SCIENCE CHINA
Chemistry

•ARTICLES•

September 2020 Vol.63 No.9: 1230–1239
https://doi.org/10.1007/s11426-020-9794-3

Synergy of activating substrate and introducing C–H···O interaction to achieve Rh_2(II)-catalyzed asymmetric cycloisomerization of 1,*n*-enynes

Rui Wu[1†], Kai Chen[2†], Jun Ma[1†], Zhi-Xiang Yu[3*] & Shifa Zhu[1*]

[1]*Key Lab of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China;*
[2]*College of Chemistry and Chemical Engineering, Central South University, Changsha 410083, 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*

Received April 24, 2020; accepted June 16, 2020; published online July 29, 2020

We report the first Rh_2(II)-catalyzed asymmetric cycloisomerization of activated enynes to provide cyclopropane-fused tetrahydropyridines in good yields and excellent enantioselectivities under mild conditions. The activated group, CHZ (Z is electron-withdrawing group (EWG)), in the enyne substrates exerts two synergetic roles, one is to activate alkyne for the cyclopropanation reaction; the other is to introduce the C–H···O interaction between substrate and catalyst (reducing the energy barrier of the reaction). This double-mode activation was supported by both density functional theory (DFT) calculations and experimental tests. This strategy was also extended to other CH_2Z (Z can be OH, OMe, F) as activating groups that made the CH_2 more acidic so that the substrates could also form increased C–H···O interaction with the catalyst.

asymmetric cycloisomerization, chiral cyclopropane, dirhodium catalysis, carbene

Citation: Wu R, Chen K, Ma J, Yu ZX, Zhu S. Synergy of activating substrate and introducing C–H···O interaction to achieve Rh_2(II)-catalyzed asymmetric cycloisomerization of 1,*n*-enynes. *Sci China Chem*, 2020, 63: 1230–1239, https://doi.org/10.1007/s11426-020-9794-3

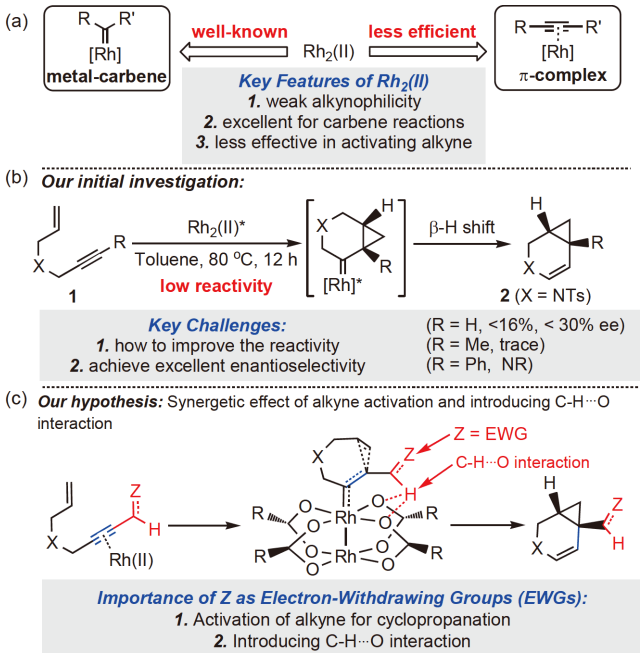
1 Introduction

Chiral cyclopropane-annulated bicyclic system represents a kind of unique and important motif, which has been found in many natural products and bioactive molecules [1]. Among the reported synthetic methods towards these bicyclic scaffolds, transition metal-catalyzed asymmetric cycloisomerization of 1,*n*-enynes is one of the most efficient methods [2]. The widely used chiral catalysts for the asymmetric transformations are based on Au and Pt complexes [3,4]. Chiral dirhodium(II) complexes, structurally well-defined paddlewheel compounds with Rh_2^{4+} motif, have been known to catalyze carbene-transfer and nitrene-transfer reactions. Their structural uniqueness and excellent stereoselection in catalytic chemical reactions place them among the most important asymmetric catalysts employed for chemical transformations, especially in carbene chemistry by the decomposition of diazo compounds [5]. However, they were rarely used to activate the carbon-carbon triple bond. This is mainly because the Rh_2(II) unit has too low alkynophilicity to activate an alkyne (Scheme 1(a)) [6]. In our preliminary reaction condition screening, we found that dirhodium(II) nonfluorocarboxylate complexes $Rh_2(O_2CR)_4$ displayed very low reactivity and asymmetric induction (Scheme 1(b)). These negative results further implied the low alkynophili-

†These authors contributed equally to this work.
*Corresponding authors (email: yuzx@pku.edu.cn; zhusf@scut.edu.cn.)
Dedicated to the 70th Anniversary of Shanghai Institute of Organic Chemistry

city of Rh_2(II) complexes. It is therefore highly desirable but challenging to develop an effective strategy to enhance the reactivity of Rh_2(II) complexes towards C≡C bonds and finally achieve asymmetric cycloisomerization of 1,*n*-enynes.

It has been reported that metal carbenoids possessing adjacent electron-withdrawing groups (EWGs) were more reactive for carbene transfer reactions [7]. We then hypothesized that an electron-withdrawing substituted alkyne might help the cycloisomerization of 1,*n*-enyne occur through the generation of a more reactive dicarbene, because of electron-withdrawing capping group could benefit the separation of the alkyne π-electrons and then stabilize the dicarbene resonance structure of metal-alkyne complex [2a,6a,8]. We also reasoned that in addition to the electronic effect, the steric effect should be taken into considerations for the design of reaction (Scheme 1(c)). Inspired by different cooperative interactions, such as hydrogen bonding [9], halogen bonding [10], and electrostatic bonding [11], we then designed a double-mode activation to achieve the effective cycloisomerization: 1) using electron-withdrawing capping group, CHZ (Z is EWG), to activate the alkyne for cyclopropanation through generating a more reactive carbene; 2) introducing a C–H···O interaction between the small CHZ and the carboxylate ligand to promote the reaction (Scheme 1(c)). Furthermore, it was expected that such C–H···O might also exert a positive influence on the asymmetric induction through the rigidification of ligand chiral environment. The small formyl group (–CHO) was initially chosen as the capping group of the C–C triple bond to test the above hypothesis. Our experimental investigations and density functional theory (DFT) calculation supported that the above double-mode activation (EWG activation and C–H···O attraction) is significant for the asymmetric cycloisomerization. This double-mode activation is a new catalytic strategy in transition metal catalysis, which may inspire organic chemists to design new reactions and new catalysts.



Scheme 1 Challenges of Rh(II)-catalyzed cycloisomerization of 1,6-enynes and our solutions (color online).

2 Experimental

To a toluene solution of **1** (0.25 mmol, 1 mL) in a Schlenk tube with a magnetic bar was added Rh_2(*S*-BTPCP)$_4$ (0.25 μmol, 0.1 mol%, 0.44 mg, the catalyst was dissolved in toluene) at 0 °C under N_2. The sealed tube was stirred at 0 °C under nitrogen atmosphere for 48 h. The mixture was then concentrated and the residue was purified by chromatography on silica gel (eluent: ethyl acetate/petroleum ether) to afford the desired product **2**.

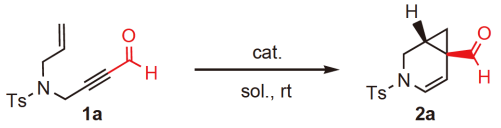
Calculations were performed with Gaussian 09 software package [12]. The hybrid B3LYP [13] functional in conjugation with the LANL2DZ [14] basis set for rhodium (augmented with a 4f-function, ζ_f(Rh)=1.350) [15] and the 6-31G(d) basis set for the other atoms [16], was applied for the optimization of all stationary points in gas phase. Frequency calculations were performed at the same level to verify that the stationary points are minima (0 imaginary frequency) or saddle points (only 1 imaginary frequency). $Rh_2(OAc)_4$ was used as the catalyst model during the investigation of reaction mechanism, to simplify the problem and reduce the computation cost. Single point energy calculations were carried out with Truhlar's M06 [17] functional with SDD [18] basis set for rhodium, and 6-311++G(d,p) for the other atoms in gas phase or in toluene with SMD [19] solvent model. For each stationary point, conformational samplings were performed, and only the most stable conformation was reported. QTAIM analysis was carried out with the Multiwfn program [20]. Computed structures are illustrated using CYLView [21] or VMD [22].

