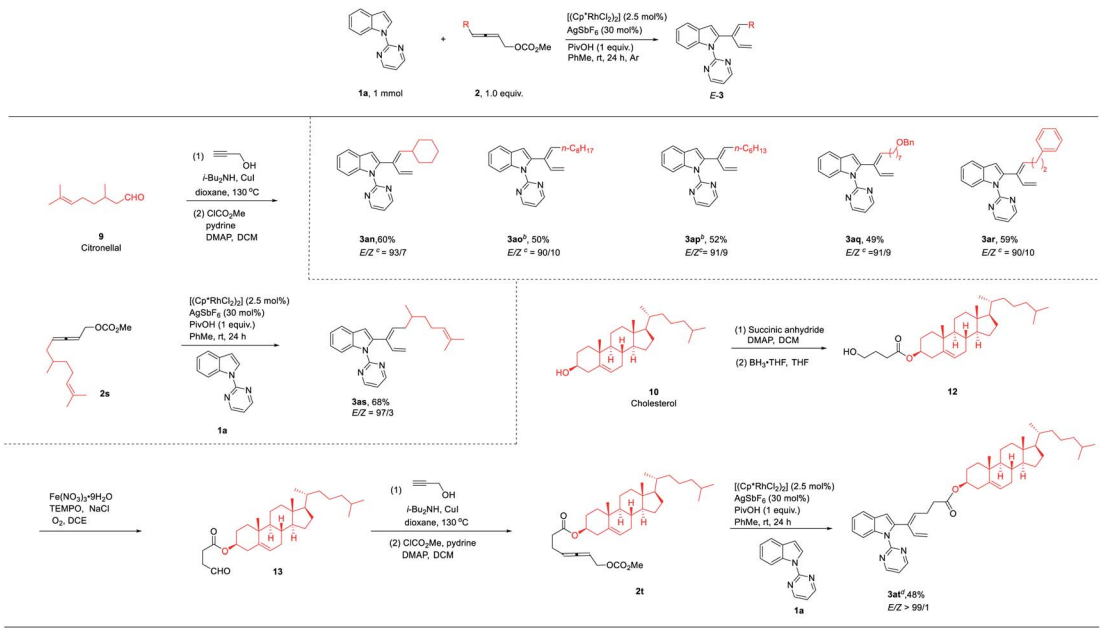
Fig. 4 LUMOs calculated for (R_a)-**2a** and (R_a)-**2n** (*R* enantiomer is selected as the example). The orbital energies are given in eV.

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=C^1 bond in the carborhodation step. Nevertheless, in the LUMO of **2n**, the π^* orbital of the C^2=C^1 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 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.

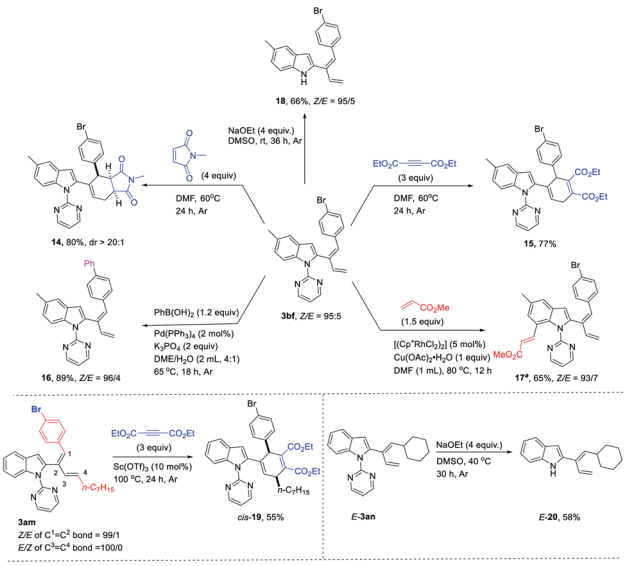
Encouraged by the above DFT calculation results, 4-alkyl-2,3-allenyl carbonates were tested under standard conditions (Table 4). As expected, the stereoselectivity was reversed, affording 2-(1*E*,3-dienyl)indoles **3an**–**3ar** smoothly in good yields and an *E*-stereoselectivity of 90 : 10–93 : 7. 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,

Table 4 Reaction scope[a]



[a] The reactions were carried out using 1 mmol of **1a**, 1.0 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 ^{1}H 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 ^{1}H 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 alkyl-substituted 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.

