Transient-axial-chirality controlled asymmetric rhodium-carbene C(sp²)-H functionalization for the synthesis of chiral fluorenes

Kuiyong Dong¹,²,⁴, Xing Fan³,⁴, Chao Pei², Yang Zheng², Sailan Chang², Ju Cai², Lihua Qiu², Zhi-Xiang Yu³ & Xinfang Xu¹,²✉

In catalytic asymmetric reactions, the formation of chiral molecules generally relies on a direct chirality transfer (point or axial chirality) from a chiral catalyst to products in the stereo-determining step. Herein, we disclose a transient-axial-chirality transfer strategy to achieve asymmetric reaction. This method relies on transferring point chirality from the catalyst to a dirhodium carbene intermediate with axial chirality, namely a transient-axial-chirality since this species is an intermediate of the reaction. The transient chirality is then transferred to the final product by C(sp²)-H functionalization reaction with exceptionally high enantioselectivity. We also generalize this strategy for the asymmetric cascade reaction involving dual carbene/alkyne metathesis (CAM), a transition-metal-catalyzed method to access chiral 9-aryl fluorene frameworks in high yields with up to 99% ee. Detailed DFT calculations shed light on the mode of the transient-axial-chirality transfer and the detailed mechanism of the CAM reaction.

¹ Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China. ² College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China. ³ Beijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China. ⁴ These authors contributed equally: Kuiyong Dong, Xing Fan. ✉ email: yuzx@pku.edu.cn; xuxinfang@mail.sysu.edu.cn
Metal carbene reaction is one of the most versatile methods for the assembly of valuable molecules with structural complexity and diversity. In this regard, the pursuit of practical and efficient catalytic approach has been of long-standing appealing, especially the catalytic asymmetric carbene transformations, such as cyclopropanation, C–H insertion, hydride migration, cycloaddition, H-insertion, hydride migration, cycloaddition, ylide formation followed by rearrangement or interception, and others. Generally, the asymmetry induction in these metal-carbene reactions heavily relied on the chiral catalyst-associated species, and the asymmetric transfer strategy is a point-to-point chirality transfer manner. For example, the enantioselectivity control in catalytic asymmetric electrophilic aromatic substitution reaction, which happens at the H-shift step, is enabled by the point chirality of the catalyst via a metal-associated zwitterionic intermediate or Wheland-type intermediate. However, in most cases, partially leaving or even dissociation of the metal catalyst could occur to form the free zwitterionic intermediate, especially in the case with the neutral dirhodium(II) complex, so the subsequent transformation will not secure the high stereoselectivity. Therefore, it is highly challenging and desirable for the development of stereoselective carbene transformations with efficient and practical strategies.

On the other hand, the axial chirality has been found in a variety of rotation-hindered molecules, such as BINAP and BINOL derivatives, which have been widely used as privileged ligands or catalysts in asymmetric catalysis. Inspired by the unique structures of these chiral ligands with axial chirality, we describe the transient axial-chirality-controlled asymmetric C(sp²)-H functionalization. The pink crescent = chiral ligand (L = large group, S = small group). M = metal catalyst. Rh₂L₄⁺ = chiral dirhodium complex.