3 Results and discussion

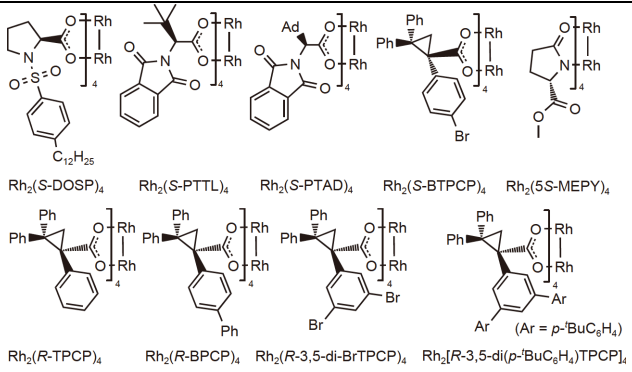
3.1 Catalyst screening and reaction condition optimization

Our double-mode activation strategy was tested initially by using enynal **1a** as the substrate for cycloisomerization. The reactivities of gold and platinum salts, which were typically effective catalysts for the cycloisomerization of 1,*n*-enyne, have been examined, but they were almost ineffective for this transformation (Table 1, entries 1–2). When dirhodium(II) tetracarboxylate $Rh_2(OPiv)_4$ was used instead, the catalytic reaction occurred smoothly, giving the desired cyclopro-

Table 1 Condition screening of the cycloisomerization of 1,6-enynal[a)]



Entry	cat. (mol%)	sol.	yield[b)]	ee[c)]
1	Ph_3PAuBF_4 (5)	DCE	Trace	–
2	$PtCl_2$ (5)	DCE	Trace	–
3	$Rh_2(OPiv)_4$ (1)	DCE	89%	–
4	Rh_2(*S*-DOSP)$_4$ (1)	DCE	42%	8%
5	Rh_2(*S*-PTAD)$_4$ (1)	DCE	34%	11%
6	Rh_2(*S*-PTTL)$_4$ (1)	DCE	40%	19%
7	Rh_2(*S*-BTPCP)$_4$ (1)	DCE	94%	76%
8[d)]	Rh_2(5*S*-MEPY)$_4$ (1)	DCE	36%	7%
9	Rh_2(*S*-BTPCP)$_4$ (1)	PhMe	96%	89%
10	Rh_2(*R*-TPCP)$_4$ (1)	PhMe	97%	−86%
11	Rh_2(*R*-BPCP)$_4$ (1)	PhMe	95%	−88%
12	Rh_2(*R*-3,5-di-BrTPCP)$_4$ (1)	PhMe	85%	−46%
13	Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$ (1)	PhMe	87%	−41%
14[e)]	Rh_2(*S*-BTPCP)$_4$ (1)	PhMe	91%	91%
15[e),f)]	Rh_2(*S*-BTPCP)$_4$ (0.1)	PhMe	93%	91%
16[e),g)]	Rh_2(*S*-BTPCP)$_4$ (0.01)	PhMe	43%	87%

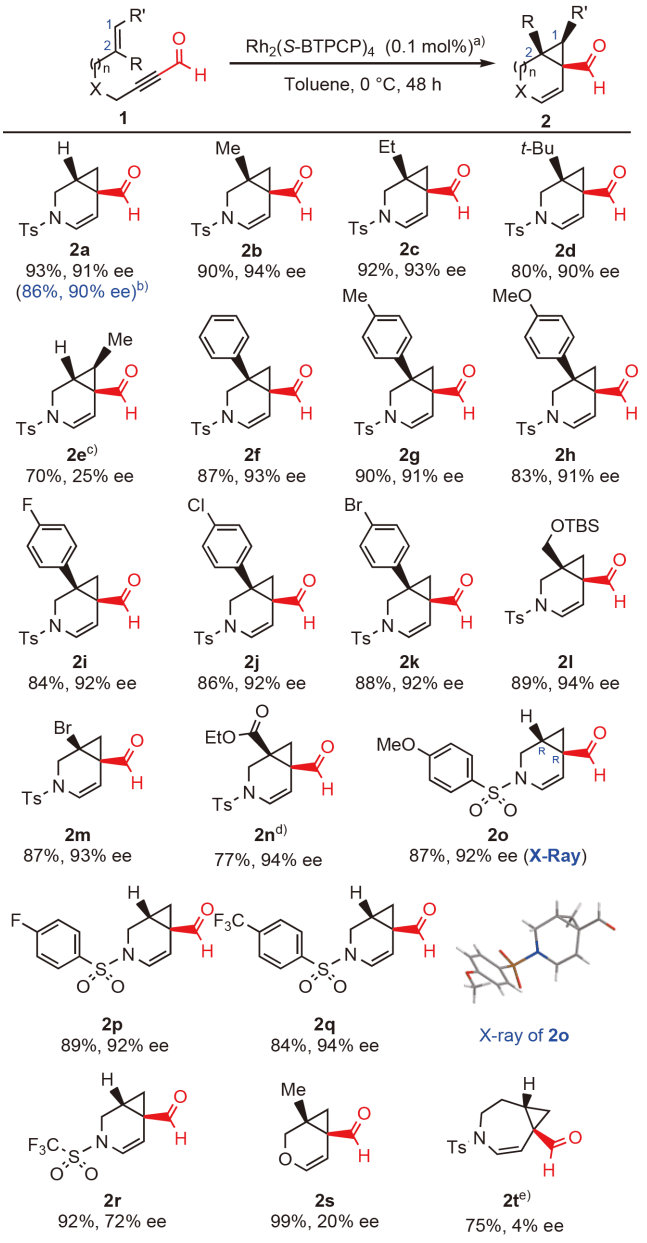


a) **1a** (0.25 mmol), **[1a]** = 0.25 M, 12 h. b) Isolated yield. c) Determined by chiral HPLC. d) 80 °C, 120 h. e) 0 °C. f) 48 h. g) 120 h. (cat. = catalyst; sol. = solvent; rt = room temperature; ee = enantiomeric excess; Ad = adamantyl).