Acknowledgements

Financial support from the National Natural Science Foundation of China (grant no. 21690063 and 21988101 to S. M.) and Natural Science Foundation of Shanghai (grant no. 19ZR1468500 to X. Z.) is greatly appreciated. We also thank Mr Jie Wang in this group for reproducing the results for **3ap** and **3as** presented in Table 3 and **3am** in eqn (1), and we thank Mr Yifan Cui and Mr Weiyi Wang in this group for providing **2s** and **2l′** (see the ESI) respectively.

Notes and references

1 For selected reviews on C-H activation, see: (*a*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*b*) G. Rousseau and B. Breit, *Angew. Chem., Int. Ed.*, 2011, **50**, 2450; (*c*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (*d*) F. Zhang and D. R. Spring, *Chem. Soc. Rev.*, 2014, **43**, 6906; (*e*) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li and W. Su, *Org. Chem. Front.*, 2014, **1**, 843; (*f*) Z. Huang, H. N. Lim, F. Mo, M. C. Young and G. Dong, *Chem. Soc. Rev.*, 2015, **44**, 7764; (*g*) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107; (*h*) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900; (*i*) J. R. Hummel, J. A. Boerth and J. A. Ellman, *Chem. Rev.*, 2017, **117**, 9163; (*j*) L. Ping, D. S. Chung, J. Bouffard and S. Lee, *Chem. Soc. Rev.*, 2017, **46**, 4299; (*k*) C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnürch, *Chem. Soc. Rev.*, 2018, **47**, 6603; (*l*) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.*, 2019, **119**, 2192; (*m*) Ł. Woźniak, J.-F. Tan, Q.-H. Nguyen, A. Madron du Vigné, V. Smal, Y.-X. Cao and N. Cramer, *Chem. Rev.*, 2020, **120**, 10516.

2 For selected examples on the use of directing groups as an internal oxidant to construct cyclic compounds, see (*a*) N. Guimond, C. Gouliaras and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 6908; (*b*) Y.-F. Wang, K. K. Toh, J.-Y. Lee and S. Chiba, *Angew. Chem., Int. Ed.*, 2011, **50**, 5927; (*c*) B.-J. Li, H.-Y. Wang, Q.-L. Zhu and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2012, **51**, 3948; (*d*) X. Xu, Y. Liu and C.-M. Park, *Angew. Chem., Int. Ed.*, 2012, **51**, 9372; (*e*) B. Liu, C. Song, C. Sun, S. Zhou and J. Zhu, *J. Am. Chem. Soc.*, 2013, **135**, 16625; (*f*) H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga and M. Kanai, *J. Am. Chem. Soc.*, 2014, **136**, 5424; (*g*) R. B. Dateer and S. Chang, *J. Am. Chem. Soc.*, 2015, **137**, 4908; (*h*) T. K. Hyster, L. Knorr, T. R. Ward and T. Rovis, *Science*, 2012, **338**, 500; (*i*) B. Ye and N. Cramer, *Science*, 2012, **338**, 504; (*j*) W. Zhen, F. Wang, M. Zhao, Z. Du and X. Li, *Angew. Chem., Int. Ed.*, 2012, **51**, 11819; (*k*) H. Zhang,

K. Wang, B. Wang, H. Yi, F. Hu, C. Li, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 13234; (*l*) S. Wu, R. Zeng, C. Fu, Y. Yu, X. Zhang and S. Ma, *Chem. Sci.*, 2015, **6**, 2275; (*m*) T. K. Hyster, K. E. Ruhl and T. Rovis, *J. Am. Chem. Soc.*, 2013, **135**, 5364.

