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Rh_2(II)-catalyzed enantioselective intramolecular Büchner reaction and aromatic substitution of donor–donor carbenes†

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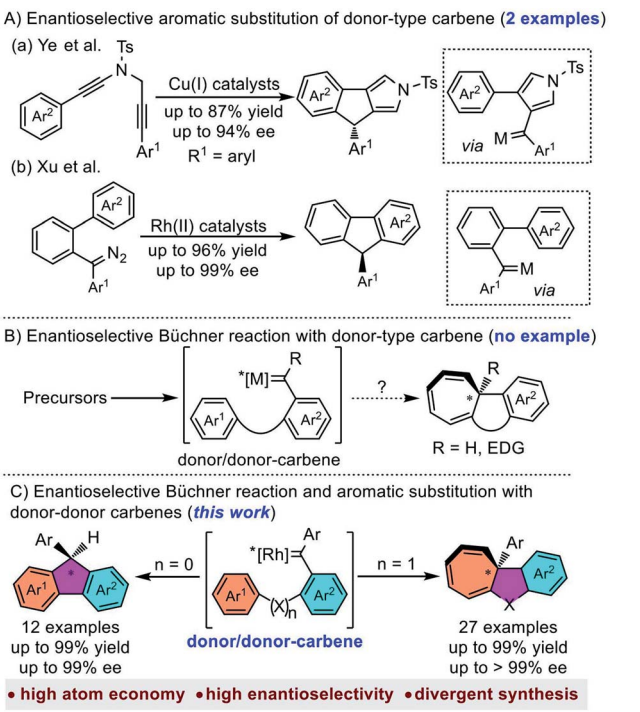
The chiral dirhodium(II) tetracarboxylate-catalyzed enantioselective intramolecular Büchner reaction of donor/donor-carbenes was reported and a series of valuable chiral polycyclic products were synthesized. Both aryloxy enynones and diazo compounds were efficient carbene precursors for this reaction. Excellent yields (up to 99%) and outstanding enantioselectivities (up to >99% ee) were achieved under standard conditions. For furyl substituted chiral cyclohepta[*b*]benzofurans bearing a substituent at the C4 position on cycloheptatrienes, control reactions showed that the chiral Büchner products could slowly racemize either under dark or natural light conditions. A diradical-involved mechanism rather than a zwitterionic intermediate was proposed to explain the racemization. Furthermore, furyl substituted chiral fluorene derivatives were obtained *via* asymmetric aromatic substitution when biaryl enynones were employed as carbene precursors.

Introduction

Metal-carbene is one of the most important reactive intermediates in organic synthesis.[1] Among the numerous carbene-transfer reactions, the reaction of metal-carbene with arenes has gained much interest in the past few decades.[2] The main reaction pathways of metal-carbene with arenes include aromatic substitution and Büchner reaction, which could provide efficient approaches to polycyclic molecules, especially in an intramolecular manner.[3] Compared to the well-developed non-asymmetric Büchner reaction[4] and aromatic substitution,[5] the asymmetric ones were much less explored,[6] especially for donor type carbene (donor- and donor/donor-carbenes) involved reactions.[7] The main reason is that donor-type carbenes were usually regarded as less efficient for carbene-transfer reactions than acceptor-type carbenes (acceptor-, donor/acceptor-, and acceptor/acceptor-carbenes).[8] Recently, Ye *et al.* disclosed the first enantioselective aromatic substitution with donor–donor copper carbenes through diyne cyclization.[9] Xu *et al.* also reported a rhodium catalysed asymmetric carbene arylation reaction with diazo compounds as donor–donor carbene precursors (Scheme 1A).[10] These achievements indicated the tunability of donor or donor–donor type carbenes in asymmetric synthesis. However, to the best of our knowledge, there is still no example of donor-type carbene involved asymmetric Büchner reaction (Scheme 1B), which could be partially



Scheme 1 Donor-type carbene mediated enantioselective aromatic substitution and Büchner reactions.

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attributed to (1) the dual electron donating aryl groups making the carbene carbon less electrophilic;[11] (2) the commonly-used diazo precursors are highly unstable, potentially explosive and easily dimerized.[12]

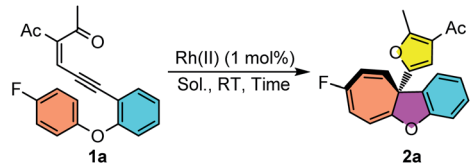
Over the past two decades, carbene chemistry with non-diazo precursors has experienced tremendous growth due to the emerging gold chemistry.[13] Despite that these newly developed carbene precursors provide several useful means in the transformation of donor type metal-carbenes, the commonly used gold catalyst usually suffered inefficient chiral induction due to the linear geometry.[14] As a reliable and safe donor-type metal-carbene source, enynones have received much attention due to its versatile activities.[15] In our previous work, we realized the asymmetric intramolecular C–H insertion and cyclopropanation with enynones as carbene precursors.[16] With our continuous interest in the development of donor type metal-carbenes,[17] herein we would like to report the first example of the chiral Rh_2(II)-catalyzed enantioselective Büchner reaction with donor–donor carbenes (Scheme 1C, right). In addition, the asymmetric aromatic substitution is also achieved using the same catalyst as well (Scheme 1C, left).