Fig. 1 Asymmetry induction in metal-carbene reactions. a Asymmetry induction in catalytic metal-carbene C(sp²)-H functionalization. b Chirality in transient carbene intermediate. c This work describes the transient axial-chirality-controlled asymmetric C(sp²)-H functionalization. The pink crescent = chiral ligand (L = large group, S = small group). M = metal catalyst. Rh₂L₄⁺ = chiral dirhodium complex.
hypothesized that, when the dirhodium complexes catalyze the
generation of metal-carbene species with steric bulky carbene
precursors, such as ortho-substituted aryl carbene, a transient
axial-chirality will be formed in the corresponding carbene
intermediate (Fig. 1b). The axial chirality in the intermediate is
called transient axial chirality, considering this chirality will then
be transfer to the final product by the followed reaction. In other
word, instead of heavily relying on the point chirality of the metal
catalyst in the later stereo-determining step (e.g., Fig. 1a), the final
chirality transfer from catalyst to product in this mode would be
determined by the initially formed axial chirality between the
catalyst and the substrate, due to the restricted rotation of these
carbene intermediates in the followed transformations. Thus,
high enantioselectivity could be envisioned in metal-carbene
reactions based on this transient axial-chirality transfer strategy.
Herein, we report our recent results by applying this asymmetric
transfer strategy, the asymmetric formal C(sp²)-H bond insertion
reactions based on this transient axial-chirality transfer strategy.
Over, we generalize this strategy for asymmetric cascade reaction,
in which the donor/donor carbene is generated in situ via a dual
carbene/alkyne metathesis (CAM) process, and directly
construction of polycyclic 9-aryl fluorenes with high enantioselec-
itivity (Fig. 1c, reaction 2). Considering the chiral
fluorenes have found broad applications in various fields, including in
pharmaceuticals, photoelectrical materials, and theoretical
studies; the present asymmetric reaction could add comple-
mentary values in this respect.

Results

Reaction optimization. We began our investigation of the
asymmetric C–H functionalization reaction with diaryl diazo
compound 1a, which is a typical donor/donor-type carbene
precursor, as model substrate (Table 1). To optimize reaction
conditions, Rh₂(S-TCPTTL)₄ was used as the catalyst, and sol-
vents were initially evaluated (entries 1–5), from which we found
that reaction in tert-butyl methyl ether (TBME) afforded 2a with
the highest selectivity (entry 5, 82% ee and 92% yield). Lowering
the reaction temperature did not improve the selectivity (entry 6).
Further investigation of a variety of dirhodium complexes turned
out that the optimum enhancement was achieved by Rh₂(S-
TFPTTL)₄ with four electron-withdrawing fluoro substituents on
the phthalimide ring (entry 10, 90% yield, 99% ee). It should be
mentioned that slowly addition of the rhodium catalyst to the
diazo compound is essential in all these reactions to ensure the

Table 1 Condition optimization.

| Entry  | Rh(II)          | Solvent      | Yield (%) | Ee (%) |
|--------|-----------------|--------------|-----------|--------|
| 1      | Rh₂(S-TCPTTL)₄ | DCM          | 91        | 60     |
| 2      | Rh₂(S-TCPTTL)₄ | DCE          | 90        | 63     |
| 3      | Rh₂(S-TCPTTL)₄ | Toluene      | 85        | 75     |
| 4      | Rh₂(S-TCPTTL)₄ | Hexane       | 90        | 62     |
| 5      | Rh₂(S-TCPTTL)₄ | TBME         | 92        | 82     |
| 6d     | Rh₂(S-TCPTTL)₄ | TBME         | 80        | 81     |
| 7d     | Rh₂(S-TCPTTL)₄ | TBME         | 82        | 15     |
| 8      | Rh₂(S-NNTTL)₄  | TBME         | 90        | 65     |
| 9      | Rh₂(S-TBPTTL)₄ | TBME         | 92        | 70     |
| 10     | Rh₂(S-TFPTTL)₄ | TBME         | 90        | 99     |
| 11     | Rh₂(S-PFTA)₄   | TBME         | 75        | 5      |
| 12     | Rh₂(S-PTA)₄    | TBME         | 72        | 2      |
| 13     | Rh₂(S-DOSP)₄   | TBME         | 90        | 13     |
| 14d    | Rh₂(S-PTAD)₄   | TBME         | 92        | 25     |

DCM dichloromethane, DCE 1,2-dichloroethane, TBME tert-butyl methyl ether.

*The reaction was carried out on a 0.2 mmol scale: 1a (0.2 mmol), and 4 Å MS (100 mg) in 1.0 mL solvent, was added a solution the catalyst in 1.0 mL of the same solvent via syringe pump in 40 min under inert atmosphere.

*bIsolated yields.

*cDetermined by chiral HPLC analysis, see SI for details.

