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Copper-catalyzed asymmetric cyclization of alkenyl diynes: method development and new mechanistic insights†

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Metal carbenes have proven to be one of the most important and useful intermediates in organic synthesis, but catalytic asymmetric reactions involving metal carbenes are still scarce and remain a challenge. Particularly, the mechanistic pathway and chiral induction model in these asymmetric transformations are far from clear. Described herein is a copper-catalyzed asymmetric cyclization of alkenyl diynes involving a vinylic C(sp^2)–H functionalization, which constitutes the first asymmetric vinylic C(sp^2)–H functionalization through cyclopentannulation. Significantly, based on extensive mechanistic studies including control experiments and theoretical calculations, a revised mechanism involving a novel type of endocyclic copper carbene *via* remote-stereocontrol is proposed, thus providing new mechanistic insight into the copper-catalyzed asymmetric diyne cyclization and representing a new chiral control pattern in asymmetric catalysis based on remote-stereocontrol and vinyl cations. This method enables the practical and atom-economical construction of an array of valuable chiral polycyclic-pyrroles in high yields and enantioselectivities.

Introduction

In the past decades, metal carbenes have proven to be one of the most important and useful intermediates.[1] However, catalytic asymmetric reactions involving metal carbene intermediates are relatively rare and remain a challenge.[2] In particular, the mechanistic pathway and chiral induction model in these asymmetric systems are far from clear.[3] Therefore, the exploration of novel enantioselective transformations based on metal carbenes, especially with high enantioselectivity and new chiral control pattern, is significantly important.

Among the catalytic transformations of metal carbene species, transition-metal-catalyzed carbene insertion into C–H bonds has attracted much attention during the last decade.[4] Compared to the well-established C(sp^3)–H bond insertion and aromatic C(sp^2)–H bond, carbene insertion into vinylic C(sp^2)–H bonds remains much less developed, presumably due to the competing cyclopropanation of the alkene. Such a side reaction can be prohibited in intramolecular reactions. In this context, significant advances have been made in recent years on formal intramolecular carbene insertion into vinylic C(sp^2)–H bonds *via* cyclopentannulation of metallahexatrienes, which consist of the aryl- or alkenyl-linked metal carbenes and alkenyl moieties, as elegantly exploited by the groups of Sarpong,[5a] R. Liu,[5b] Echavarren,[5c] Y. Liu,[5d,e] Davies,[6a] Xu,[6b] Wang[6c] and others.[7] Here, the metal carbenes of metallahexatrienes could be trapped by the intramolecular alkenyl groups *via* a cyclopentannulation process but not the typical cyclopropanation, thus providing a novel way for rapid and efficient assembly of cyclopentadiene derivatives (Scheme 1a). However, these alkenyl carbene cyclizations have been mostly limited to noble metal catalysts, such as Pt, Au, Rh, Pd, Ru, *etc.* Furthermore, no direct catalytic asymmetric formal carbene insertion into vinylic C(sp^2)–H bonds have been reported to the best of our knowledge.

In recent years, transition-metal catalyzed diyne cyclization has been of increasing importance for the rapid assembly of various synthetically useful cyclic molecules due to their high bond-forming efficiency and atom economy, but there remain significant challenges regarding the catalytic asymmetric diyne cyclization.[8] In this respect, our group in 2019 reported an unprecedented copper-catalyzed diyne cyclization through presumable donor/donor carbenes,[9] and importantly, the asymmetric version could be achieved by employing chiral copper catalysts, thus allowing the practical and divergent synthesis of various chiral polycyclic pyrroles.[10a] After that, our group very recently demonstrated a copper-catalyzed

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† Electronic supplementary information (ESI) available. CCDC 2046032 and 2046033. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc02773e

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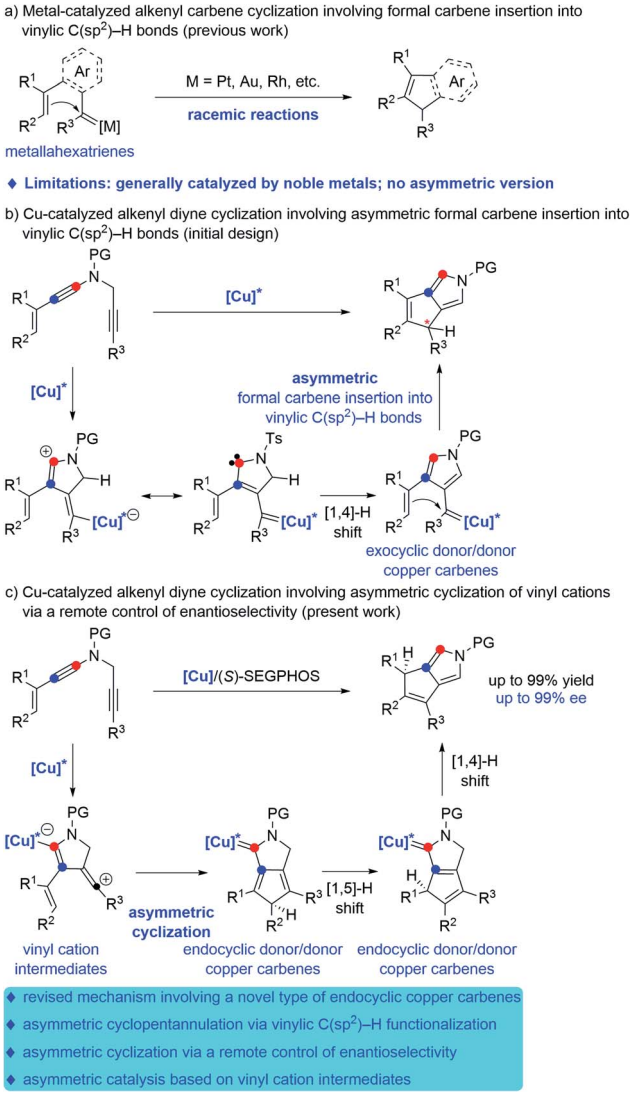