Results and discussion

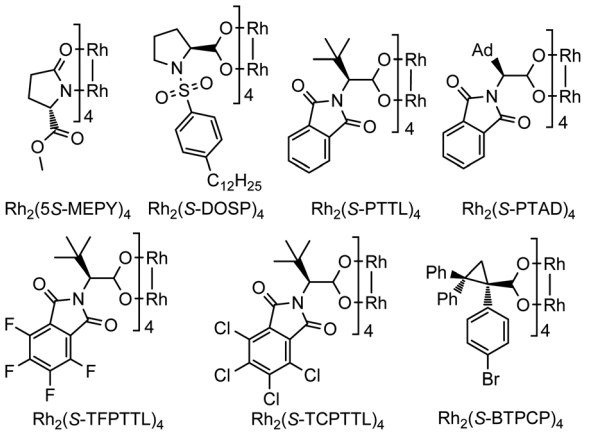
Rh_2(II)-catalyzed asymmetric Büchner reaction of enynones

To start this investigation, enynone **1a** was chosen as the model substrate to screen the asymmetric Büchner reaction conditions. As shown in Table 1, the desired furyl substituted cyclohepta[*b*]benzofuran **2a** was obtained in 94% yield under the catalysis of 1 mol% $Rh_2(OPiv)_4$ at room temperature (Table 1, entry 1). In line with our speculation, the electron-rich chiral dirhodium(II) carboxamide catalyst [Rh_2(5*S*-MEPY)$_4$] proved to have no catalytic activity for this reaction, which indicated that the more d-π donating catalyst would further decrease the electrophilicity of the donor–donor carbene carbon (entry 2). Dirhodium *N*-sulfonylprolinate [Rh_2(*S*-DOSP)$_4$] resulted in a quantitative yield, but without asymmetric induction (entry 3). The phthalimide-based catalysts showed better selectivity, giving the desired product **2a** in 91–99% yields and 6–73% ee (entries 4–7). For example, the enantioselectivity was only 6% ee when [Rh_2(*S*-PTTL)$_4$] was used as the catalyst (entry 4). When *t*-butyl was replaced with the adamantly group, catalyst [Rh_2(*S*-PTAD)$_4$] gave 29% ee and 91% yield (entry 5). The enantioselectivity of **2a** can be increased dramatically to 73% ee when more electron–deficient complexes [Rh_2(*S*-TFPTTL)$_4$] and [Rh_2(*S*-TCPTTL)$_4$] were applied (entries 6 and 7). To our delight, when dirhodium triarylcyclopropane carboxylate [Rh_2(*S*-BTPCP)$_4$] was used as the catalyst, the highest enantioselectivity of 83% ee was obtained with 99% yield (entry 8). The solvents were screened as well and DCE proved to be the optimal one, which gave the desired product in 92% ee and quantitative yield (entry 11). Lowering the reaction temperature to −20 °C further improved the enantioselectivity to 96% ee (entry 12), which was then used as the optimal reaction condition. In addition, the catalyst loading could be reduced to 0.5 mol%, and both the reaction yield and enantioselectivity were unaffected, albeit with a longer reaction time (entry 13).

Table 1 Optimization of the reaction conditions[a]