*dThe reaction was conducted at 0 °C for 24 h.
Substrate scope. With the optimized reaction conditions in hand for reaction 1, the catalytic asymmetric C–H insertion reaction with a variety of substituted diaryl diazo compounds has been tested, and the results are summarized in Table 2. Unexceptionally, a series of substrates 1a–1f bearing electron-neutral, -deficient, or -rich substitutions on the aromatic ring react smoothly to give the corresponding products in 90–96% yields with 90–99% ee (2a–2f). Substrates with 1-naphthyl, 2-fluorophenyl, and 3-fluorophenyl groups are all tolerated under current conditions, delivering the corresponding products in excellent yields and selectivity (2g–2l). For the detail of the regioselectivity of 2i, see Supplementary Fig. 147. Substrates with substitutions on the other aryl group do not affect the high reactivity, the corresponding products 2j and 2k are isolated in high yields with 95% and 92% ee, respectively.

Considering the limited accessibility and inherent instability of the precursors of the donor/donor-type carbene species, we intend to utilize the carbene/alkyne metathesis reaction for the generation of the analogous carbene intermediate in situ (Fig. 1c, reaction 2). After a brief optimization, polycyclic fluorene product 4a was obtained in 90% yield with 92% ee from the alkyne-tethered propargyl diazoacetate 3a in the presence of 1.0 mol% Rh$_2$(S-TFPTTL)$_4$ in TBME at 40 °C, and a detrimental effect on the selectivity by increasing the amounts of the chiral rhodium complex has been observed in this case (see Supplementary Table 1 for details). It is worth mentioning that the only catalyst involved in this four-step cascade transformation is a chiral dirhodium catalyst; and this catalyst is responsible for the observed asymmetry induction with high enantiocontrol in this carbene/alkyne metathesis-aromatic substitution cascade reaction. The (R)-configuration of the generated chiral center in the 9-aryl fluorene is confirmed by single-crystal X-ray diffraction analysis of its chloro-derivative 4b, and the configurations of other compounds are assigned by analogy.

Table 2 Substrates scope of direct asymmetric C–H functionalization.  

| Substrate | Reaction Conditions | Yield | enantiomeric Excess |
|-----------|---------------------|-------|---------------------|
| 2a, 5 h, 90%, 99% ee | 4 Å MS, TBME, 1 h (1.0 mol%) | 90% | 92% |
| 2b, 5 h, 91%, 98% ee | | 91% | 96% |
| 2c, 5 h, 92%, 95% ee | | 95% | 96% |
| 2d, 5 h, 95%, 96% ee | | 96% | 96% |
| 2e, 1 h, 96%, 93% ee | | 93% | 95% |
| 2f, 1 h, 93%, 90% ee | | 90% | 91% |
| 2g, 1 h, 95%, 92% ee | | 92% | 93% |
| 2h, 5 h, 95%, 91% ee | | 91% | 94% |
| 2i, 5 h, 95%, 94% ee | | 94% | 95% |
| 2j, 5 h, 93%, 95% ee | | 95% | 96% |
| 2k, 5 h, 91%, 92% ee | | 92% | 93% |

*The reaction was carried out on a 0.2 mmol scale: Rh$_2$(S-TFPTTL)$_4$ (1.0 mol%) was added as a solution in TBME (1.0 mL) via syringe pump in 40 min under inert atmosphere at room temperature.
which could be initially generated in higher ee). In addition, the naphthyl group was also tolerated for the terminating step, providing the hexacyclic fluorene 4i in 89% yield with 92% ee. In line with our previous work, the alkyl propargyl alcohol derived diazo compound 3j only led to the \( \beta \)-elimination product 4j after the first CAM process. The substitution pattern on the second alkyne unit (R, 4k–4u) was then examined, its scope was general regardless of the electronic-influence (4k–4o and 4r) or steric-effect (4o–4q) of the substituted groups on the aromatic ring, and high yields with \( \geq 90\% \) ee were obtained in these reactions. Notably, the alkyl alkyne-tethered substrate 3s was equally reactive and offered the corresponding product in 83% yield with 68% ee. In addition, we found that the desired product 4t could be obtained in 78% yield with 84% ee in the case of the TIPS protected alkyne under the conditions with minor optimization. The terminal alkyne was also accommodated to give achiral product (4u, 44%). To show the synthetic potential of this strategy, a gram-scale reaction of 3c was performed at 0.5 mol% catalyst loading (Table 3, note b), affording 4c with comparative results (1.52 g, 89%, 94% ee). Derivatizations of these products were also carried out to give corresponding fluorene derivatives with structural complexity, including bromination at the benzyl