Scheme 1 Transition-metal-catalyzed cyclopentannulation involving vinylic C(sp^2)–H functionalization.

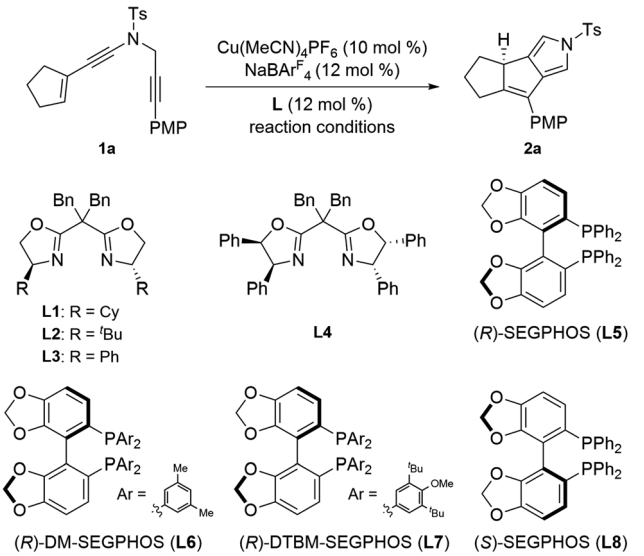
asymmetric reaction of alkenyl diynes with styrenes by formal [3 + 2] annulation, leading to a range of chiral pyrrole-fused bridged [2.2.1] skeletons.[10b] Encouraged by these results and our recent study on developing ynamide chemistry for heterocycle synthesis,[11,12] we envisaged that the direct copper-catalyzed tandem cyclization of alkenyl *N*-propargyl ynamides might produce exocyclic donor/donor copper carbene intermediates, which would undergo further formal carbene insertion into vinylic C(sp^2)–H bonds (Scheme 1b). On the basis of this assumption, we herein disclose a copper-catalyzed asymmetric cyclization of alkenyl *N*-propargyl ynamides involving a vinylic C(sp^2)–H functionalization, which constitutes the first example of asymmetric vinylic C(sp^2)–H functionalization through cyclopentannulation. Significantly, extensive mechanistic studies based on control experiments and density functional theory (DFT) calculations revealed that vinyl cations[13] and endocyclic donor/donor copper carbenes are presumably involved as key intermediates, and remote-stereocontrol is established in this cyclopentannulation,[14] thus providing new mechanistic insight into the copper-catalyzed asymmetric diyne cyclization (Scheme 1c). In particular, this type of endocyclic donor/donor copper carbenes can be regarded as Bertrand's cyclic (alkyl) (amino)carbene (CAAC),[15] which now can be generated directly from alkynes. This method enables the practical and atom-economic synthesis of a diverse array of chiral dicyclic- and polycyclic-pyrroles in generally good to excellent yields (up to 99% yield) with high enantioselectivities (up to 99% ee). Notably, dicyclic- and polycyclic-pyrroles[16] and their reductive derivatives, dicyclic- and polycyclic-pyrrolidines,[17] are two kinds of important N-heterocycle skeletons found in a wide range of bioactive molecules and natural products.

Results and discussion

We commenced our investigation by using readily prepared cyclopentenyl *N*-propargyl ynamide[18] **1a** as the model substrate under previous Cu-catalyzed reaction conditions. As shown in Table 1, at the outset, various substituted bisoxazoline (BOX) ligands **L1–L4** (12 mol%) were employed as the chiral ligands in the presence of 10 mol% of $Cu(CH_3CN)_4PF_6$ as the catalyst and 12 mol% of $NaBAr^F{}_4$ as the additive, and the expected chiral tricyclic pyrrole **2a** was furnished in excellent yields (>90%) but with low enantioselectivities (<40% ee, Table 1, entries 1–4). Inspired by these preliminary results, we next investigated different types of chiral biphosphine ligands. To our delight, the enantioselectivity was significantly improved by the use of (*R*)-SEGPHOS **L5** as a ligand, and the corresponding chiral product **2a** was formed in 92% yield with 85% ee (Table 1, entry 5). Further screening of SEGPHOS ligands **L6** and **L7** with large steric hindrance led to the decreased enantioselectivities (Table 1, entries 6 and 7). Interestingly, the enantioselectivity was slightly improved by employing opposite (*S*)-SEGPHOS **L8** as a ligand, and the chiral **2a** was formed in 91% yield with 87% ee (Table 1, entry 8). Afterward, solvent examination showed that other typical solvents such as DCE, THF and Et_2O failed to further improve the enantioselectivity (Table 1, entries 9–11). Gratifyingly, an obvious temperature influence was observed (Table 1, entries 12 and 13), and decreasing the reaction temperature to 0 °C allowed for the formation of the desired **2a** in 90% yield with 93% ee (Table 1, entry 13). Of note, the use of other copper catalysts such as CuOTf and CuI led to a comparable enantioselectivity but slightly decreased yields.