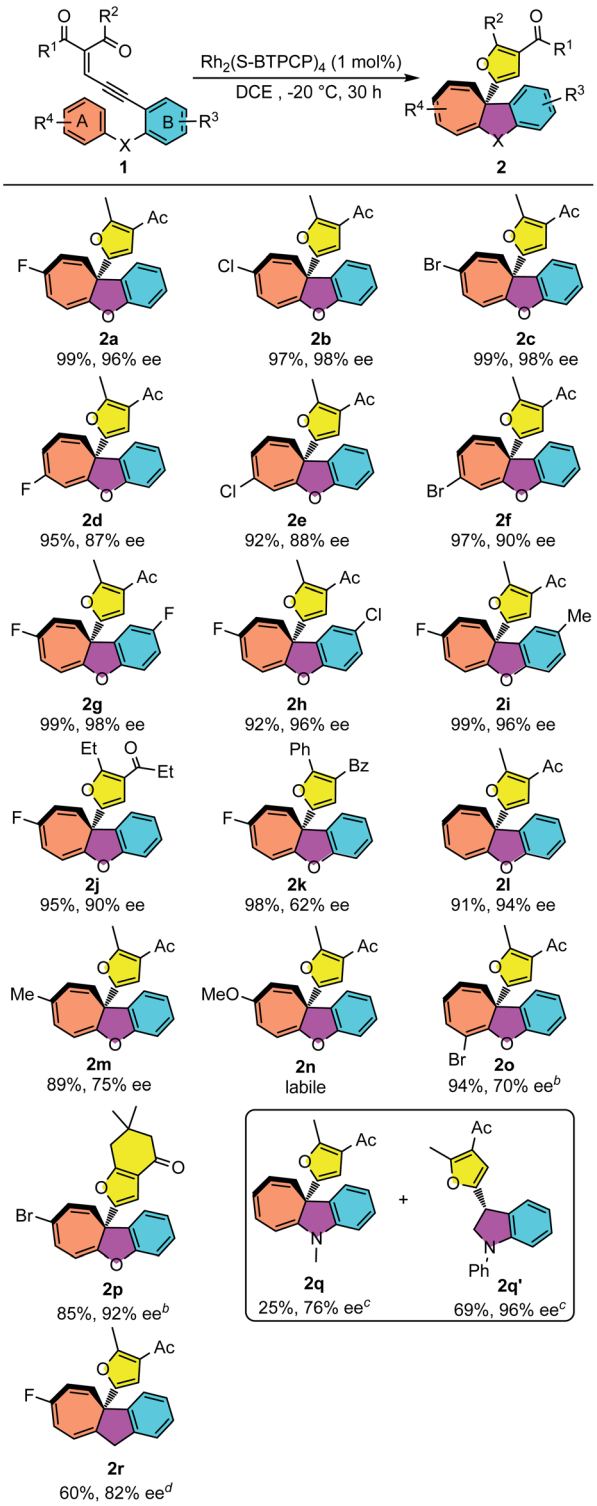
Entry	Cat.	Sol.	Time	Yield[b]	ee[c]
1	$Rh_2(OPiv)_4$	DCM	3 h	94%	—
2	Rh_2(5*S*-MEPY)$_4$	DCM	4 h	Trace	—
3	Rh_2(*R*-DOSP)$_4$	DCM	4 h	99%	Racemic
4	Rh_2(*S*-PTTL)$_4$	DCM	12 h	97%	6%
5	Rh_2(*S*-PTAD)$_4$	DCM	12 h	91%	29%
6	Rh_2(*S*-TFPTTL)$_4$	DCM	4 h	99%	−20%
7	Rh_2(*S*-TCPTTL)$_4$	DCM	4 h	99%	73%
8[d]	Rh_2(*S*-BTPCP)$_4$	DCM	2 h	99%	83%
9	Rh_2(*S*-BTPCP)$_4$	PhMe	4 h	99%	60%
10	Rh_2(*S*-BTPCP)$_4$	$CHCl_3$	8 h	99%	70%
11	Rh_2(*S*-BTPCP)$_4$	DCE	2 h	99%	92%
12[d]	**Rh_2(*S*-BTPCP)$_4$**	**DCE**	**30 h**	**99%**	**96%**
13[e]	Rh_2(*S*-BTPCP)$_4$	DCE	53 h	99%	96%



[a] The reaction was performed in DCE under N_2; **1a** = 0.2 mmol and [**1a**] = 0.1 M. [b] Isolated yield. [c] The ee value of **2a** was determined by HPLC using a chiral stationary phase. [d] −20 °C. [e] −20 °C, 0.5 mol% Rh_2(S-BTPCP)$_4$.

With the optimized reaction conditions for the Büchner reaction in hand (Table 1, entry 12), we next examined the reaction scope with different enynones. As shown in Table 2, enynones tethered with *para*-halogen-substituted aryloxy reacted smoothly, giving the desired polycyclic products **2a–c** in 97–99% yields with excellent enantioselectivities (96–98% ee). The reactions of *meta*-halogenated enynones (R^4 is halogen) proceeded smoothly as well, giving the corresponding products **2d–f** in good enantioselectivities (87–90% ee) and excellent yields (92–97%). Variations in the R^3 group of enynones were also investigated, which led to the desired Büchner ring-expansion products in high yields and excellent enantioselectivities with both electron-withdrawing and donating groups (**2g–i**). The enynones with different carbonyl substituents showed good reactivities as well. Moderate to good enantioselectivity of products **2j** and **2k** was achieved. It seems that the

Table 2 Scope of the asymmetric Büchner reaction[a]



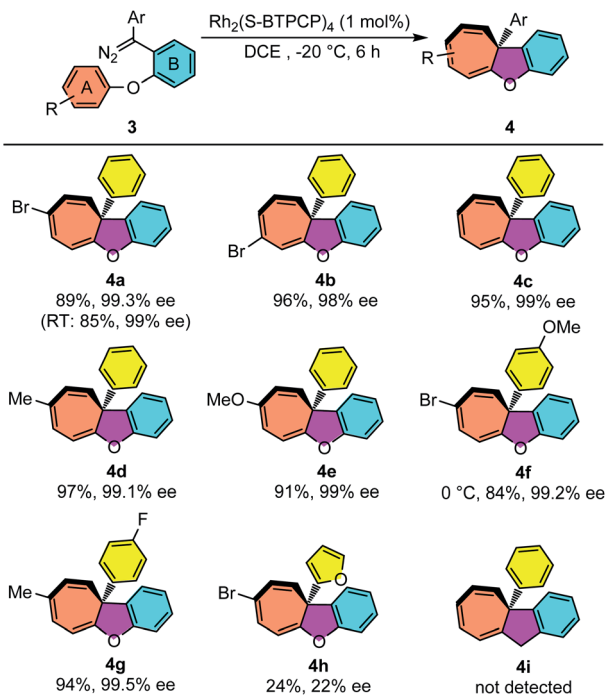
[a] Reaction conditions: **1** = 0.2 mmol, [**1**] = 0.1 M, isolated yield. [b] −10 °C, 48 h. [c] 69% N–Me C–H insertion product **2q′** was isolated. [d] 40 °C, 24 h.