| Table 3 Substrates scope of carbene/alkyne metathesis terminated with asymmetric C-H functionalization. |

| Entry | R   | Product         | Yield | ee  |
|-------|-----|-----------------|-------|-----|
| 1     | H   | 4a              | 90%   | 92% ee |
| 2     | Cl  | 4b              | 88%   | 93% ee |
| 3     | Br  | 4c              | 86%   | 92% ee |
| 4     | Ph  | 4d              | 73%   | 99% ee |
| 5     | Ph  | 4e              | 63%   | 85% ee |
| 6     | Ph  | 4f              | 88%   | 93% ee |
| 7     | Ph  | 4g              | 53%   | 97% ee |
| 8     | Ph  | 4h              | 38%   | <5% ee |
| 9     | Ph  | 4i              | 89%   | 92% ee |
| 10    | Ph  | 4j              | 43%   |       |
| 11    | Cl  | 4k              | 90%   | 93% ee |
| 12    | Cl  | 4l              | 91%   | 99% ee |
| 13    | Cl  | 4m              | 90%   | 97% ee |
| 14    | Cl  | 4n              | 86%   | 90% ee |
| 15    | Cl  | 4o              | 89%   | 90% ee |
| 16    | Cl  | 4p              | 91%   | 93% ee |
| 17    | Cl  | 4q              | 87%   | 96% ee |
| 18    | Br  | 4r              | 89%   | 90% ee |
| 19    | Bu  | 4s              | 83%   | 68% ee |
| 20    | TIPS| 4t              | 78%   | 84% ee |

\(^{a}\) The reaction was carried out on a 0.2 mmol scale, and Rh\(_2\)(S-TFPTTL)\(_4\) (1.0 mol%) was added as a solution in TBME (1.0 mL) via syringe pump in 40 min under inert atmosphere at 40 °C. The yields are given in isolated yields.

\(^{b}\) The reaction was carried out on a 4.0 mmol scale with 0.5 mol% catalyst loading.

\(^{c}\) At 60 °C for 12 h.

\(^{d}\) Rh\(_2\)(S-PTAD)\(_4\) (1.0 mol%) was used as the catalyst.

\(^{e}\) The reaction was carried out in cyclohexane:TBME = 1:10 at 30 °C.
position, Suzuki coupling with the bromo-derivative, and saponification of the lactone (see Supplementary Methods for the synthesis of 6c, 7c, and 8c for details).

**DFT calculations on reaction 1.** To support our hypothesis on enantiocontrol by the transient axial chirality, DFT calculations were carried out for reaction 1 (Tables 1 and 2). Substrate 1a was chosen as the model substrate. Calculation results show that the Rh(II)-catalyst provides a helical chirality environment (Fig. 2). Analogous acceptor-type carbene structures have been investigated by Hashimoto, Charette, Müller, Fox, Davies, and Sigman, independently in their corresponding metal-carbene reactions. Initially, the dirhodium catalyst and the diazo substrate forms a complex reversibly. In the diazo-decomposition transition state, the formed chiral carbon (C*) induces the formation of the axial chirality after the leaving of N₂ gas. Based on the conformation analysis of diaryl-substituted dirhodium(II) carbene, two chiral conformers were located. DFT calculation results show that forming of the S-configuration is the favored one (TS-S is favored over TS-R by 2.7 kcal/mol). In the structure of TS-S, remarkable π-π stacking interaction between substrate and chiral ligand can be observed. The diazo decomposition is irreversible and an activation-controlled process (not a diffusion-controlled process, see discussion in the DFT study of reaction 2 below), suggesting that the reaction will favor the S-pathway via TS-S to generate chiral rhodium(II) carbene intermediate IN-S, which has transient axial chirality because the rotation of the C–C bond is hindered by the bulky dirhodium catalysts (we did not calculate this step, but this can be well understood by the DFT study of reaction 2 below, where rotation of the axial chiral intermediate is difficult). This transient-axial chirality is then transferred to the final product via formal C–H insertion reaction (only one transition state is available).