Having established the optimized reaction conditions (Table 1, entry 13), we next explored the substrate scope of this copper-catalyzed asymmetric annulation of alkenyl *N*-propargyl ynamides. As shown in Table 2, apart from the Ts-protected ynamide **1a**, the reaction proceeded smoothly with various *N*-protected ynamides, including $PhSO_2$-, MBS-, Bs-, 2-naphthyl-SO_2- and 2-thienyl-SO_2-protected alkenyl *N*-propargyl ynamides, providing the corresponding chiral tricyclic pyrroles **2b–2f** in generally excellent yields and excellent enantioselectivities. Then, we changed PMP to other *O*-containing electron-donating groups (EDGs). For instance, different *O*-containing aryl-substituted alkenyl *N*-propargyl ynamides encompassing

Table 1 Optimization of reaction conditions for asymmetric annulation of cyclopentenyl *N*-propargyl ynamide **1a**[a]

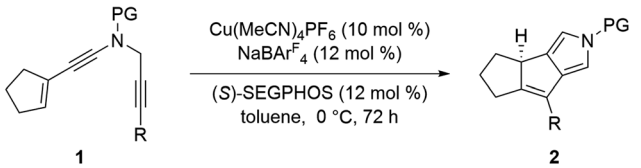


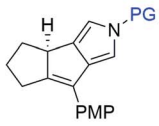
Entry	L	Conditions	Yield[b] (%)	Ee[c] (%)
1	**L1**	Toluene, 35 °C, 2 h	93	35 (+)
2	**L2**	Toluene, 35 °C, 2 h	90	<5 (+)
3	**L3**	Toluene, 35 °C, 2 h	93	<5 (+)
4	**L4**	Toluene, 35 °C, 2 h	92	21 (−)
5	**L5**	Toluene, 35 °C, 2 h	92	85 (+)
6	**L6**	Toluene, 35 °C, 2 h	86	81 (+)
7	**L7**	Toluene, 35 °C, 5 h	80	15 (+)
8	**L8**	Toluene, 35 °C, 2 h	91	87 (−)
9	**L8**	DCE, 35 °C, 2 h	82	83 (−)
10	**L8**	THF, 35 °C, 12 h	75	82 (−)
11	**L8**	Et_2O, 35 °C, 4 h	72	82 (−)
12	**L8**	Toluene, 20 °C, 12 h	89	90 (−)
13	**L8**	**Toluene, 0 °C, 72 h**	**90**	**93 (−)**

[a] Reaction conditions: **1a** (0.05 mmol), $Cu(CH_3CN)_4PF_6$ (0.005 mmol), **L** (0.006 mmol), $NaBAr^F_4$ (0.006 mmol), solvent (1 mL), in Schlenk tubes. [b] Measured by ^1H NMR using diethyl phthalate as the internal standard. [c] Determined by HPLC analysis. Ts = *p*-toluenesulfonyl, PMP = 4-methoxyphenyl, $NaBAr^F_4$ = sodium tetrakis[3,5-bis(trifluoromethyl) phenyl]borate, DCE = 1,2-dichloroethane.

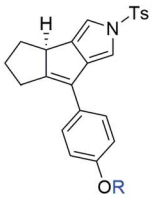
functional groups (*e.g.* phenyl, benzyl, silyl, Ac) were suitable substrates for this tandem annulation, affording the desired chiral pyrroles **2g–2k** in 63–88% yields with 84–94% ees. The methoxyl group at the *ortho* position of the aryl ring led to slightly decreased yield and ee (71%, 80% ee). Besides mono-substituted aryl groups, di-substituted aromatic groups were also readily tolerated, leading to products **2m–2o** in 81–86% yields with 90–92% ees. In addition, the reaction was also extended to heteroatom-containing electron-rich aryl groups, and we were pleased to find that NMe_2-substituted ynamide **1p** occurred efficiently under the standard conditions, delivering the expected tricyclic pyrrole **2p** in 86% yield with 99% ee. Subsequently, other heteroatom-containing EDGs (*e.g.* NBn_2, $NPMB_2$, SMe) substituted diynes were also applicable substrates for this reaction to produce the desired pyrroles **2q–2s** in

Table 2 Scope of the asymmetric cyclization of cyclopentenyl *N*-propargyl ynamides **1**[a]

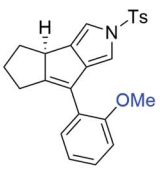




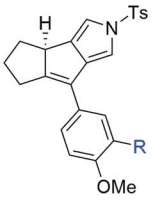
2a, PG = Ts, 91%, 93% ee
2b, PG = SO_2Ph, 88%, 90% ee
2c, PG = MBS, 85%, 88% ee
2d, PG = Bs, 85%, 92% ee
2e, PG = SO_2-2-naphthyl, 90%, 93% ee
2f, PG = SO_2-2-thienyl, 87%, 89% ee