enantioselectivity of this Büchner reaction was sensitive to the electronic properties of aromatic ring A; the ee values for cyclohepta[*b*]benzofurans **2l** and **2m** dropped to 94% and 75% when phenoxyl- and 4-methylphenoxyl-enynones were utilized as substrates. When electronically richer 4-methoxy-substituted substrate **1n** was applied, the product **2n** could be observed from the ^{1}H NMR spectrum but decomposed quickly after purification on the silica gel. *Ortho*-halogenated enynones **1o** was tested as well, giving the desired cyclohepta[*b*]benzofuran **2o** in 94% yield and 70% ee. It should be pointed out that the 1,3-diketone derived substrate **1p** performed well in this annulation and gave **2p** in 85% yield and 92% ee under −10 °C conditions. Lastly, N–Me phenyl substituted enynone **1q** and CH_2 tethered enynone **1r** were also tested under these catalytic conditions. Interestingly, the Büchner product **2q** was obtained only in 25% yield and 76% ee, accompanied by the C–H insertion product dihydroindole **2q′** (69%, 96% ee).[18] Indan fused cycloheptatriene **2r** was achieved with both moderate yield and good enantioselectivity.

Rh_2(II)-catalyzed Büchner reaction of diazo compounds

The reaction conditions of Rh_2(*S*-BTPCP)$_4$-catalyzed enantioselective intramolecular Büchner reaction were not only applied well for enynones, but also showed excellent performance when diazo compounds were used as donor–donor carbene sources. As shown in Table 3, aryl substituted cyclohepta[*b*]benzofurans were produced from aryloxy substituted diphenyl diazo compounds **3**. Unlike the enynone-based system, the diazo-based system was found to be almost not noticeably affected by the electronic properties of the substituents on aromatic ring

Table 3 Scope of the asymmetric Büchner reaction with diazo compounds as carbene sources[a]



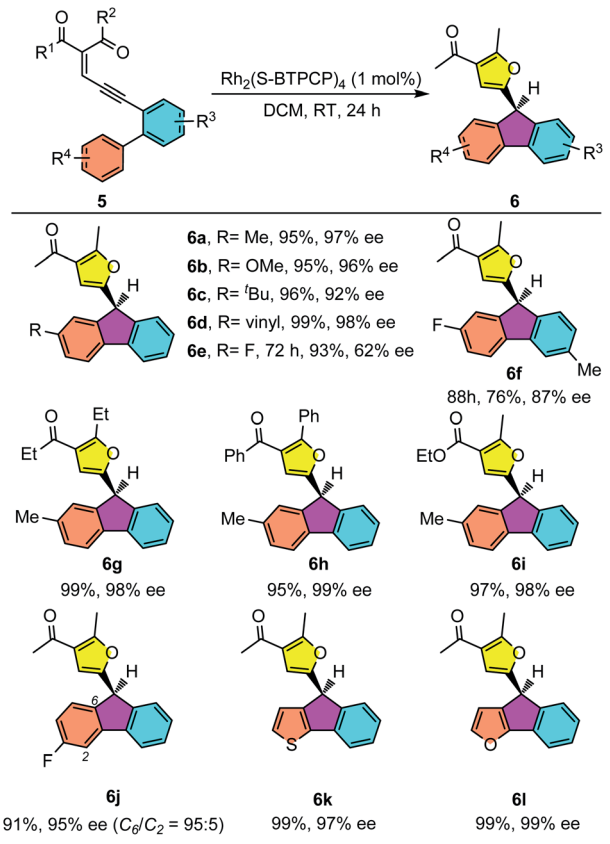
[a] Reaction conditions: **3** = 0.1 mmol, [**3**] = 0.025 M, isolated yield; the diazo compound **3** was added dropwise over 1 h.

A. The phenyl substituted cyclohepta[*b*]benzofurans **4a–e** were obtained with high yields (84–97%) and outstanding enantioselectivity (98–99.5% ee). The cyclohepta[*b*]benzofuran **4e** derived from the diazo compound with electron-rich aromatic ring A could also be obtained in 91% yield and 99% ee. The product **4e** was stable and no decomposition was observed when purified on silica gel, which is different with the enynone-based system (see **2n**). Furthermore, the introduction of electron-donating and -withdrawing groups on the Ar group of diazo compounds also provided the desired products **4f–g** with excellent enantioselectivities. Furyl substituted diazo compound **3h** was synthesized and reacted under the standard conditions, and only Büchner product **4h** was isolated with 24% yield and 22% ee. Interestingly, an unexpected furan ring-opening product enynal **4h′** was obtained in 55%.[15a] Lastly, CH_2-tethered diazo compound **3i** was not an effective substrate for this Büchner reaction and only vinyl product **4i′** *via* carbene dimerization was detected (see the ESI†).