3 For selected examples on directing groups participating in the reaction directly to construct cyclic compounds, see: (*a*) M. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art and M. Nomura, *J. Org. Chem.*, 1998, **63**, 5211; (*b*) K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita and M. Tokuda, *J. Am. Chem. Soc.*, 2004, **126**, 14342; (*c*) W. C. P. Tsang, N. Zheng and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 14560; (*d*) N. Chernyak and V. Gevorgyan, *J. Am. Chem. Soc.*, 2008, **130**, 5636; (*e*) X.-F. Cheng, Y. Li, Y.-M. Su, F. Yin, J.-Y. Wang, J. Sheng, H. U. Vora, X.-S. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 1236; (*f*) Y. Kuninobu, A. Kawata and K. Takai, *J. Am. Chem. Soc.*, 2005, **127**, 13498; (*g*) K. Ueura, T. Satoh and M. Miura, *Org. Lett.*, 2007, **9**, 1407; (*h*) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 16474; (*i*) F. W. Patureau, T. Besset, N. Kuhl and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2154; (*j*) X. Tan, B. Liu, X. Li, B. Li, S. Xu, H. Song and B. Wang, *J. Am. Chem. Soc.*, 2012, **134**, 16163; (*k*) L. Ackermann, A. V. Lygin and N. Hofmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 6379; (*l*) S. C. Reddy, I. Khan and H. W. Lam, *Angew. Chem., Int. Ed.*, 2012, **51**, 12115; (*m*) R. He, Z.-T. Huang, Q.-Y. Zheng and C. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 4950; (*n*) Y. Sun and N. Cramer, *Angew. Chem., Int. Ed.*, 2017, **56**, 364; (*o*) H. Chen, Y.-X. Wang, Y.-X. Luan and M. Ye, *Angew. Chem., Int. Ed.*, 2020, **59**, 9428; (*p*) C.-Q. Wang, L. Ye, C. Feng and T.-P. Loh, *J. Am. Chem. Soc.*, 2017, **139**, 1762; (*q*) Z. Zhou, G. Liu and X. Lu, *Org. Lett.*, 2016, **18**, 5668; (*r*) S. Wu, X. Wu, C. Fu and S. Ma, *Org. Lett.*, 2018, **20**, 2831; (*s*) J. Karthikeyan, R. Haridharan and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2012, **51**, 12343; (*t*) Y. Lian, R. G. Bergman, L. D. Lavis and J. A. Ellman, *J. Am. Chem. Soc.*, 2013, **135**, 7122; (*u*) Y. Kuninobu, K. Yamauchi, N. Tamura, T. Seiki and K. Takai, *Angew. Chem., Int. Ed.*, 2013, **52**, 1520; (*v*) B. Su and J. F. Hartwig, *J. Am. Chem. Soc.*, 2017, **139**, 12137; (*w*) W. Du, Q. Gu, Z. Li and D. Yang, *J. Am. Chem. Soc.*, 2015, **137**, 1130.

4 For the use of directing group as an internal oxidant to construct acyclic compounds, see (*a*) S. Rakshit, C. Grohmann, T. Besset and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2350; (*b*) R. Zeng, S. Wu, C. Fu and S. Ma, *J. Am. Chem. Soc.*, 2013, **135**, 18284; (*c*) G. Liu, Y. Shen, Z. Zhou and X. Lu, *Angew. Chem., Int. Ed.*, 2013, **52**, 6033; (*d*) X. Huang, J. Huang, C. Du, X. Zhang, F. Song and J. You, *Angew. Chem., Int. Ed.*, 2013, **52**, 12970; (*e*) X. Zhang, Z. Qi and X. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 10794; (*f*) J. Zhou, J. Shi, Z. Qi, X. Li, H. E. Xu and W. Yi, *ACS Catal.*, 2015, **5**, 6999; (*g*) B. Li, J. Lan, D. Wu and J. You, *Angew. Chem., Int. Ed.*, 2015, **54**, 14008; (*h*) X. Wang, T. Gensch, A. Lerchen, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2017, **139**, 6506; (*i*) Y. Wu, Z. Chen, Y. Yang, W. Zhu and B. Zhou, *J. Am. Chem. Soc.*, 2018, **140**, 42; (*j*) W. Yi, W. Chen, F.-X. Liu, Y. Zhong, D. Wu, Z. Zhou and H. Gao, *ACS Catal.*, 2018, **8**, 9508; (*k*) G. Zheng, Z. Zhou, G. Zhu, S. Zhai, H. Xu, X. Duan, W. Yi and X. Li, *Angew. Chem., Int. Ed.*, 2020, **59**, 2890; (*l*) K. Ozols, S. Onodera, Ł. Woźniak and N. Cramer, *Angew. Chem., Int. Ed.*, 2021, **60**, 655.

5 For as seminal report, see: Y. Zhang, E. Skucas and M. J. Krische, *Org. Lett.*, 2009, **11**, 4248.

6 For selected reports with Rh-catalysis, see: (*a*) D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2010, **49**, 8181; (*b*) R. Zeng, C. Fu and S. Ma, *J. Am. Chem. Soc.*, 2012, **134**, 9597; (*c*) H. Wang and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 7318; (*d*) B. Ye and N. Cramer, *J. Am. Chem. Soc.*, 2013, **135**, 636; (*e*) H. Wang, B. Beiring, D.-G. Yu, K. D. Collins and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 12430; (*f*) T.-J. Gong, W. Su, Z.-J. Liu, W.-M. Cheng, B. Xiao and Y. Fu, *Org. Lett.*, 2014, **16**, 330; (*g*) C. Ghosh, P. J. Nagtilak and M. Kapur, *Org. Lett.*, 2019, **21**, 3237.