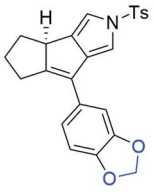
2g, R = Ph, 85%, 90% ee
2h, R = Bn, 84%, 92% ee[b]
2i, R = TBS, 82%, 92% ee[b]
2j, R = TIPS, 88%, 94% ee
2k, R = Ac, 63%, 84% ee[b]



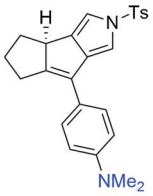
2l, 71%, 80% ee[b]



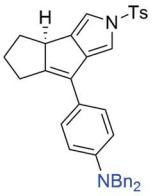
2m, R = Me, 81%, 92% ee
2n, R = OMe, 86%, 90% ee



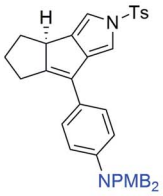
2o, 85%, 92% ee[b]



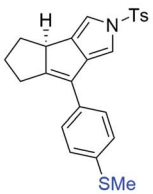
2p, 86%, 99% ee



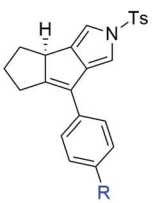
2q, 99%, 96% ee



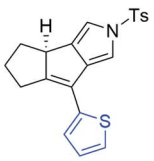
2r, 92%, 97% ee



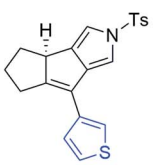
2s, 77%, 91% ee



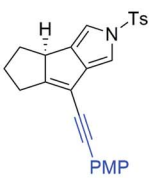
2t, R = Me, 88%, 73% ee[c]
2u, R = H, 73%, 64% ee[c]
2v, R = Br, 61%, 56% ee[c]



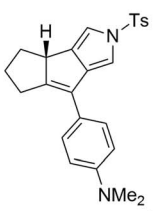
2w, 82%, 84% ee[b]



2x, 92%, 84% ee[b]

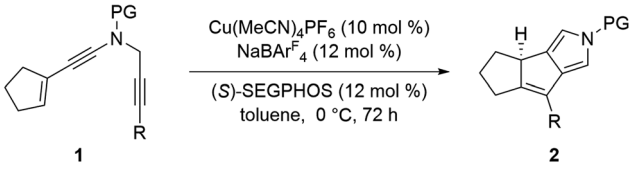


2y, 72%, 90% ee



2z, 88%, 99% ee[d]

Table 2 (*Contd.*)



[a] Reaction conditions: **1** (0.2 mmol), $Cu(MeCN)_4PF_6$ (0.02 mmol), $NaBAr^F_4$ (0.024 mmol), (*S*)-SEGPHOS (0.024 mmol), toluene (2 mL), 0 °C, 72 h, in Schlenk tubes; yields are those for the isolated products; ees are determined by HPLC analysis. [b] 10 °C, 72 h. [c] 20 °C, 5 d. [d] (*R*)-SEGPHOS as the ligand. MBS = 4-methoxybenzenesulfonyl, Bs = 4-bromobenzenesulfonyl, PMB = *p*-methoxybenzyl.

excellent yields with 91–97% ees. We then attempted to decrease the electric density of the aryl groups, such as methyl- and bromo-substituted phenyl rings, and the apparent diminution occurred on both yields and enantioselectivities. In addition to the aryl-substituted diynes, heteroaryl-substituted alkenyl *N*-propargyl ynamides **1w** and **1x** were also tolerated, allowing the assembly of the desired products **2w** (82%, 84% ee) and **2x** (92%, 84% ee), respectively. Interestingly, the alkenyl substituted triyne substrate **1y** was also compatible with this asymmetric annulation, and the corresponding chiral product **2y** was formed in 72% yield and 90% ee, which has great potential in further derivatizations. Finally, the synthesis of tricyclic pyrrole **2z** (88%, 99% ee) with the opposite enantioselectivity could also be achieved by employing the opposite (*R*)-SEGPHOS as a chiral ligand. Our attempts to extend the reaction to the alkenyl- and alkyl-substituted ynamides **1al–1am** and terminal ynamide **1an** have been unsuccessful as yet.[19] The absolute configuration of product **2s** was verified by X-ray crystallographic analysis (Fig. 1).[20]

Various alkenyl moieties of the diynes were then explored under the optimized conditions. As depicted in Table 3, we were delighted to observe that acyclic alkenyl *N*-propargyl ynamides also served as appropriate substrates to afford the corresponding enantioenriched dicyclic-pyrroles **2aa–2ac** in good yields with the ees of 90–93%. Besides 5-membered alkenyl substitution, other ring systems on alkenyl *N*-propargyl ynamides (*e.g.* cyclohexenyl, cycloheptenyl, cyclooctenyl) were also suitable