Rh_2(II)-catalyzed asymmetric aromatic substitution reaction of enyones

Having established the eantioselective intramolecular Büchner reaction as a reliable and efficient synthetic protocol, biaryl enynones **5** were then employed as donor carbene precursors to test the asymmetric aromatic substitution reaction. As shown in Table 4, the intramolecular aromatic substitution reactions proceeded smoothly and gave the desired furyl substituted fluorenes with high yields and excellent enantioselectivities under slightly modified reaction conditions (see the ESI†). It was shown that the catalytic process could be successfully applied to different enynone substrates bearing different R^4 groups. For example, in addition to enynone **5a**, various enynone derivatives **5** with *para*-substituted groups could be efficiently converted into the desired fluorenes **6** in good enantioselectivities (62–98% ee) (**6a–e**). The yields were typically higher than 90% for most substrates. The substrates with electron-rich aryl groups have higher reactivity, furnishing the fluorene products **6a–e** in almost quantitative yields. Moreover, enynones with different substituents on carbonyl groups were also suitable for this transformation, leading to fluorenes **6g–i** in excellent yields (95–99%) and enantioselectivities (98–99% ee). In addition to the enynones with *para*-substituted phenyl groups, the *meta*-substituted enynone was also investigated. The reaction took place smoothly to give the desired product **6j** in excellent yield and enantioselectivity. More importantly, a good regioselectivity was observed (C_6/C_2 = 95 : 5). This result indicated that the aromatic substitution reaction is sensitive to the steric effects of the substrates. Notably, thienyl and furyl substituted enynones were also suitable substrates to provide the desired aromatic substation products **6k** and **6l** with excellent results. It is worthy of note that a similar non-asymmetric divergent Büchner reaction and aromatic substitution reaction were reported by Wang and co-workers in a metal free manner with hydrazones as donor carbene precursors.[19]

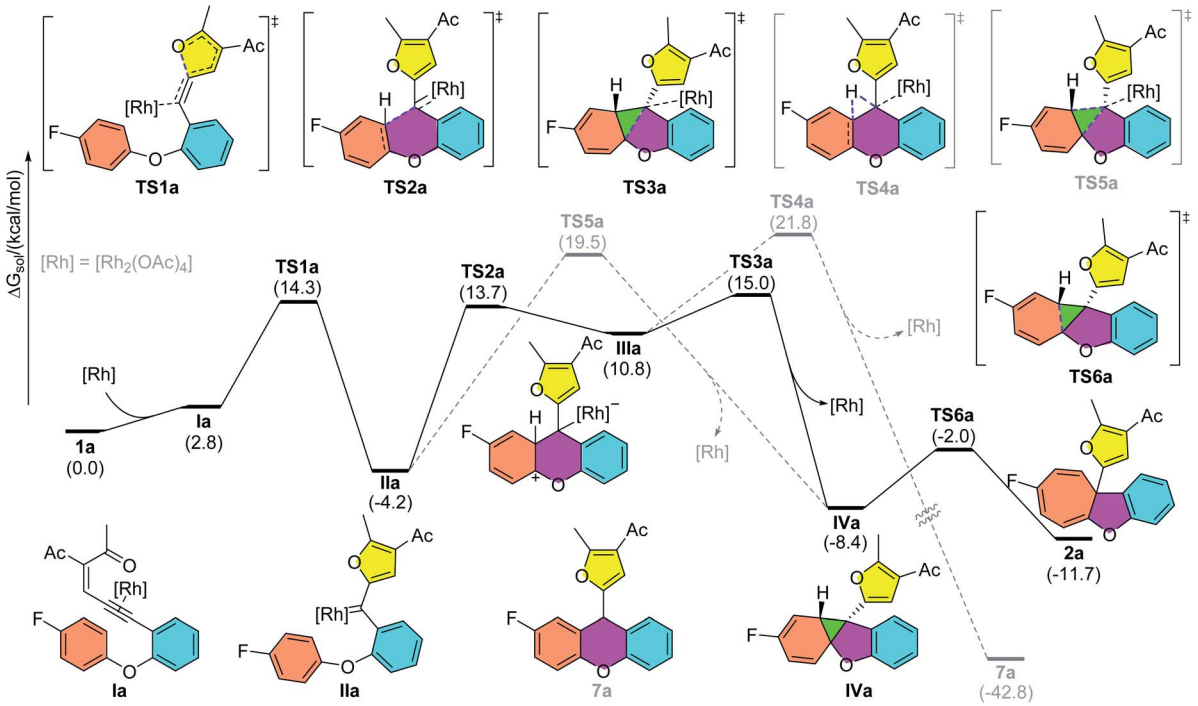
Table 4 Scope of the aromatic substitution reaction[a]



[a] Reaction conditions: **5** = 0.2 mmol, [**5**] = 0.1 M, isolated yield.

DFT studies on the reaction mechanism and chemoselectivity

To gain insights into the reaction mechanism, DFT calculations were carried out using Gaussian16 at the M06/def2TZVP-SMD(dichloroethane)//B3LYP-D3(BJ)/def2SVP theoretical level.[20–22] As shown in Scheme 2, the reaction starts with the coordination of the rhodium catalyst with the alkyne moiety, followed by a 5-*exo-dig* cyclization to afford dirhodium carbene intermediate **IIa**. This is supported by our experiments, as diazo compounds could also undergo a similar Büchner reaction under standard conditions. Then, a stepwise cyclopropanation process involving electrophilic addition of carbene to the phenyl ring and a subsequent ring-closure step will lead to the formation of the cyclopropane intermediate **IVa**. Moreover, a concerted cyclopropanation step *via* **TS5a** is also considered, which is disfavored over the stepwise pathway (*via* **TS3a**) by 4.5 kcal mol^{-1}. Finally, an electrocyclic step *via* **TS6a** opens the cyclopropane ring to form the Büchner reaction product **2a**. The whole potential energy surface shows that the ring-closure step is the rate-determining step, with an activation barrier about 19.2 kcal mol^{-1} in terms of the Gibbs free energy. In addition, intermediate **IIIa** could also undergo a [1,2]-H shift *via* **TS4a**, with the release of the rhodium catalyst, to give the aromatic substitution product **7a**. DFT calculations indicated that the Büchner reaction pathway *via* ring-closure transition state **TS3a** is favored over the aromatic substitution pathway *via* [1,2]-H