**DFT calculations on reaction 2.** Detailed DFT calculations have also been carried out for understanding the mechanism of the key

![Fig. 2 Enantioselectivity transition states of reaction 1 with 1a to 2a as example.](image)

The forming of the S-configuration product 2a is the favored one (TS-S is favored over TS-R by 2.7 kcal/mol. Calculations at SMD(toluene)-M06L-D3/Def2TZVP//PBE-D3/Def2SVP/W06 level).

![Fig. 3 Gibbs energy profile for catalytic cascade reaction 2 with 3a to 4a as example.](image)

The discovery of carbene–Rh-dimer complex formation via ISC process in CAM process. Calculations at SMD(DCM)-M06L-6-31G(d,p)&SDD//PBE-6-31G(d,p)&SDD level. MECP minimum energy-crossing point.
Suggesting that the experimental ee% value should be up to 80%. Calculations at SMD(toluene)-M06L-D3/Def2TZVP//PBE-D3/Def2SVP/W06 level. The above computed potential energy surface provides us with a complete picture of the present cascade reaction. This mechanism has also been used to explain why the substrate 3h has lower reactivity, mainly due to the slower C–H insertion step (see Supplementary Fig. 148 and Supplementary Table 7 for details). Of the same importance, the discovery of carbene–Rh-dimer complex formation via ISC process is significant for the future understanding of similar processes.

Stereochemistry discussion for the reaction 2. The enantioselectivity of the real system was then investigated based on the above mechanistic insights. After formation of the complex with the diazo substrate, two possible transition states with different orientations were obtained. The pro–R TS is 1.34 kcal/mol higher than the corresponding pro–S TS, suggesting that the experimental ee% value should be up to 80% (Fig. 4). We found that in the favored one, the phenylpropargyl group has less steric repulsion with the ligand. This transition state also benefits from weak π–π stacking interaction between phenyl-propargyl group and aromatic ring of the ligand. Low-barrier intramolecular CAM process inhibits the dissociation of the catalyst and other side reactions, thus this initially formed transient axial chirality in the metal-carbene intermediate that controlled the following asymmetric transfer processes, and enabling the stereospecificity chirality transfer in the final formal C–H insertion step via an axial-to-point chirality transfer model. According to the above results, the mechanistic proposal of this fluorene ring formation using chiral dirhodium as a catalyst is depicted in Fig. 5. In the initial step, Rh(II)-mediated decomposition of diazo compound 3a generated the first chiral carbene intermediate I with axial chirality due to the hindered rotation of the congested geometry. Followed by a dual-carbene/alkyne metathesis process to form the third axial chirality–carbene-intermediate III via the second one II. Finally, the catalytic cycle is finished by a selective C(sp3)-H insertion with the axial chirality transfer to the carbon chirality center via an axial-induced-point chirality transfer model. Considering the C–H insertion is the rate-determining step in this tandem reaction, we calculated the barrier of C–H insertion and rotation of c-INT3 in real system (Fig. 6), the barrier of final C–H insertion reaction is 23.7 kcal/mol, which is consistent with the experimental result. The rotation barrier here is 13.4 kcal/mol higher than C–H insertion reaction, so the chiral transfer is complete in this step and the enantioselective determining step is not C–H insertion step here. For other two optimized key structures of I and II in real system, see Supplementary Fig. 152 for details.
Discussion
In summary, we have reported a transient axial-chirality transfer strategy for asymmetric reaction, which takes advantage of the point chirality of the dirhodium catalyst that can be transferred to a Rh–carbene intermediate with transient axial chirality due to the hindered rotation introduced by the bulky carbene species. Further applications of this transient axial-chirality transfer concept could be envisioned for other asymmetric reactions.

Methods
General methods. See Supplementary Methods for further details.