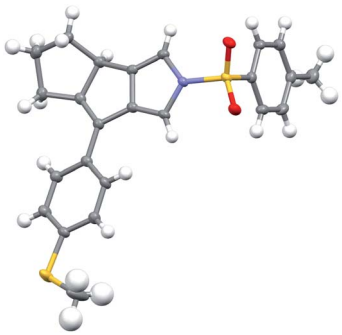
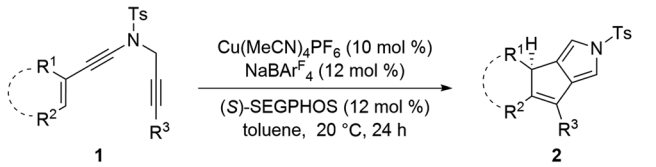
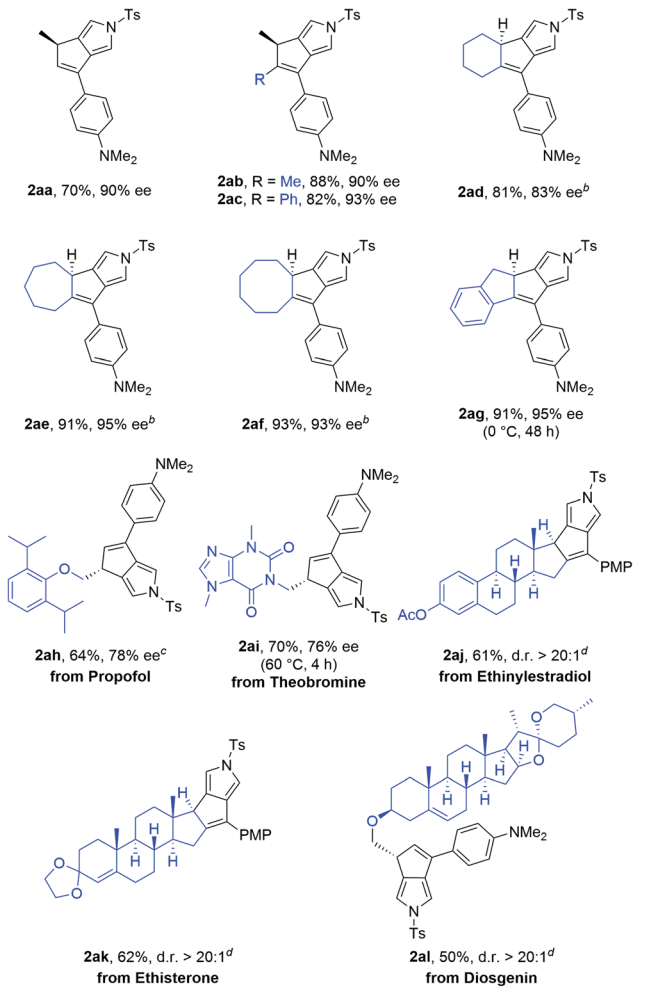


Fig. 1 Structure of compound **2s** in its crystal.

Table 3 Scope of the asymmetric cyclization of alkenyl *N*-propargyl ynamides **1**[a]



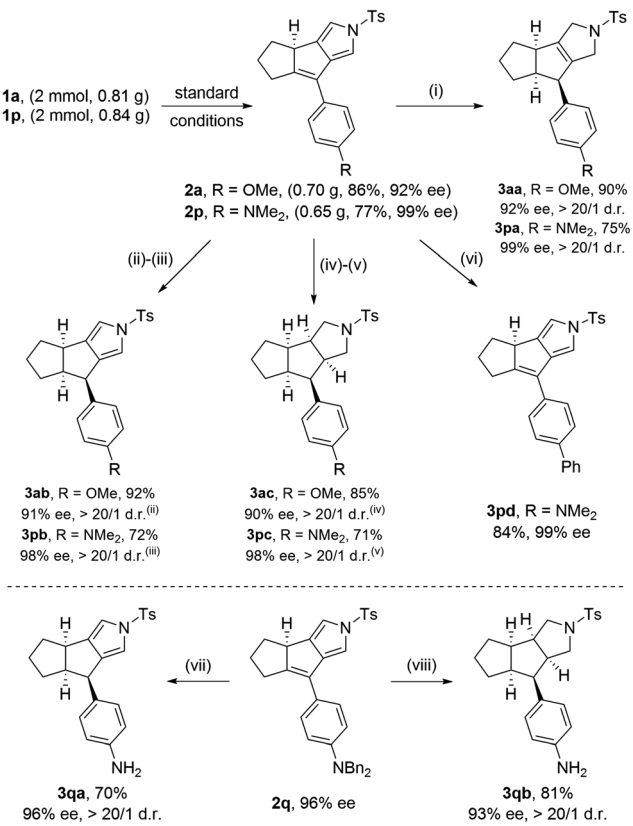


[a] Reaction conditions: **1** (0.2 mmol), $Cu(MeCN)_4PF_6$ (0.02 mmol), $NaBAr^F_4$ (0.024 mmol), (*S*)-SEGPHOS (0.024 mmol), toluene (2 mL), 20 °C, 24 h, in Schlenk tubes; yields are those for the isolated products; ees are determined by HPLC analysis; d.r.s are determined by ^1H NMR. [b] 2-Me-THF as the solvent. [c] DCE as the solvent, 0 °C. [d] DCE as the solvent, 40 °C.

substrates for this annulation, furnishing the anticipated chiral tricyclic-pyrroles **2ad–2af** in generally excellent yields and enantioselectivities. Of note, indenyl substituted diyne was able to undergo smooth asymmetric cyclization to provide the desired enantioenriched polycyclic-pyrrole **2ag** efficiently (91%, 95% ee). Importantly, this asymmetric annulation could be extended to alkenyl diynes bearing the complex pharmaceutical molecule scaffolds. For example, the propofol and theobromine derived diynes were applicable substrates to generate the

pharmaceutical derived pyrroles **2ah–2ai** in moderate to good yields with acceptable enantioselectivities. In addition, more complex chiral polycyclic-pyrroles **2aj–2al** could be obtained smoothly with excellent diastereoselectivities (d.r. > 20/1) from the corresponding complicated substrates bearing pharmaceutical moieties such as ethinylestradiol, ethisterone and diosgenin, and it is notable that low efficiency (<10% yield) was observed in these cases in the absence of chiral ligands.[10b]