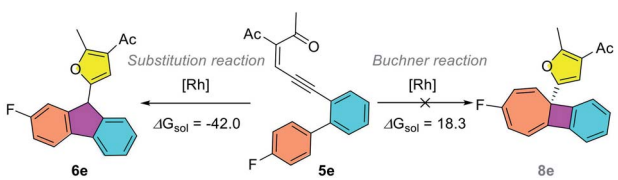


Scheme 2 Free energy profiles of Rh_2(II)-catalyzed reaction pathways of enynone **1a**. If not otherwise noted, relative Gibbs free energies computed at the M06/def2TZVP-SMD(dichloroethane)//B3LYP-D3(BJ)/def2SVP theoretical level are reported in kcal mol^{-1}.

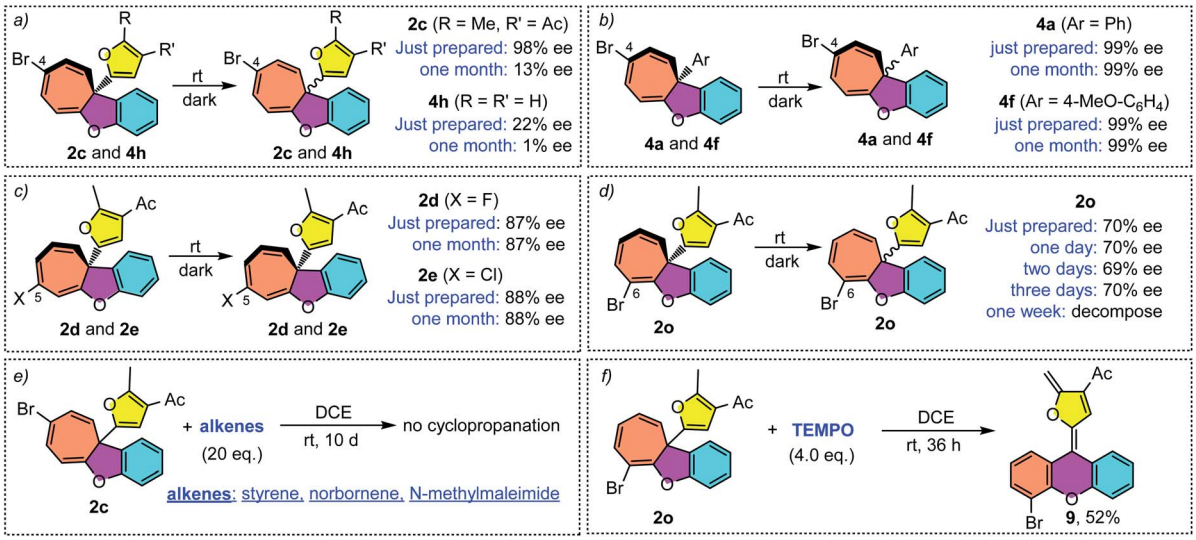
shift transition state **TS4a** by 6.8 kcal mol^{-1}. In contrast, for biaryl enynone **5**, a similar Büchner reaction was not observed, possibly due to the high ring strain of the fused cyclic butene moiety in **8** (Scheme 3). Thermochemistry calculations show that the Büchner process of **5e** is endergonic (ΔG_{sol} = 18.3 kcal mol^{-1}), and thus could not happen spontaneously. However, the overall aromatic substitution reaction of biaryl enynone **5e** is exergonic by 42.0 kcal mol^{-1}, leading to the formation of stable 9*H*-fluorene **6e** (see the ESI†).

Control experiments and mechanism for the rationalization of the chiral Büchner products

It should be noted that the ee value of furyl substituted Büchner products **2c** and **4h** was found to slowly decrease when preserved in *i*-PrOH at room temperature (Scheme 4a). Similar racemization was also found for other C4-substituted chiral cyclohepta[*b*]benzofurans (see the ESI†). This interesting phenomenon drove us to figure out the reason for racemization. Controlled experiments indicated that this racemization is independent of the solvent (Table S3†) but both temperature and natural light will accelerate the racemization rate. Interestingly, the phenyl substituted Büchner products (**4a** and **4f**) derived from diazo compounds maintained good enantioselectivity. Surprisingly, the chiral cyclohepta[*b*]benzofuran products derived from *ortho*- and *meta*-substituted phenoxy enynones (such as **2d**, **2e** and **2o**) did not racemize (Scheme 4c and d). These results implied that both the type of substituents attached to cyclohepta[*b*]benzofurans (**2c** and **4a**) and the position of the functional groups on cycloheptatriene (**2c** and **2f**) had a great influence on racemization. In view of this racemization, several following possible mechanisms were proposed. First, we speculated that furyl substituted chiral cyclohepta[*b*]benzofurans might racemize *via* a free donor–donor carbene intermediate through a *retro*-Büchner reaction. To validate this conjecture, various alkenes were added into the solution of **2c** to trap the proposed free carbene intermediate (Scheme 4e). However, no desired cyclopropanation product was detected, which suggested that the racemization process might not proceed through a reversible Büchner reaction. Furthermore, the results that only C4-substituted Büchner products (such as **2c** and **4h**) were observed to racemize also exclude the free carbene process because cycloheptatriene bearing functional groups at other positions (such as **2d** and **2o**) will racemize through free carbene intermediates as well. In addition, studies by Dolye, Moody and Maguire suggested that a zwitterionic intermediate is also operative for the racemization of the Büchner products, wherein the C–C bond of cyclopropane could break and form reversibly.[23–25] Similarly, Houk *et al.* also suggested a diradical species to explain the "walk