Typical procedure for the direct asymmetric C–H functionalization reaction. To a 10–mL oven-dried vial containing a magnetic stirring bar, diazo compound 1 (0.2 mmol), and 4 Å MS (100 mg) in TBME (1.0 mL) and Rh2(S-TFPTTL)4 (3.0 mg, 1.0 mol%) was added as a solution in TBME (1.0 mL) via a syringe pump over 40 min under argon atmosphere at room temperature. After addition, the reaction mixture was stirred for additional 1–5 h, as indicated, and then purified by column chromatography on silica gel without any additional treatment (hexanes: DCM = 20:1 to 10:1) to give the desired 9-aryl fluorene products 2.

Typical procedure for the asymmetric cascade reaction. To a 10–mL oven-dried vial containing a magnetic stirring bar, diazo compound 3 (0.2 mmol), and 4 Å MS (100 mg) in TBME (1.0 mL) and Rh2(S-TFPTTL)4 (3.0 mg, 1.0 mol%) was added as a solution in TBME (1.0 mL) via a syringe pump over 40 min under argon atmosphere at 40 °C. After addition, the reaction mixture was stirred for additional 20 min, and then purified by column chromatography on silica gel without any additional treatment (hexanes: DCM = 2:1 to 1:1) to give the desired polycyclic products 4.

Data availability
Additional data and computational study details supporting the findings described in this manuscript are available in the Supplementary Information. For full characterization data of new compounds and experimental details, see Supplementary Methods and Figures in Supplementary Information file. The X-ray crystallographic coordinates for structure 4b reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number 1502218. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. All other data are available from the authors upon reasonable request.