pane-fused tetrahydropyridine product **2a** in 89% isolated yield (entry 3). It was noteworthy that no diene and other byproducts had been observed [6]. Encouraged by this result, several representative chiral dirhodium(II) complexes were then employed as the catalysts to investigate the asymmetric cycloisomerization of **1a**. The dirhodium carboxylates Rh_2(*S*-DOSP)$_4$, Rh_2(*S*-PTAD)$_4$ and Rh_2(*S*-PTTL)$_4$, which have been reported for their asymmetric catalysis carbene transfer reactions [7,23], resulted in moderate yield and low enantioselectivities (entries 4–6, 34%–42% yields and 8%–19% ee). Gratifyingly, dirhodium triaryl cyclopropanecarboxylate Rh_2(*S*-BTPCP)$_4$ significantly improved both the yield and enantioselectivity (entry 7, 94% yield and 76% ee) [24]. For comparison, dirhodium carboxamidate Rh_2(5*S*-MEPY)$_4$, which was previously employed in the hetero-Diels-Alder, carbonyl-ene and carbene transfer reactions in Doyle's systems [25,26], was ineffective for this reaction (entry 8). The asymmetric induction could be further increased to 89% ee when toluene was used as the solvent instead in the presence of Rh_2(*S*-BTPCP)$_4$ (entry 9). To further evaluate the performance of the triarylcyclopropanecarboxylate-based catalysts, four Rh_2(*S*-BTPCP)$_4$ analogues, Rh_2(*R*-TPCP)$_4$, Rh_2(*R*-BPCP)$_4$, Rh_2(*R*-3,5-di-BrTPCP)$_4$, and Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$ were synthesized [24c,24i] and tested for the reaction as well. Catalytic results disclosed that all four Rh$_2$(II) complexes were capable of promoting the reaction to produce the desired product **2a** in excellent yields (entries 10–13). Rh_2(*R*-TPCP)$_4$ and Rh_2(*R*-BPCP)$_4$ furnished the product **2a** in −86% and −88% ee, respectively. However, the enantioselectivity dropped significantly when using Rh_2(*R*-3,5-di-BrTPCP)$_4$, and Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)-TPCP]$_4$ as the catalysts. With Rh_2(*S*-BTPCP)$_4$ as the catalyst, further improvement of enantioselectivity could be achieved by decreasing the temperature to 0 °C (entry 14, 91% ee). The amount of catalyst could even be reduced to 0.1 mol% without any loss of enantioselectivity (entry 15). Further decreasing the amount of Rh_2(*S*-BTPCP)$_4$ to 0.01 mol% could afford the desired product **2a** as well, albeit with a slight loss of the enantioselectivity (87% ee) and reduction of the yield (entry 16) [27].

3.2 Substrate scope evaluation

Based on the optimized reaction conditions (Table 1, entry 15), the substrate scope of the Rh$_2$(II)-based catalytic system was then examined (Scheme 2). Initially, the reaction could be conducted in gram scale without significant loss of yield for product **2a** (86% yield and 90% ee). Furthermore, the catalytic system could be successfully applied to a variety of enynals **1**. For example, in addition to 1,6-enynal **1a**, 1,6-enynal derivatives with different substituents attached to the C=C double bond could also be used as effective substrates, and the asymmetric induction was typically greater than 90% ee (Scheme 2, **2b**–**2n**). 1,6-Enynals with alkyl substituents at 2-position of the C=C double bond gave the desired products **2b**–**2d** in high yields (80%–92%) and excellent ee (90%–94%). However, the substituent at terminal position of the C=C double bond had a significantly negative effect on the asymmetric induction, producing the desired product **2e** in 70% yield and 25% ee. The substrates with aryl group at 2-position of the C=C double bond furnished the desired products **2f**–**2k** in high yields (83%–90%) and excellent ee (91%–93%). The reaction was not sensitive to the electronic properties of substrates as the enynals substituted with both electron-rich and -deficient aryl groups gave similar results (**2g**–**2k**). By adjusting the conditions slightly, it is worth to mention that the enynals with a TBS-protected hydro-



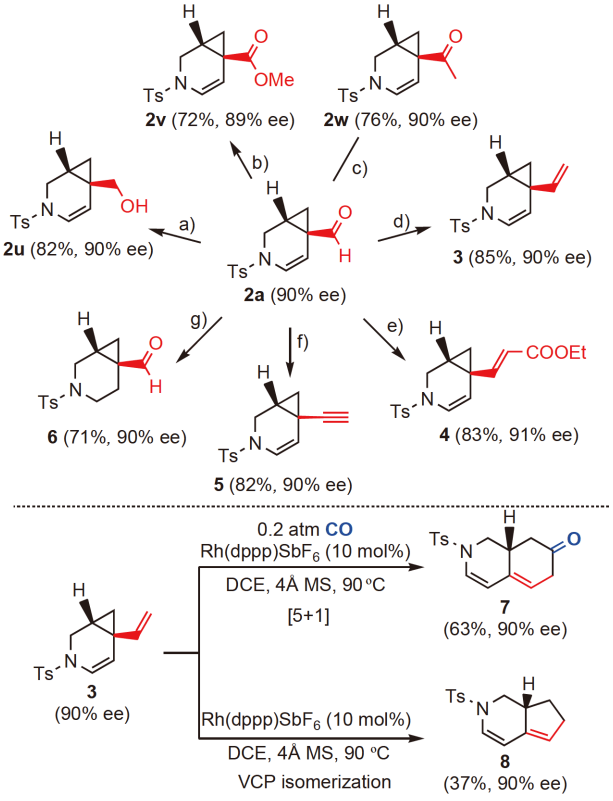
Scheme 2 Substrate scope for the Rh_2(*S*-BTPCP)$_4$-catalyzed asymmetric cycloisomerization of 1,6-enynals and 1,7-enynal. a) **1** (0.25 mmol), [**1**] = 0.25 M. Isolated yield. The ee values were determined by HPLC analysis with a chiral stationary phase. b) **1a** (4.5 mmol,1.25 g). c) dr = 6/1 (the *E*/*Z* ratio of 1,6-enynal **1d** was 6/1). d) 1 mol% catalyst, rt, 60 h. e) 2.5 mol% catalyst, 80 °C (color online).

xymethyl group (TBS-OCH$_2$–), bromine atom (Br), and ester group (–CO$_2$Et) at 2-position of the C=C bond could be utilized as the suitable substrates as well, giving the corresponding products **2l–2n** in good yields (77%–89%) and excellent ee (93%–94%). These functional groups (TBS–OCH$_2$–, Br, –CO$_2$Et) might serve as useful chemical handles for further manipulations.

In addition to the enynals with *p*-toluenesulfonyl amide tether, the substrates with other aryl sulfonyl amide tether worked equally well under the standard reaction conditions (**2o–2q,** 92%–94% ee). The absolute configuration of (*R*,*R*)-**2o** was determined by the X-ray crystallography analysis. A less sterically bulky amide tether (triflic amide) reduced the enantioinduction to 72% ee (**2r**). The enynal with ether tether led to the cyclopropane-fused dihydropyran **2s** in quantitative yield (99%), but with much poorer enantioselectivity (20%). It seemed that the enantioinduction was highly sensitive to the tether size. Furthermore, this catalytic reaction could be extended to 1,7-enynal, giving the desired cyclopropane-fused tetrahydroazepine **2t** in 75% yield, but the enantioselectivity decreased sharply to only 4%.

3.3 Synthetic applications

With an efficient route to the highly functionalized formyl-substituted cyclopropane-fused bicyclic compounds **2** in enantioenriched form by Rh_2(II)-catalyzed cycloisomerization of 1,*n*-enynals in hand, we then proceeded to explore their potential applications as chiral building blocks for further transformations. As shown in Scheme 3, the formyl group of **2a** could be easily converted into the alcohol **2u**, ester **2v**, or ketone **2w** in good yields with full retention of the configuration [28]. Furthermore, the formyl moiety could



Scheme 3 Further chemical transformation of **2a**. a) $NaBH_4$ (2.0 eq.), MeOH. b) i) NaOClO (3.0 eq.), NaH_2PO_4 (4.0 eq.), 2-methyl-2-butene/^{t}BuOH/H_2O (3/3/1); ii) MeI (2.0 eq.), K_2CO_3 (2.0 eq.), DMF. c) i) MeMgBr (1.5 eq.), THF; ii) DMP (1.2 eq.), DCM. d) *n*-BuLi (1.5 eq.), Ph_3PMeBr (2.0 eq.), THF. e) $Ph_3PCHCOOEt$ (1.2 eq.), DCM. f) i) CBr_4 (1.5 eq.), PPh_3 (2.0 eq.), DCM; ii) *n*-BuLi (3.0 eq.), THF, −78 °C. g) Et_3SiH (2.0 eq.), TFA (2.0 eq.), DCM (color online).

also be transformed into alkenyl and alkynyl groups through the well-established methods [29], leading to the synthetically highly useful vinylcyclopropanes [30] (VCPs: **3** and **4**) or acetylenylcyclopropane (**5**) in excellent yields. Alternatively, the C=C double bond in **2a** could be selectively reduced to give cyclopropane-fused piperidine **6** without affecting the aldehyde functionality under the reduction of Et_3SiH [31]. In all cases, the stereochemistry was completely preserved. Furthermore, cationic Rh(I) could catalyze the [5+1] cycloaddition and rearrangement of VCP **3** with or without CO, affording bicyclic heterocycles **7** and **8** with full retention of the configuration [30e].