Further synthetic applications of the as-synthesized chiral tricyclic-pyrroles such as **2a** and **2p** were then investigated, as indicated in Scheme 2. First, preparative scales could be obtained for the synthesis of **2a** (0.70 g, 86%, 92% ee) and **2p** (0.65 g, 77%, 99% ee) respectively. Then, the treatment of **2a** and **2p** with $NaBH_3CN$ as the reductant led to tricyclic-dihydropyrroles **3aa** and **3pa** bearing three contiguous stereocenters in good yields with >20/1 d.r.s. (Scheme 2). Next, selective reduction of tricyclic-pyrroles **2a** and **2p** by H_2 in the presence of Pd/C as the catalyst could allow the formation of the corresponding chiral pyrroles **3ab** and **3pb** containing three contiguous stereocenters, and tricyclic-pyrrolidines **3ac** and **3pc** encompassing five contiguous stereocenters in good yields with excellent diastereoselectivities, respectively. The absolute



Scheme 2 Scale-up reaction and product elaboration. Reagents and conditions: (i) $NaBH_3CN$ (5 equiv.), TFA, rt, 1 h. (ii) Pd/C (10 mol%) H_2 (1 atm), MeOH, rt, 2 h. (iii) Pd/C (10 mol%) H_2 (4 MPa), MeOH/EA, 60 °C, 36 h. (iv) Pd/C (10 mol%) H_2 (4 MPa), MeOH, 60 °C, 36 h. (v) PtO_2 (10 mol%), H_2 (4 MPa), AcOH, 80 °C, 72 h. (vi) MeOTf (1.2 equiv.), Et_2O, 0 °C to rt, 2 h; $Pd(PPh_3)_2Cl_2$ (5 mol%), PhMgBr (2 equiv.), THF, rt, 2 h. (vii) Pd/C (10 mol%) H_2 (4 MPa), MeOH/EA, 60 °C, 72 h. (viii) Pd/C (20 mol%) H_2 (5 MPa), EtOH/EA, 80 °C, 96 h.

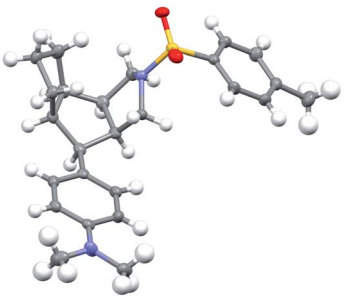
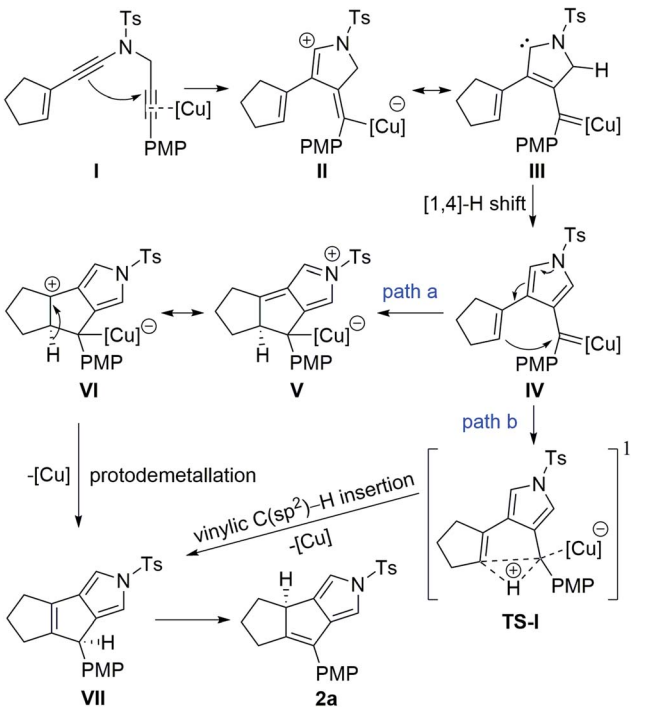


Fig. 2 Structure of compound **3pc** in its crystal.

configuration of compound **3pc** was confirmed by X-ray diffraction analysis (Fig. 2).[20] The NMe_2 group of pyrrole **2p** could be easily transferred into the aryl group in 84% yield *via* a Pd-catalyzed cross coupling with the aryl Grignard reagent. Finally, products **3qa** and **3qb** with the free anilines could be readily obtained respectively from the NBn_2-substituted pyrrole **2q** *via* a debenzylation process with Pd/C under a H_2 atmosphere, which might undergo smooth further functionalization. Importantly, almost no erosion of the enantiopurity of the compounds was observed and excellent diastereoselectivities (d.r. > 20 : 1) were achieved in all these elaborations.