Received: 16 October 2019; Accepted: 9 April 2020; Published online: 12 May 2020

References
1. Ford, A. et al. Modern organic synthesis with α-diazocarbonyl compounds. Chem. Rev. 115, 9981–10080 (2015).
2. Doyle, M. P., Ratnikov, M. & Liu, Y. Intramolecular catalytic asymmetric carbon–hydrogen insertion reactions. Synthetic advantages in total synthesis in comparison with alternative approaches. Org. Biomol. Chem. 9, 4007–4016 (2011).
3. Lombard, F. J. & Coster, M. J. Rhodium(n)–catalysed intramolecular C–H insertion α– to oxygen: reactivity, selectivity and applications to natural product synthesis. Org. Biomol. Chem. 13, 6419–6443 (2015).
4. Fuwa, H. & Sasaki, M. Exploiting ruthenium carbene-catalyzed reactions in total synthesis of marine oxacyclic natural products. Bull. Chem. Soc. Jpn. 89, 1403–1415 (2016).
5. Davies, H. M. L. & Denton, J. R. Application of donor/acceptor-carbenoids to the synthesis of natural products. Chem. Soc. Rev. 38, 3061–3071 (2009).
6. Shim, S. Y. & Ryu, D. H. Enantioselective carbonyl 1,2- or 1,4-addition reactions of nuclophilic silyl and diazo compounds catalyzed by the chiral oxazaborolidinium ion. Acc. Chem. Res. 52, 2349–2360 (2019).
7. Herndon, J. W. The chemistry of the carbon-transition metal double and triple bond: annual survey covering the year 2015. Coord. Chem. Rev. 329, 53–162 (2016).
8. Candela, N. R., Paterna, R. & Goï, P. M. P. Homolagation reaction of ketones with diazo compounds. Chem. Rev. 116, 2937–2981 (2016).
9. Lebel, H., Marcoux, J. F., Molinario, C. & Charette, A. B. Stereoselective cyclopropanation reactions. Chem. Rev. 103, 977–1050 (2003).
10. Eibner, C. & Carreira, E. M. Cyclopropanation strategies in recent total syntheses. Chem. Rev. 117, 11651–11679 (2017).
11. Zhu, S. & Zhou, Q. Transition–metal–catalyzed enantioselective heteroatom–hydrogen bond insertion reactions. Acc. Chem. Res. 45, 1365–1377 (2012).
12. Keipour, H., Carreras, V. & Ollevier, T. Recent progress in the catalytic carbene insertion reactions into the silicon–hydrogen bond. Org. Biomol. Chem. 15, 5441–5456 (2017).
13. Davies, H. M. L. & Manning, J. R. Catalytic C–H functionalization by metal carbendenitrogeninsertion. Nature 451, 417–424 (2008).
14. Peña–López, M. & Beller, M. Functionalization of unactivated C(sp3)–H bonds using metal-carbene insertion reactions. Angew. Chem. Int. Ed. 56, 46–48 (2017).
15. Che, C., Lo, V. K., Zhou, C. & Huang, J. Selective functionalisation of saturated C–H bonds with metalloporphyrincatalysts. Chem. Soc. Rev. 40, 1950–1975 (2011).
18. Guo, X. & Hu, W. Novel multicomponent reactions via trapping of protic...  
19. Zhang, Z. K. et al. Catalytic asymmetric tri...  
20. Hashmi, A. S. K. & Toste, F. D. Gold catalysis...  
21. Barluenga, J. & Valdés, C. Tosylhydrazones: new uses for classic reagents in...  
22. Echavarren, A. M., Hashmi, A. S. K. & Toste, F. D. Gold catalysis...  
23. Deng, R., Xi, J., Li, Q. & Gu, Z. H. Enantioselective carbon...  
24. Qi, L. W., Mao, J. H., Zhang, J. & Tan, B. Organocatalytic asymmetric...  
25. Liang, Y., Zhou, H. & Yu, Z. X. Why is copper(I) complex more competent...  
26. Xie, J. H. & Zhou, Q. L. Chiral diphosphine and monodentate phosphorus...  
27. Archambeau, A., Miege, F., Meyer, C. & Cossy, J. Intramolecular...  
28. Torres, Ó. & Pía–Quintana, A. The rich reactivity of transition metal carbonyls...  
29. González–Rodríguez, C., Suárez, J. M., Varela, J. A. & Sá, C. C. Nucleophilic addition of amines to ruthenium carbene: ortho-(alkynylxoy)benzylamine cyclizations towards 1,3-benzoazines. Angew. Chem. Int. Ed. 54, 2724–2728 (2015).  
30. Ni, Y. & Montgomery, J. Synthetic studies and mechanistic insight in nickel-catalyzed [4+2+1] cycloadditions. J. Am. Chem. Soc. 128, 2609–2614 (2016).  
31. Le, P. Q. & May, J. A. Hydrazine-initiated carbene/alkyne cascades to form polycyclic products: ring-fused cyclopropanes as mechanistic intermediates. J. Am. Chem. Soc. 137, 12219–12222 (2015).  
32. Yao, R., Rong, G., Yan, B., Qu, L. & Xu, X. Dual-functionalization of alkynes via copper–carbene/alkyne metathesis: a direct access to the 4-carboxyl quinolines. ACS Catal. 6, 1024–1027 (2016).  
33. Dong, K. et al. Selective C(spn)-H bond insertion in carbene/alkyne metathesis reactions. Enantioselective construction of dihydroiodanes. ACS Catal. 8, 9543–9549 (2018).  