3.4 Reaction mechanism

In this part, we will first present the favored pathway of the cycloisomerization of **1a** using $Rh_2(OAc)_4$ to obtain information of the reaction mechanism and the rate- and stereo-determining step (Figure 1). Then in-depth analysis of the double-mode activation strategy will be given.

3.4.1 Reaction pathway

DFT calculations indicate that the reaction starts with ligand exchange reaction between substrate and the product-catalyst complex (which comes from the previous catalytic cycle) to give **I(a)-Ene** and **I(a)-Yne**. The former one is alkene coordination to Rh and the latter one is alkyne coordination. **I(a)-Ene** is more stable than the **I(a)-Yne** by 1.8 kcal/mol (ΔG_{sol}). Therefore, reaction starts from **I(a)-Ene**, then *via* **I(a)-Yne**, followed by cyclopropanation. The cyclopropantion step takes place with an activation free energy of 17.1 kcal/mol. Then 1,2-H shift occurs with a lower activation barrier, 13.4 kcal/mol in terms of free energy. Finally, the product **2a** is released by exchange reaction between substrate and complex **III(a)**. The whole potential energy surface shows that cyclopropanation step is the rate-determining step. This conclusion was further supported by the experimental results in Scheme 4: no obvious kinetic isotope effects (KIE) was observed in the intermolecular competition KIE experiments (Eq. (1)). The intramolecular 1,2-H shift was also supported by deuterated experiment: 100% deuteration at the propargylic position of **1a** led to 100% incorporation of deuterium at alkene carbon (Eq. (2)). We have also considered the 5-*exo* and [1,2]-H shift/cyclopropanation pathways. The reaction pathway starting from the aldehyde binding to dirhodium(II) catalyst was also considered. However, these pathways are disfavored (see Figure S1 in Supporting Information online for details). In transition state **I-TS-II(a)**, the forming C–C bonds are 2.28 and 2.41 Å. The forming and breaking C–H bonds in **II-TS-III(a)** are 1.38 and 1.28 Å, respectively. To our delight, novel double C–H···O interactions can be observed in the transition states. The distances between the formyl hydrogen and two carboxyl oxygen atoms are about 2.47 and 2.54 Å in **I-TS-II(a)**, which are below the sum of the van der Waals radii of 2.72 Å (H=1.20 Å and O=1.52 Å) [32]. These C–H···O interactions play some roles to decrease the steric repulsion between substrate and catalyst's

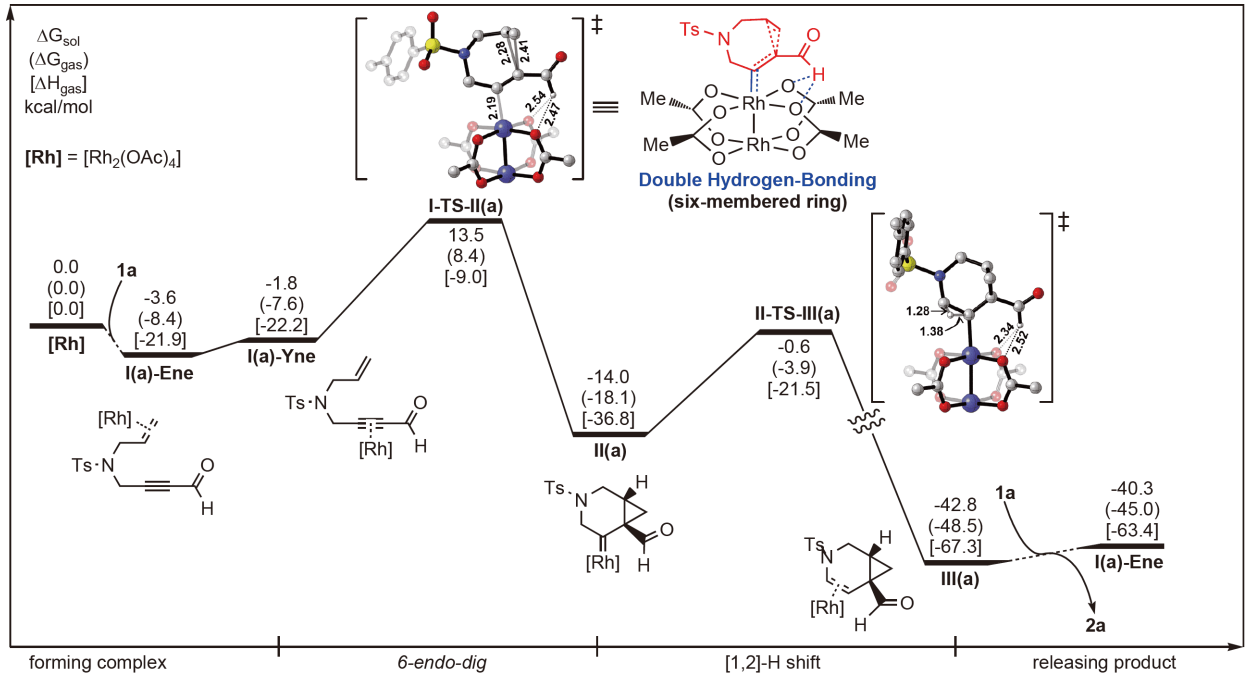
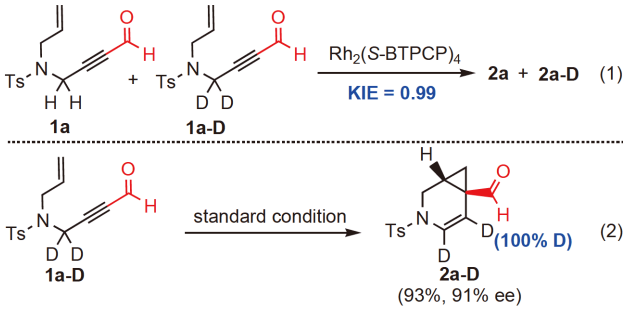


Figure 1 Possible reaction pathway for the cycloisomerization of 1,6-enynal **1a** in toluene at M06/(6-311++G(d,p), SDD)-SMD//B3LYP/(6-31G(d), LanL2DZ+f) theoretical level. ΔG_{sol} (the relative Gibbs free energies in toluene), ΔG_{gas} (the relative Gibbs free energies in gas phase), ΔH_{gas} (the relative enthalpies in gas phase) are given in kcal/mol, and distances in Å (color online).



Scheme 4 Deuterated experiments (color online).

acetate ligands which will be discussed later.

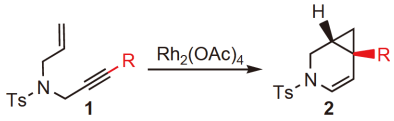
3.4.2 Computational data and control experiments of the double-mode activation

As indicated in the introduction part, we hypothesized two synergetic effects: the electron withdrawing effect to activate alkyne, and the introduction of C–H···O interaction. To better understand this synergy and further expand the present activation mode, we have carried out a series of calculations of the enynes with different substituents. It is found that the 6-*endo*-dig cyclopropanation step is rate-determining in the 6-*endo*-dig/[1,2]-H shift pathway for all the substrates shown in Table 2 (see Table S5 for details). The activation free energy of substrate **1a** is obviously lower than those of other substituted enynes such as enynones **1w** and **1x**, enynester **1v**, alkyl/aryl-substituted enynes **1y** and **1z**, enynol **1u**, fluoromethyl enyne **1aa**, methoxymethyl enyne **1ab**, and even terminal enyne **1ac** (Table 2), which could be attributed to the double-mode activation.