On the basis of our previous studies on copper-catalyzed diyne cyclization,[10] a plausible mechanism for the synthesis of tricyclic pyrrole **2a** is depicted in Scheme 3. The reaction commences with attacking of electron-rich ynamide moiety to the copper-activated C≡C bond of *N*-propargyl moiety, providing the vinyl copper intermediate **II** or its resonance form

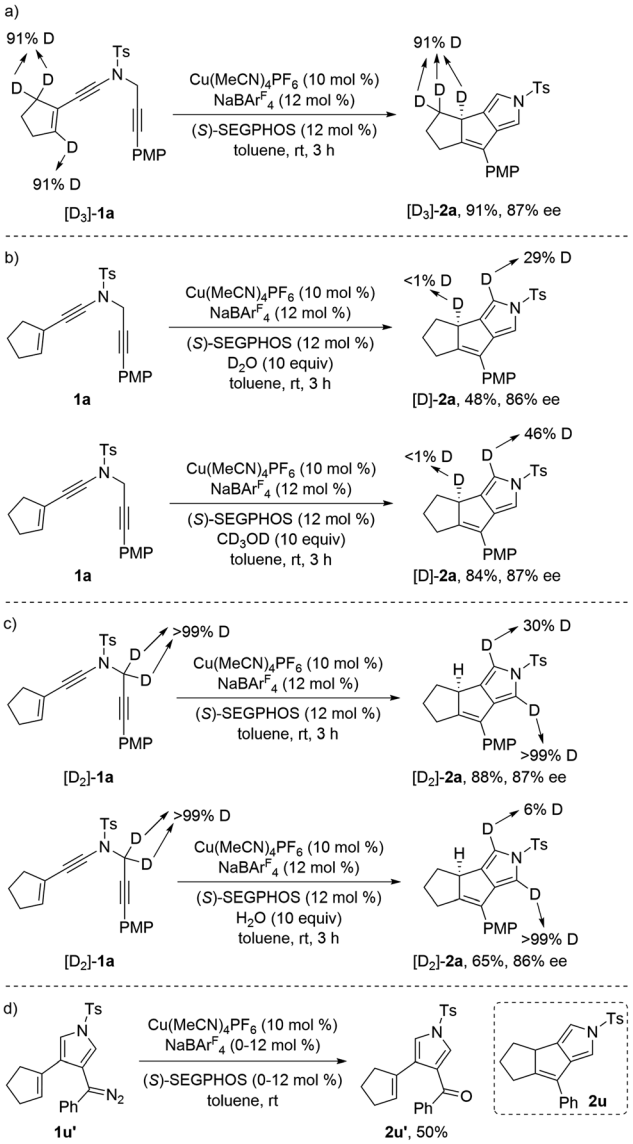


Scheme 3 Original mechanism proposed for the formation of product **2a**.

III. Subsequent [1,4]-H shift generates donor/donor copper carbene **IV**. Then, this copper carbene may undergo two pathways. In path a, intramolecular nucleophilic attack of the electron-rich alkene moiety on the carbene carbon delivers the five-membered intermediate **VI**. This intermediate would go through a protodemetallation to afford the intermediate **VII** with the regeneration of the copper catalyst, followed by tautomerism to produce the final product **2a**, which may be thermodynamically more stable than **VII**. Alternatively, in path b, direct intramolecular vinylic C(sp^2)–H bond insertion into copper carbene may occur to deliver intermediate **VII** *via* **TS-I**,[6c] eventually leading to the desired **2a** by a tautomerization process. However, the above proposed mechanism is difficult to explain the stereospecific [1,3]-H transfer in the tautomerism process, which is extremely rare and has to rely the use of extra base to promote the suprafacial [1,3]-hydrogen atom transfer.[21] Furthermore, no formation of intermediate **VII** was observed by ^{1}H NMR monitoring of this annulation under the standard conditions.

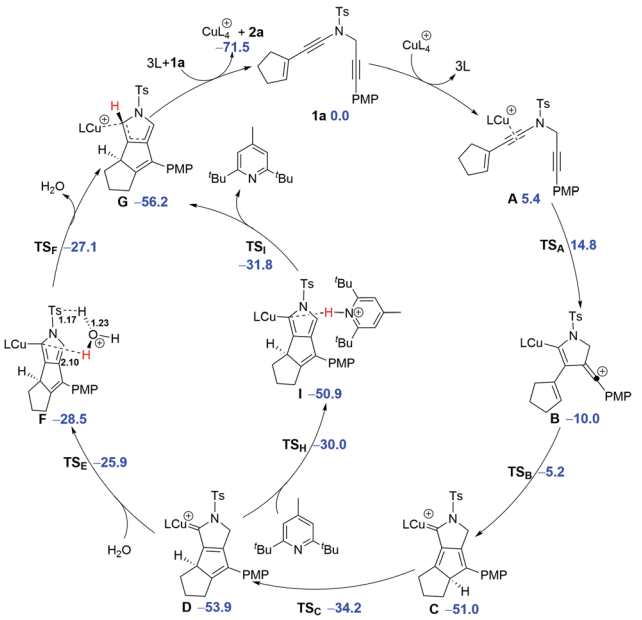
To further probe the reaction mechanism, we carried out several control experiments. First, deuterium labeling experiment was performed with the substrate [D_3]-**1a**. It was found that the deuterium atoms were thoroughly retained in [D_3]-**2a** under the standard conditions (Scheme 4a). Then, we also subjected ynamide **1a** with D_2O or CD_3OD (10 equiv.) under standard conditions, and found that <1% deuterium incorporation into the carbocycle partner of the desired product was observed (Scheme 4b). Thus, these results indicate that path a of Scheme 3 is unlikely, as H/D exchange should occur in the deprotonation/protonation sequence.[6c] Meanwhile, it is notable that significant deuterium incorporation into the pyrrole partner of **2a** was detected. To confirm this, we also synthesized substrate [D_2]-**1a** and subjected it under the standard conditions and in the presence of 10 equiv. of H_2O, and found that only 30% deuterium and 6% deuterium were retained on one of the α-position pyrrole, respectively (Scheme 4c). Moreover, the use of 2,6-di-*tert*-butyl-4-methylpyridine as base with large steric hindrance substantially accelerated the reaction (rt: 1.5 h *vs.* 3 h).[19] These results suggested that proton transfer but not the previously proposed hydride shift was presumably involved in the formation of pyrrole moiety, and the proton transfer could be assisted by proper organic base or water. In addition, it was found that the reaction of alkenyl diazo compound **1u′** under the current copper catalysis only led to the formation of the corresponding oxidized ketone **2u′** in 50% yield, and no desired cyclization product **2u** was obtained (Scheme 4d). Finally, kinetic isotope effect (KIE) experiment was also conducted with the mixture of substrates **1a** and [D_3]-**1a**, and the KIE data (k_H/k_D = 1.5) suggest that the cleavage of vinylic C(sp^2)–H bond is not the rate-determining step.[19]