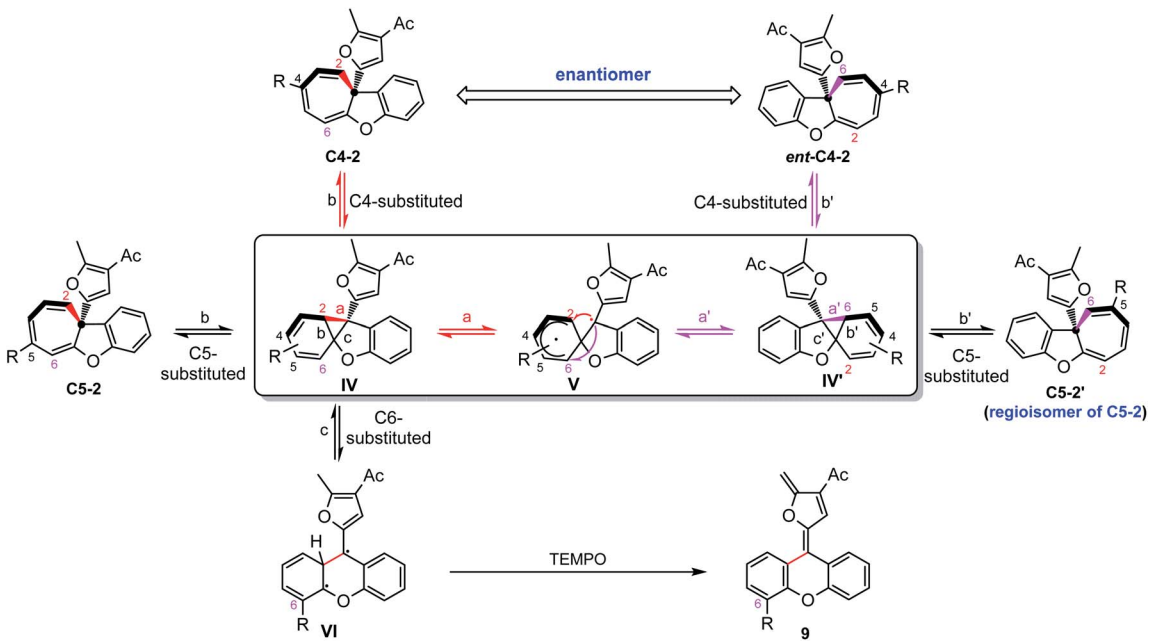
Scheme 3 Competition between the Büchner reaction and aromatic substitution pathways for biaryl enynone **5e**.



Scheme 4 Control experiments and mechanistic investigation.

rearrangement" substituted norcaradiene.[26] Compared to the zwitterionic intermediate, we preferred a diradical mediated racemization process in our system because no electron-withdrawing group could stabilize the electronic mismatched zwitterionic species. Thus, a control experiment intended to intercept the postulated diradical species was then designed. Interestingly, a ring isomerization product **9** was obtained in 52% when TEMPO was used as the trapping reagent (Scheme 4f), which makes the reaction more likely to go through a diradical mechanism.

Taken together, a diradical process is the probable mechanism for the racemization of furyl substituted chiral cyclohepta[*b*]benzofurans. As shown in Scheme 5, the chiral cyclohepta[*b*]benzofuran **C4-2** bearing a substituent at the C4 position first generates norcaradiene **IV** and then leads to the diradical tautomer **V** through homolytic cleavage of the cyclopropane (bond a). The diradical **V** has two possible pathways to evolve, one is to norcaradiene **IV** through the reversible process by attacking the C2 position, and another is attacking the C6 position to give the dissymmetric norcaradiene **IV'** which leads to the enantiomer ***ent*-C4-2** after ring expansion, which eventually results in the racemization of chiral cyclohepta[*b*]benzofuran **2**. It's also possible that the diradical **VI** could be generated *via* cleavage of bond c of intermediate **IV** due to the