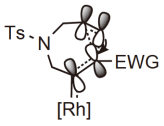
To further confirm the electronic effect, we used enyne cycloisomerization catalyzed by AuCl for comparison, where steric effects and C–H···O interaction are absent. DFT calculations really support that the electron-withdrawing group facilitates the reaction (Table S5). Now let's explain the present cyclopropanation step catalyzed by dirhodium(II) catalyst.

The formyl group (–CHO) facilitates the cyclopropanation step through a synergetic activation strategy: EWG group activating alkyne, and introducing C–H···O interaction with the catalyst. Generally, electron-rich alkynes are easier to coordinate with the metal centers, but in our case, there is no significant difference for these substrates and catalysts complexation *via* alkyne-Rh (Figure S4). Since the most difficult step of the cyclopropanation is from substrates' alkene-coordinated complexes (not substrates' alkyne coordinated complexes), which are all similar in energy for all substrates, to the transition states, the relative easiness of these reactions depends on how the alkene part of the substrates reacts with the alkyne part's π^* orbitals (Scheme 5). NBO [33] analysis of the transition states shows that the major interaction is alkene's π orbital (alkene can be regarded as the nucleophile), to π^* orbital of the alkyne-coordinated by Rh catalyst (alkyne can be regarded as the electrophile). The π^* orbital energies of Rh catalyst coordinated alkynes are −0.214, −0.208, 0.388, 0.932 eV for CHO, CH_2F, CH_2OMe, Me, suggesting that alkyne with electron-withdrawing group is stronger electrophile [34] and should be more reactive in cyclopropanation. Similar analysis has been taken in the reaction of gold-catalyzed intramolecular alkenylation of furans with alkynes [35].

Table 2 The calculated activation free energy barriers (given in kcal/mol) of different substrates at M06/(6-311++G(d,p), SDD)-SMD(toluene)//B3LYP/(6-31G(d), LanL2DZ+f) theoretical level.



1	R	I-TS-II ($\Delta G_{sol}^{\ddagger}$)	1	R	I-TS-II ($\Delta G_{sol}^{\ddagger}$)
1a	–CHO	17.1	**1z**	–Ph	25.9
1w	–COMe	25.2	**1u**	$-CH_2OH$	18.3
1x	–COPh	26.2	**1aa**	$-CH_2F$	19.9
1v	$-CO_2Me$	26.6	**1ab**	$-CH_2OMe$	21.1
1y	–Me	24.4	**1ac**	–H	22.6



Scheme 5 Interaction between alkene's π orbital and alkyne part's π^* orbital in the cyclopropanation transition states.

The CHO group certainly introduces steric effects, which can be partially appreciated by considering the C–Rh bond distance elongation in the cyclopropane transition state **I-TS-II(a)** (Figure 1) compared to the cyclopropanation transition state **I-TS-II(ac)** with R = H (2.19 *vs.* 2.18 Å). Unfortunately, it is difficult to compute the strength of this steric repulsion. Although usually the C–H···O interaction is weak, about 0.5 to 1.0 kcal/mol in most cases [36], the contribution of this C–H···O interaction in **I-TS-II(a)** is about −4.4 kcal/mol, evaluated from a Rh(II) carbene-acetaldehyde complex (Figure 2(a)). The relative strong C–H···O interaction in Rh(II) carbene-aldehyde complex should be attributed to the polarized C–H bond and carboxylic acid which can be regarded as an anionic group. The result is in agreement with Du and coworkers' theoretical studies on the acetic acid-acetaldehyde complex model, where the C–H···O attraction between formyl hydrogen and acid oxygen was calculated to be −4.5 kcal/mol at B3LYP-D3/aug-cc-pVTZ level [36c]. Distance of C–H···O between 2.40–2.50 Å is preferred, while decreasing or increasing the distance will weaken the attraction a little bit (Figure 2(b)) [37]. This C–H···O attraction was also supported by QTAIM analysis, as there are

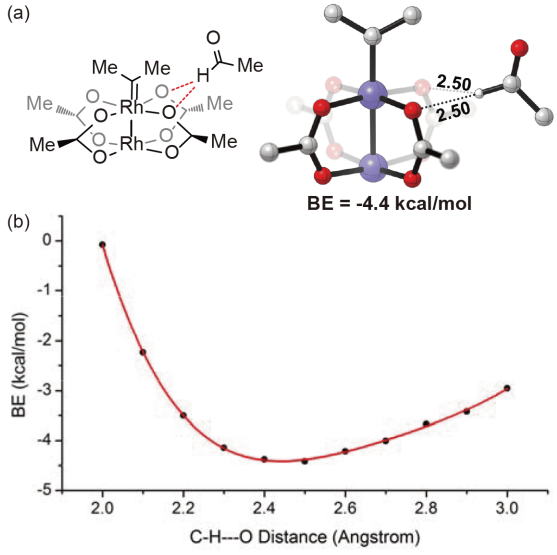


Figure 2 Binding energies (BE) of acetaldehyde and Rh(II) carbene complex at M06/(6-311++G(d,p), SDD)//B3LYP/(6-31G(d), LanL2DZ+f) theoretical level. (a) Investigated model; (b) dependence of BE on the C–H···O distance. BE of the complexes were obtained through subtracting the energies of the isolated acetaldehyde and Rh(II) catalyst from the energy of the complex, and corrected for BSSE [37]. During the optimization, all the heavy atoms of carbene and acetaldehyde were kept in the symmetry plane to avoid the unexpected interaction between acetaldehyde oxygen and electrophilic carbene (color online).

two (3, −1) type critical points between the formyl hydrogen atom and nearby ligand oxygen atoms in **I-TS-II(a)** (Figure 3).

This synergetic effect seems to be very important for the activation. If only considering EWG activation of alkyne, the reaction becomes difficult. The activation barriers of **1w** (R = –COMe), **1x** (R = –COPh), and **1v** (R = $–CO_2Me$) are 25.2, 26.2 and 26.6 kcal/mol, respectively, which are much higher than that of **1a** (R = –CHO). These high activation barriers could be explained by the loss of C–H···O interaction, but more importantly, the presence of steric repulsion, which is not easily evaluated computationally due to the replacement of hydrogen atom in –CHO by other substituents. Electron-donating capping group such as –Ph (**1z**) is surely inert due to the loss of both of the desired beneficial effects, and the activation barriers of these two substrates are higher than that of **1a** by more than 8.8 kcal/mol.

As replacing the hydrogen atom of –CHZ by other groups always comes up with steric repulsion, we wondered whether the formyl group could be extended to CH_2Z group if Z is strong enough to polarize the C–H bond. The activation barrier of 1,6-enynol **1u** with a hydroxyl group was then computed. We reasoned that hydroxymethyl group was also an EWG, but this was much weaker than formyl group to activate alkyne (because O is connected to alkyne by an CH_2 unit). DFT calculations indicated that a seven-membered ring and mono hydrogen-bonding interaction exists for the reaction of 1,6-enynol **1u** (see **I-TS-II(u)** in Figure 3). The H···O

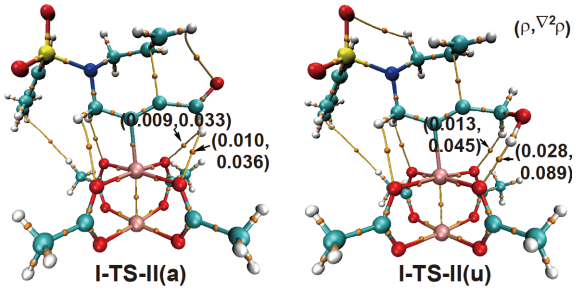


Figure 3 QTAIM analysis of **I-TS-II(a)** and **I-TS-II(u)**. Bond critical bonds were shown in orange dots. Electron density and its Laplacian for selected BCPs are in a.u. (color online).

distance between the hydroxyl hydrogen of enynol **1u** and the carbonyl oxygen of the catalyst is about 1.92 Å. QTAIM analysis also indicated C–H···O interaction in **I-TS-II(u)**, and the electron density of the C–H···O critical point is about half that of the strong O–H···O hydrogen bond (Figure 3). Interestingly, the substrate of 1,6-enynol **1u** possesses a stronger cooperative O–H···O hydrogen-bonding interaction but with a lower reactivity (18.3 kcal/mol) than that of **1a** (17.1 kcal/mol) (Table 2).