7 X. Huang and S. Ma, *Acc. Chem. Res.*, 2019, **52**, 1301.

8 (*a*) R. Liu, Y. Wei and M. Shi, *Chem. Commun.*, 2019, **55**, 7558; (*b*) Z. Shen, I. Maksso, R. Kuniyil, T. Rogge and L. Ackermann, *Chem. Commun.*, 2021, **57**, 3668.

9 (*a*) D. R. Stuart, E. Villemure and K. Fagnou, *J. Am. Chem. Soc.*, 2007, **129**, 12072; (*b*) A. J. Borah and Z. Shi, *J. Am. Chem. Soc.*, 2018, **140**, 6062.

10 For selected recent reviews concerning CMD processes, see: (*a*) O. Baudoin, *Acc. Chem. Res.*, 2017, **50**, 1114; (*b*) X. Qi, Y. Li, R. Bai and Y. Lan, *Acc. Chem. Res.*, 2017, **50**, 2799; (*c*) Y.-F. Yang, X. Hong, J.-Q. Yu and K. N. Houk, *Acc. Chem. Res.*, 2017, **50**, 2853; (*d*) D. L. Davies, S. A. Macgregor and C. L. McMullin, *Chem. Rev.*, 2017, **117**, 8649; (*e*) W. Zhu and T. B. Gunnoe, *Acc. Chem. Res.*, 2020, **53**, 920.

11 For selected recent examples concerning CMD processes, see: (*a*) P. Gao, W. Guo, J. Xue, Y. Zhao, Y. Yuan, Y. Xia and Z. Shi, *J. Am. Chem. Soc.*, 2015, **137**, 12231; (*b*) S. Yu, S. Liu, Y. Lan, B. Wan and X. Li, *J. Am. Chem. Soc.*, 2015, **137**, 1623; (*c*) M. Simonetti, G. J. P. Perry, X. C. Cambeiro, F. Juliá-Hernández, J. N. Arokianathar and I. Larrosa, *J. Am. Chem. Soc.*, 2016, **138**, 3596; (*d*) S. Y. Lee and J. F. Hartwig, *J. Am. Chem. Soc.*, 2016, **138**, 15278; (*e*) H. M. Omer and P. Liu, *J. Am. Chem. Soc.*, 2017, **139**, 9909; (*f*) W. Liu, J. Zheng, Z. Liu, W. Hu, X. Wang and Y. Dang, *ACS Catal.*, 2018, **8**, 7698; (*g*) D. D. Beattie, A. C. Grunwald, T. Perse, L. L. Schafer and J. A. Love, *J. Am. Chem. Soc.*, 2018, **140**, 12602; (*h*) W. Li, D. Yuan, G. Wang, Y. Zhao, J. Xie, S. Li and C. Zhu, *J. Am. Chem. Soc.*, 2019, **141**, 3187; (*i*) L. Wang and B. P. Carrow, *ACS Catal.*, 2019, **9**, 6821; (*j*) Y. Luo, C. Shan, S. Liu, T. Zhang, L. Zhu, K. Zhong, R. Bai and Y. Lan, *ACS Catal.*, 2019, **9**, 10876; (*k*) Z. Fan, K. L. Bay, X. Chen, Z. Zhuang, K.-S. Park, H. S. Yeung, K. N. Houk and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2020, **59**, 4770; (*l*) B. A. Suslick and T. D. Tilley, *J. Am. Chem. Soc.*, 2020, **142**, 11203.

12 (*a*) T. Lu and F. Chen, *J. Comput. Chem.*, 2012, **33**, 580; (*b*) T. Lu, *Multiwfn, version 3.5*, 2018.

13 W. Humphrey, A. Dalke and K. Schulten, *J. Mol. Graphics*, 1996, **14**, 33.

14 (*a*) N. Miyaura, T. Yanagi and A. Suzuki, *Synth. Commun.*, 1981, **11**, 513; (*b*) J. Shi, Y. Yan, Q. Li, H. E. Xu and W. Yi, *Chem. Commun.*, 2014, **50**, 6483.