34. Torres, O., Roglans, A. & Pía–Quintana, A. An enantioselective cascade cyclopropanation reaction catalyzed by rhodium(I): asymmetric synthesis of vinylcyclopropanes. Adv. Synth. Catal. 358, 3512–3516 (2016).  
35. Sun, F., Zeng, M., Gu, Q. & You, S. Enantioselective synthesis of fluorine derivatives by chiral phosphoric acid catalyzed tandem double Friedel–Crafts reaction. Chem. Eur. J. 15, 8709–8712 (2009).  
36. Kim, J., Oh, Y., Park, S., Jung, Y. & Yang, C. Intramolecular aromatic carbene insertion of biaryldiazoacetates for the regioselective synthesis of fluorenes. Chem. Asian J. 6, 2040–2047 (2011).  
37. Veiga, M. I. et al. Globally prevalent PIMDR1 mutations modulate Plasmodium falciparum susceptibility to artesiminin-based combination therapies. Nat. Commun. 7, 11535–11536 (2016).  
38. Beaupré, S., Boudreaud, P. L. & Leclerc, M. Solar-energy production and energy-efficient lighting: photovoltaic devices and white-light-emitting diodes using poly(2,7-fluorene), poly(2,7-carbazole), and poly(2,7-diindenozulene) derivatives. Adv. Mater. 22, 6–27 (2010).  
39. Tian, Y. et al. Design and synthesis of new stable fluorenyl-based radicals. J. Am. Chem. Soc. 136, 12784–12793 (2014).  
40. Liu, Z. et al. Transition-metal-free intramolecular carbene aromatic substitution/büchner reaction: synthesis of fluorenes and [6, 5, 7] benzo-fused rings. Angew. Chem. Int. Ed. 54, 3056–3060 (2015).  
41. Soldi, C. et al. Enantioselective intramolecular C–H insertion reactions of donor–donor metal carbeneoids. J. Am. Chem. Soc. 136, 15142–15145 (2014).  
42. Gott, T. et al. Highly enantioselective cyclopropanation reaction of 1-alkynes with α-alkyl-a-diazoesters catalyzed by dirhodium (II) carbonylates. Angew. Chem. Int. Ed. 60, 6803–6808 (2011).  
43. Duncan, J. V. N., Lin, W. & Charette, A. B. Experimental evidence for the all-up reactive conformation of chiral rhodium(II) carbonylate catalysts: enantioselective synthesis of cis-cyclopropane α-amino acids. J. Am. Chem. Soc. 131, 16383–16385 (2009).  
44. Ghanem, A., Gardiner, M. G., Williamson, R. M. & Müller, P. First X–ray structure of a N-naphthyl-tethered chiral dirhodium(II) complex: structural basis for tether substitution improving asymmetric control in olefin cyclopropanation. Chem. Eur. J. 16, 3291–3295 (2010).  
45. DeAngelis, A., Dmitrenko, O., Yap, G. P. A. & Fox, J. M. Chiral crown conformation of Rh3(SPh)3PTTL: enantioselective cyclopropanation with α-alkyl-a-diazoesters. J. Am. Chem. Soc. 131, 7230–7231 (2009).  
46. Liao, K. et al. Site-selective carbene-induced C–H functionalization catalyzed by dirhodium tetrakis(triarylcarboxyl)carbonylates. ACS Catal. 8, 678–682 (2018).  
47. Gliaš, J. H. et al. Intramolecular cycloadditions of cyclobutadiene with olefins. J. Am. Chem. Soc. 124, 14748–14758 (2002).  
48. Wang, Y., Cai, P.-J. & Yu, Z.-X. Mechanistic study on gold-catalyzed cycloisomerization of dienedienes involving aliphatic C–H functionalization and inspiration for developing a new strategy to access polycarbocycles. J. Am. Chem. Soc. 142, 2777–2786 (2020).  
49. Kang, C. et al. Living metatllotropy and metallopolymorphism gives conjugated polyanhydrides from multialkyenes: how to design sequence-specific cascades for polymers. J. Am. Chem. Soc. 140, 16320–16329 (2018).  
50. Gheewala, C. D., Collins, B. E. & Lambert, T. H. An aromatic ion platform for enantioselective Bronsted acid catalysis. Science 351, 961–965 (2016).
Acknowledgements
Support for this research from the National Natural Science Foundation of China (21971262, 91856105), Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery (2019B030301005), and The Program for Guangdong Introducing Innovative and Entrepreneurial Teams (No. 2016ZT06Y337) is greatly acknowledged.

Author contributions
X.X. and Z.Y. conceived and designed the study; K.D. performed the initial and most of the experiments; X.F. carried out the calculations, X.F and Z.Y. analyzed the computational data; C.P. and Y.Z. repeated the experiments; S.C. and J.C. analyzed the experimental data; L.Q. collected and refined the X-ray diffraction data. All the authors contributed to scientific discussion. X.X. and Z.Y. wrote the paper.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information is available for this paper at https://doi.org/10.1038/s41467-020-16098-8.

Correspondence and requests for materials should be addressed to Z.-X.Y. or X.X.

Peer review information Nature Communications thanks the anonymous reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2020