As mentioned earlier, the rhodium catalyst could coordinate with the alkene or alkyne group in the starting Rh-complex. Meanwhile, the alkene coordination mode is more stable than the alkyne coordination mode in all cases, but except the Rh-complex of 1,6-enynol **1u**. The presence of this strong O–H···O hydrogen-bonding interaction leads to an over-stabilization of the alkyne coordination complex **I(u)-Yne**, which will counteract its beneficial effect on the reaction activity to some extent. We further envisioned that other strong electronegative atoms, such as fluorine (F) or oxygen (O), might efficiently activate the neighboring propargylic CH_2 and then create potential cooperative C–H···O interactions with the carboxy oxygen atoms of catalyst so that these substrate enynes **1aa** (R = $–CH_2F$) and **1ab** (R = $–CH_2OMe$) could be also suitable for the cyclopropanation reaction. We did DFT calculations first to test this idea. As shown in Table 2, enynes **1aa** and **1ab** have free energy barriers of 19.9 and 21.1 kcal/mol for cyclopropanation step, which are much lower than that of the methyl counterpart **1y** (24.4 kcal/mol) and even lower than that of the terminal alkyne **1ac** (22.6 kcal/mol). In the structures of transition states **I-TS-II(aa)** and **I-TS-II(ab)**, there are also weak cooperative hydrogen bonds (see Figure 4 and Supporting Information online for details).

Guided by these calculation results, we then tested the reactivities and enantioselectivities of the catalytic reactions with enynes **1u–1ab**. As shown in Scheme 6, when the formyl group of 1,6-enynal **1a** was replaced with acyl or ester group (**1v–1x**), only trace desired products were detected even with 5 mol% $Rh_2(OPiv)_4$ at 80 °C (Eq. (1)).

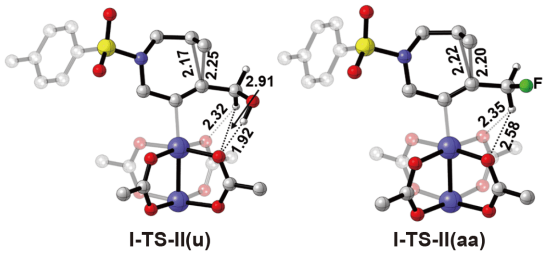
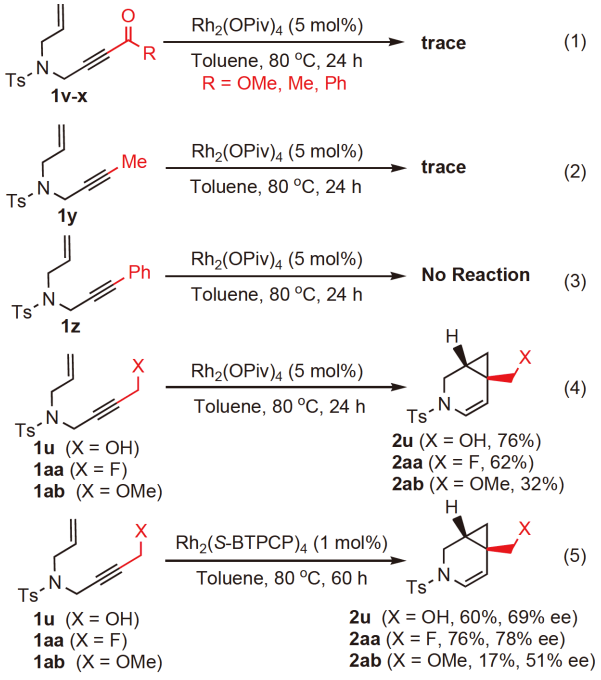


Figure 4 Structures of selected transition states. Distances are shown in Å (color online).



Scheme 6 Control experiments of double-mode activation (color online).

Negative results were also observed for enynes **1y–1z**, wherein the formyl group was replaced by Me or Ph (Eqs. (2–3)). These enynes (**1v–1z**) were typically used as effective substrates for the gold- or platinum-catalyzed cycloisomerization [3,4]. When enynes **1u**, **1aa**, and **1ab** were used as substrates, in which EWG activation and C–H···O interaction existed cooperatively, the desired products **2u**, **2aa** and **2ab** could be obtained in 76%, 62% and 32% yields, respectively (Eq. (4)). Asymmetric transformations of **1u**, **1aa**, **1ab** were also achieved when 1 mol% chiral catalyst Rh_2(*S*-BTPCP)$_4$ was used. The cyclopropanation product **2u** was obtained in 60% yield and 69% ee. For the substrate **1aa**, the product **2aa** was produced in higher yield (76%) and better enantioselectivity (78% ee). Furthermore, the catalytic reaction of enyne **1ab** gave product **2ab** in 17% yield and 51% ee (Eq. (5)). The above experimental results were in good agreement with our theoretical predictions.

4 Conclusions

In summary, we have designed and developed the first Rh_2(II)-catalyzed asymmetric cycloisomerization of enynes. It was found that chiral dirhodium(II) carboxylate Rh_2(*S*-BTPCP)$_4$ was a highly effective catalyst for the cycloisomerization of 1,*n*-enynals to obtain formyl-substituted cyclopropane-fused bicyclic compounds **2** in high yields and excellent enantioselectivities under mild conditions. The reaction could be performed well with only 0.1 mol% catalyst loading. In addition, the resulted chiral formyl-substituted cyclopropane-fused bicyclic compounds **2** could be used as chiral building blocks for many useful transformations. The reaction was proposed to proceed through a pathway of 6-*endo*-dig cyclization/[1,2]-H shift to give the cyclopropane-fused bicyclic compounds **2**. A novel double-mode activation strategy between enyne substrate and carboxylate ligand *via* electronic (using electron-withdrawing capping group, CHZ (Z is EWG), to activate the alkyne for cyclopropanation) and steric effects (introducing a C–H···O interaction between the small capping group and the carboxylate ligand) was proposed, which has been supported by both DFT calculations and control experiments. Furthermore, the above double-mode activation was also successfully extended to other CH_2Z groups, in which the cycloisomerization of enynes was also realized albeit with a weaker electron-withdrawing effect than that of formyl group. This Rh_2(II)-catalyzed asymmetric cycloisomerization of enynes enabled by double-mode activation represents a new application of dirhodium(II) complexes. It is a significant advance for both the asymmetric cycloisomerization of enynes and the dirhodium catalysis. We believe the present studies could also inspire further new reaction and catalyst design for organic chemists.

Acknowledgements This work was supported by the National Natural Science Foundation of China (21871096, 21672071, 91856105), the Ministry of Science and Technology of China (2016YFA0602900), the Natural Science Foundation of Guangdong (2018B030308007, 2018A030310359, 2016A030310433), the Science and Technology Program of Guangzhou (201707010316), and the Fundamental Research Funds for the Central Universities, South China University of Technology. Calculations were performed at the cluster of National Supercomputer Center in Guangzhou. Dr Li-Juan Song at Peking University Shenzhen Graduate School was acknowledged for her help in NBO analysis. Prof. Xinhao Zhang and Dr. Yi Wang of Peking University, Prof. Olaf G. Wiest of Notre Dame University, Dr. Gui-Juan Cheng of Max-Planck-Institut für Kohlenforschung, Dr. Lufeng Zou of Gaussian Company, Prof. Li Zhang of Sun Yat-sen University and Dr. Lianfen Chen of Zhaoqing University were appreciated for their kind help and useful suggestions.

Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or

editing. The responsibility for scientific accuracy and content remains entirely with the authors.

1 (a) Kobayashi T, Suemasa A, Igawa A, Ide S, Fukuda H, Abe H, Arisawa M, Minami M, Shuto S. *ACS Med Chem Lett*, 2014, 5: 889–893; (b) Berger G, Vilchis-Reyes M, Hanessian S. *Angew Chem Int Ed*, 2015, 54: 13268–13272; (c) Talele TT. *J Med Chem*, 2016, 59: 8712–8756; (d) Maslovskaya LA, Savchenko AI, Pierce CJ, Boyle GM, Gordon VA, Reddell PW, Parsons PG, Williams CM. *Chem Eur J*, 2019, 25: 1525–1534

2 (a) Zhang L, Sun J, Kozmin S. *Adv Synth Catal*, 2006, 348: 2271–2296; (b) Fehr C, Galindo J. *Angew Chem Int Ed*, 2006, 45: 2901–2904; (c) Fürstner A. *Acc Chem Res*, 2014, 47: 925–938; (d) Masutomi K, Noguchi K, Tanaka K. *J Am Chem Soc*, 2014, 136: 7627–7630; (e) Dieckmann M, Jang YS, Cramer N. *Angew Chem Int Ed*, 2015, 54: 12149–12152

3 Gold-catalyzed the synthesis of chiral cyclopropane-annulated bicyclic systems from enynes: (a) Hashmi ASK. *Chem Rev*, 2007, 107: 3180–3211; (b) Jimenez-Nunez E, Echavarren AM. *Chem Rev*, 2008, 108: 3326–3350; (c) Chao CM, Beltrami D, Toullec PY, Michelet V. *Chem Commun*, 2009, 6988; (d) Pradal A, Chao CM, Toullec PY, Michelet V. *Beilstein J Org Chem*, 2011, 7: 1021–1029; (e) Teller H, Fürstner A. *Chem Eur J*, 2011, 17: 7764–7767; (f) Deschamps NM, Elitzin VI, Liu B, Mitchell MB, Sharp MJ, Tabet EA. *J Org Chem*, 2011, 76: 712–715; (g) Teller H, Corbet M, Mantilli L, Gopakumar G, Goddard R, Thiel W, Fürstner A. *J Am Chem Soc*, 2012, 134: 15331–15342; (h) Guitet M, Zhang P, Marcelo F, Tugny C, Jiménez-Barbero J, Buriez O, Amatore C, Mouriès-Mansuy V, Goddard JP, Fensterbank L, Zhang Y, Roland S, Ménand M, Sollogoub M. *Angew Chem Int Ed*, 2013, 52: 7213–7218; (i) Obradors C, Echavarren AM. *Chem Commun*, 2014, 50: 16–28; (j) Obradors C, Echavarren AM. *Acc Chem Res*, 2014, 47: 902–912; (k) Yavari K, Aillard P, Zhang Y, Nuter F, Retailleau P, Voituriez A, Marinetti A. *Angew Chem Int Ed*, 2014, 53: 861–865; (l) Aillard P, Voituriez A, Dova D, Cauteruccio S, Licandro E, Marinetti A. *Chem Eur J*, 2014, 20: 12373–12376; (m) Barreiro EM, Boltukhina EV, White AJP, Hii KKM. *Chem Eur J*, 2015, 21: 2686–2690; (n) Vanitcha A, Damelincourt C, Gontard G, Vanthuyne N, Mouriès-Mansuy V, Fensterbank L. *Chem Commun*, 2016, 52: 6785–6788; (o) Wu Z, Isaac K, Retailleau P, Betzer JF, Voituriez A, Marinetti A. *Chem Eur J*, 2016, 22: 3278–3281; (p) Zhang PC, Wang Y, Zhang ZM, Zhang J. *Org Lett*, 2018, 20: 7049–7052; (q) Zuccarello G, Mayans JG, Escofet I, Scharnagel D, Kirillova MS, Pérez-Jimeno AH, Calleja P, Boothe JR, Echavarren AM. *J Am Chem Soc*, 2019, 141: 11858–11863

4 Platinum-catalyzed the synthesis of chiral cyclopropane-annulated bicyclic systems from enynes: (a) Brissy D, Skander M, Retailleau P, Marinetti A. *Organometallics*, 2007, 26: 5782–5785; (b) Brissy D, Skander M, Jullien H, Retailleau P, Marinetti A. *Org Lett*, 2009, 11: 2137–2139; (c) Brissy D, Skander M, Retailleau P, Frison G, Marinetti A. *Organometallics*, 2009, 28: 140–151; (d) Xia JB, Liu WB, Wang TM, You SL. *Chem-A Eur J*, 2010, 16: 6442–6446; (e) Jullien H, Brissy D, Sylvain R, Retailleau P, Naubron JV, Gladiali S, Marinetti A. *Adv Synth Catal*, 2011, 353: 1109–1124

5 (a) Timmons DJ, Doyle MP. Chiral Dirhodium(II) Catalysts and Their Applications. In: Cotton FA, Murillo CA, Walton RA, Eds. *Multiple Bonds Between Metal Atoms*. 3rd ed. New York: Springer, 2005. 591–626; (b) Doyle MP, Forbes DC. *Chem Rev*, 1998, 98: 911–936; (c) Lebel H, Marcoux JF, Molinaro C, Charette AB. *Chem Rev*, 2003, 103: 977–1050; (d) Davies HML, Lian Y. *Acc Chem Res*, 2012, 45: 923–935; (e) Cheng QQ, Deng Y, Lankelma M, Doyle MP. *Chem Soc Rev*, 2017, 46: 5425–5443; (f) Davies HML. *J Org Chem*, 2019, 84: 12722–12745; (g) Davies HML, Liao K. *Nat Rev Chem*, 2019, 3: 347–360; (h) Zhu D, Chen L, Fan H, Yao Q, Zhu S. *Chem Soc Rev*, 2020, 49: 908–950

6 (a) Chatani N, Kataoka K, Murai S, Furukawa N, Seki Y. *J Am Chem Soc*, 1998, 120: 9104–9105; (b) Ota K, Lee SI, Tang JM, Takachi M, Nakai H, Morimoto T, Sakurai H, Kataoka K, Chatani N. *J Am Chem Soc*, 2009, 131: 15203–15211

7 Davies HML, Beckwith REJ. *Chem Rev*, 2003, 103: 2861–2904

8 Alabugin IV, Gold B. *J Org Chem*, 2013, 78: 7777–7784

9 (a) Schreiner PR. *Chem Soc Rev*, 2003, 32: 289–296; (b) Doyle AG, Jacobsen EN. *Chem Rev*, 2007, 107: 5713–5743; (c) Parmar D, Sugiono E, Raja S, Rueping M. *Chem Rev*, 2014, 114: 9047–9153

10 (a) Bulfield D, Huber SM. *Chem Eur J*, 2016, 22: 14434–14450; (b) Breugst M, von der Heiden D, Schmauck J. *Synthesis*, 2017, 49: 3224–3236

11 (a) Fraile JM, García JI, Herrerías CI, Mayoral JA, Reiser O, Socuéllamos A, Werner H. *Chem Eur J*, 2004, 10: 2997–3005; (b) Michrowska A, Mennecke K, Kunz U, Kirschning A, Grela K. *J Am Chem Soc*, 2006, 128: 13261–13267