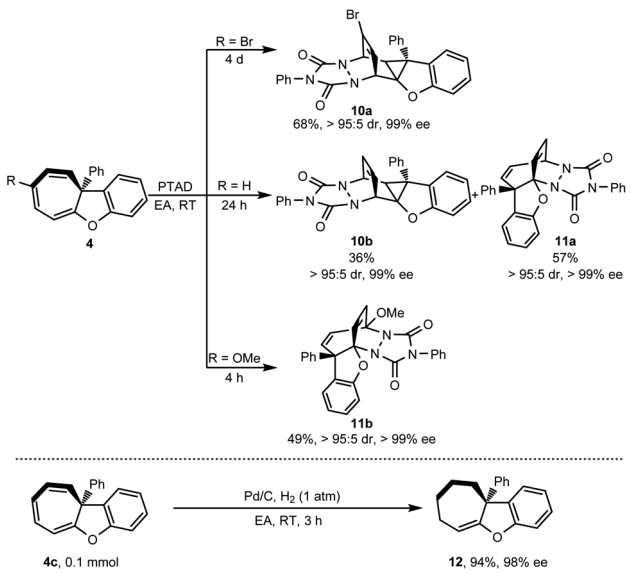
Scheme 5 Plausible mechanism for the racemization through diradical intermediates.

increasing steric hindrance when a substituent was introduced at the C6-position. The diradical **VI** could be oxidized by TEMPO to give ring isomerization product **9**. It is noteworthy that when it comes to the chiral cyclohepta[*b*]benzofuran products derived from *ortho*- and *meta*-substituted phenoxy enynones, a similar process will take place to generate a regioisomer, rather than an enantiomer, without loss of the enantiomeric excess. Numerous efforts to isolate or detect the proposed regioisomer failed, which might be ascribed to that the "walking rearrangement" to the sterically more congested isomer was highly unfavourable (see the ESI for details†). Thus, the cyclopropane would prefer to break bond c to release the steric torsion to give diradical intermediate **VI**, which could be intercepted by TEMPO to give the ring isomerization product **9**.[27]

Derivatization of the cycloheptatriene skeleton

Cycloheptatriene is usually found as a useful skeleton in natural products, such as colchicine,[28] hinokitiol[29] and other series of tropolones and azaheptafulvenes.[30] These kinds of compounds are also flexible to transform into other diverse structures. To demonstrate the synthetic potential of this methodology, [4 + 2] cycloaddition was conducted with PTAD (4-phenyl-1,2,4-triazoline-3,5-dione) as a dienophile. As shown in Scheme 6, when the R group was the Br atom, [4 + 2] cycloaddition proceeded *via* a norcaradiene intermediate because of the cycloheptatriene–norcaradiene (CHT–NCD) equilibrium.[31] Only highly fused cyclopropane **10a** was obtained as a single regioisomer in 68% yield with high stereoselectivity (>95 : 5 dr, 99% ee).

Interestingly, when the R group was the H atom, cyclopropane **10b** (36% yield) *via* norcaradiene addition competed with the bridged polycyclic product **11a** (57% yield) which was derived from direct [4 + 2] cycloaddition.[32] Both the addition products were achieved with high diastereoselectivity (>95 : 5 dr) and without loss of chiral integrity (99% ee). When a more electron-donating group such as OMe substituted cycloheptatriene was used, only direct [4 + 2] cycloaddition product **11b** was isolated in 49% yield with excellent stereoselectivity (>95 : 5 dr, >99% ee). Besides the [4 + 2] cycloaddition, cycloheptatriene **4c** was further hydrogenated in the presence of a catalytic amount of Pd/C under a hydrogen atmosphere (Scheme 6). This reaction selectively reduced two of three double bonds of cycloheptatriene and provided tetrahydro-7*H*-cyclohepta[*b*]benzofuran **12** in 94% yield while retaining the chiral integrity (98% ee).



Scheme 6 Transformation of cycloheptatriene **4**[a]. [a]The reaction was conducted on 0.1 mmol scale, PTAD (1.05 equivalent).

Conclusion

In summary, we have developed a chiral dirhodium(II) tetracarboxylate-catalyzed enantioselective intramolecular reaction of arenes with donor–donor carbenes. This reaction represents the first enantioselective intramolecular Büchner reaction of donor–donor carbenes. When enynone tethered aryloxy substrates were employed as carbene precursors, the Büchner reaction took place smoothly. The desired furyl substituted cyclohepta[*b*]benzofuran polycyclic products were synthesised in good yields and moderate to excellent enantioselectivity. Aryloxy-substituted diazo compounds were also efficient donor–donor carbene precursors for this asymmetric Büchner reaction and phenyl substituted cyclohepta[*b*]benzofurans were obtained with high yields and excellent enantioselectivities. Moreover, when biaryl enynones were used as substrates, the aromatic substitution reaction rather than the Büchner reaction occurred to produce the furyl substituted fluorene derivatives with quantitative yields and excellent enantioselectivities. For furyl substituted chiral cyclohepta[*b*]benzofurans from *para*-substituted phenoxy enynones and diazo compounds, the loss of enantioselectivity was observed. A diradical mechanism was proposed to account for the racemization which was supported by the controlled experiments. The cycloheptatriene products could be further transformed into other polycyclic compounds by [4 + 2] cycloaddition and hydrogenation.

Data availability

All the data have been included in the ESI.†

Author contributions

D. Zhu performed all the experiments. T. Cao is appreciated for his help with English language revision. K. Chen performed the DFT calculations to indicate the mechanistic difference for the Büchner reaction and the aromatic substitution reaction. D. Zhu and S. Zhu contributed to the conception of the experiments, discussion of the results and preparation of manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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