12 Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H, Caricato M, Li X, Hratchian HP, Izmaylov AF, Bloino J, Zheng G, Sonnenberg JL, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, J. A. Mont-gomery Jr., Peralta JE, Ogliaro F, Bearpark MJ, Heyd J, Brothers EN, Kudin KN, Staroverov VN, Kobayashi R, Normand J, Raghavachari K, Rendell AP, Burant JC, Iyengar SS, Tomasi J, Cossi M, Rega N, Millam NJ, Klene M, Knox JE, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Martin RL, Morokuma K, Zakrzewski VG, Voth GA, Salvador P, Dannenberg JJ, Dapprich S, Daniels AD, Farkas Ö, Foresman JB, Ortiz JV, Cioslowski J, Fox D. Wallingford: Gaussian, Inc., 2009

13 (a) Lee C, Yang W, Parr RG. *Phys Rev B*, 1988, 37: 785–789; (b) Becke AD. *J Chem Phys*, 1993, 98: 5648–5652

14 Hay PJ, Wadt WR. *J Chem Phys*, 1985, 82: 299–310

15 Ehlers AW, Böhme M, Dapprich S, Gobbi A, Höllwarth A, Jonas V, Köhler KF, Stegmann R, Veldkamp A, Frenking G. *Chem Phys Lett*, 1993, 208: 111–114

16 Hehre WJ, Radom L, Schleyer PVR, Pople JA. *Ab Initio Molecular Orbital Theory*. New York: Wiley, 1986

17 Zhao Y, Truhlar DG. *Theor Chem Account*, 2008, 120: 215–241

18 Andrae D, Häußermann U, Dolg M, Stoll H, Preuß H. *Theoret Chim Acta*, 1990, 77: 123–141

19 Marenich AV, Cramer CJ, Truhlar DG. *J Phys Chem B*, 2009, 113: 6378–6396

20 Lu T, Chen F. *J Comput Chem*, 2012, 33: 580–592

21 Legault C. 1.0b edition. Universite de Sherbrooke: 2009. http:// www.cylview.org

22 Humphrey W, Dalke A, Schulten K. *J Mol Graphics*, 1996, 14: 33–38

23 (a) Zhang Z, Wang J. *Tetrahedron*, 2008, 64: 6577–6605; (b) Davies HML, Manning JR. *Nature*, 2008, 451: 417–424; (c) Chuprakov S, Kwok SW, Zhang L, Lercher L, Fokin VV. *J Am Chem Soc*, 2009, 131: 18034–18035; (d) Doyle MP, Duffy R, Ratnikov M, Zhou L. *Chem Rev*, 2010, 110: 704–724; (e) Davies HML, Morton D. *Chem Soc Rev*, 2011, 40: 1857–1869; (f) Xu B, Zhu SF, Xie XL, Shen JJ, Zhou QL. *Angew Chem Int Ed*, 2011, 50: 11483–11486; (g) Zhu D, Ma J, Luo K, Fu H, Zhang L, Zhu S. *Angew Chem Int Ed*, 2016, 55: 8452–8456; (h) Yang JM, Li ZQ, Li ML, He Q, Zhu SF, Zhou QL. *J Am Chem Soc*, 2017, 139: 3784–3789; (i) Zhu D, Chen L, Zhang H, Ma Z, Jiang H, Zhu S. *Angew Chem Int Ed*, 2018, 57: 12405–12409

24 The D_2-symmetric dirhodium catalysts derived from a 1,2,2-triarylcyclopropanecarboxylate ligands were developed by the Davies group: (a) Qin C, Boyarskikh V, Hansen JH, Hardcastle KI, Musaev DG, Davies HML. *J Am Chem Soc*, 2011, 133: 19198–19204; (b) Qin C, Davies HML. *Org Lett*, 2013, 15: 6152–6154; (c) Qin C, Davies HML. *J Am Chem Soc*, 2013, 135: 14516–14519; (d) Guzmán PE, Lian Y, Davies HML. *Angew Chem Int Ed*, 2014, 53: 13083–13087; (e) Guptill DM, Davies HML. *J Am Chem Soc*, 2014, 136: 17718–17721; (f) Qin C, Davies HML. *J Am Chem Soc*, 2014, 136: 9792–9796; (g) He J, Hamann LG, Davies HML, Beckwith REJ. *Nat*

Commun, 2015, 6: 5943–5952; (h) Fu L, Guptill DM, Davies HML. *J Am Chem Soc*, 2016, 138: 5761–5764; (i) Liao K, Negretti S, Musaev DG, Bacsa J, Davies HML. *Nature*, 2016, 533: 230–234; (j) Liao K, Pickel TC, Boyarskikh V, Bacsa J, Musaev DG, Davies HML. *Nature*, 2017, 551: 609–613; (k) Liao K, Yang YF, Li Y, Sanders JN, Houk KN, Musaev DG, Davies HML. *Nat Chem*, 2018, 10: 1048–1055

25 Doyle MP. *J Org Chem*, 2006, 71: 9253–9260

26 (a) Doyle MP, Van Oeveren A, Westrum LJ, Protopopova MN, Clayton TW. *J Am Chem Soc*, 1991, 113: 8982–8984; (b) Wang Y, Wolf J, Zavalij P, Doyle M. *Angew Chem Int Ed*, 2008, 47: 1439–1442; (c) Xu X, Wang X, Liu Y, Doyle MP. *J Org Chem*, 2014, 79: 12185–12190

27 See the Supporting Information for more details about screening of reaction conditions

28 (a) Yamaguchi K, Kazuta Y, Abe H, Matsuda A, Shuto S. *J Org Chem*, 2003, 68: 9255–9262; (b) Melancon BJ, Perl NR, Taylor RE. *Org Lett*, 2007, 9: 1425–1428

29 (a) Hohn E, Palecek J, Pietruszka J, Frey W. *Eur J Org Chem*, 2009, 2009: 3765–3782; (b) Osler JD, Unsworth WP, Taylor RJK. *Org Biomol Chem*, 2013, 11: 7587–7594; (c) Corey EJ, Fuchs PL. *Tetrahedron Lett*, 1972, 13: 3769–3772

30 (a) Baldwin JE. *Chem Rev*, 2003, 103: 1197–1212; (b) Ylijoki KEO, Stryker JM. *Chem Rev*, 2013, 113: 2244–2266; (c) Jiao L, Yu ZX. *J Org Chem*, 2013, 78: 6842–6848; (d) Wang LN, Cui Q, Yu ZX. *J Org Chem*, 2016, 81: 10165–10171; (e) Zhuang Z, Li CL, Xiang Y, Wang YH, Yu ZX. *Chem Commun*, 2017, 53: 2158–2161; (f) Fumagalli G, Stanton S, Bower JF. *Chem Rev*, 2017, 117: 9404–9432; (g) Li CL, Yu ZX. *J Org Chem*, 2019, 84: 9913–9928

31 Sunderhaus JD, Dockendorff C, Martin SF. *Tetrahedron*, 2009, 65: 6454–6469

32 Corey EJ, Lee TW. *Chem Commun*, 2001, 1321–1329

33 Glendening ED, Badenhoop JK, Reed AE, Carpenter JE, Bohmann JA, Morales CM, Landis CR, Weinhold F. NBO 6.0. Madison: Theoretical Chemistry Institute, University of Wisconsin, 2013, http://nbo6.chem.wisc.edu/

34 Zhuo LG, Liao W, Yu ZX. *Asian J Org Chem*, 2012, 1: 336–345

35 Dong Z, Liu CH, Wang Y, Lin M, Yu ZX. *Angew Chem Int Ed*, 2013, 52: 14157–14161

36 (a) Moore KB III, Sadeghian K, Sherrill CD, Ochsenfeld C, Schaefer HF III. *J Chem Theor Comput*, 2017, 13: 5379–5395; (b) Gu Y, Kar T, Scheiner S. *J Am Chem Soc*, 1999, 121: 9411–9422; (c) Zhang Q, Du L. *Comput Theor Chem*, 2016, 1078: 123–128

37 Simon S, Duran M, Dannenberg JJ. *J Chem Phys*, 1996, 105: 11024–11031