Based on the above experimental observations, to clearly understand the mechanism for formation of the tricyclic pyrrole **2a** from cyclopentenyl *N*-propargyl ynamide **1a**, detailed DFT calculations were carried out with the achiral Cu^I catalyst and the plausible mechanism is shown in Scheme 5. Initially, the single catalytic Cu^I species is preferentially bound to the electron-richer amide-tethered C≡C bond of the substrate **1a**,



Scheme 4 (a) The reaction of [D3]-**1a** under the standard conditions. (b) Cu-catalyzed cyclization of **1a** in the presence of 10 equiv. of D_2O or CD_3OD. (c) The reaction of [D2]-**1a** under the standard conditions or in the presence of 10 equiv. of H_2O. (d) Cu-catalyzed reaction of **1u′** under the standard conditions.

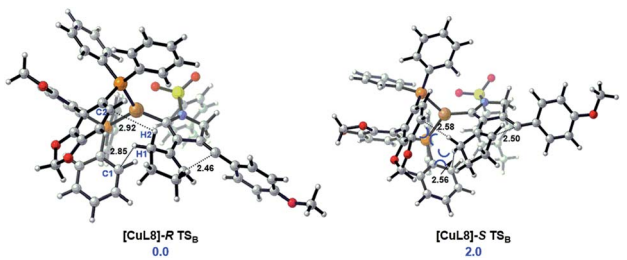
forming the precursor **A** and the possibility of dual-copper catalysis is completely excluded out.[19] Subsequent electrophilic attack of the copper-activated C≡C bond to the *N*-propargyl moiety *via* $\mathbf{TS_A}$ with a free energy barrier of 9.4 kcal mol^{-1} gives the cyclized intermediate **B**. The vinyl-cation center of **B** is highly reactive and readily attacked by the electron-rich alkene group to form the cyclopentadiene intermediate **C**; this step is highly exergonic (ΔG = −41.0 kcal mol^{-1}) with a free energy barrier of only 4.8 kcal mol^{-1}. Then, a normal suprafacial [1,5]-H shift occurs within the cyclopentadiene ring with a free energy barrier of 16.8 kcal mol^{-1} to afford the second cyclopentadiene intermediate **D**. The remaining steps include [1,4]-H shift within the five-membered N-heterocycle of **D** and demetallation to afford the final product **2a**. The [1,4]-H shift is found



Scheme 5 Revised mechanism for the formation of product **2a** (CuL = CuMeCN). Relative free energies (Δ*G*, in kcal mol^{-1}) of the key intermediates and transition states are calculated at the SMD(toluene)-M06/6-31G(d,p)/LANL2DZ level of theory at 298 K. Key bond lengths are shown in bold (unit: Å).

to be assisted by H_2O *via* two consecutive steps of proton transfer (**D** → **F** → **G**) by overcoming an activation free energy of 28.0 kcal mol^{-1},[19,22] or more readily assisted by such an organic base as 2,6-di-*tert*-butyl-4-methylpyridine with a lower activation free energy of 23.9 kcal mol^{-1}. Such rate-limiting 1,4-proton transfer mechanism is in line with the aforementioned isotopic control experiments (Scheme 4) and the observation that the use of 2,6-di-*tert*-butyl-4-methylpyridine obviously accelerated the reaction.

To unravel the origin of enantioselectivity, the transition states of the second cyclization step, *i.e.*, **B** → **C**, were explored with use of the chiral ligand **L8** coordinated onto the Cu(I) center (Scheme 6), as the stereoselectivity of this step can be completely maintained in the subsequent stereospecific suprafacial [1,5]-H shift. The free energy of the transition state **[CuL8]-*R* TS$_B$** is 2.0 kcal mol^{-1} lower than the **[CuL8]-*S* TS$_B$**, agreeing well with the experimental ee value of 93%. Despite that the chiral ligand is far away from the highly active vinyl-cation center, the steric repulsion between the bulky chiral ligand **L8** and the rigid cyclopentene ring is responsible for the stereoselectivity of such a bicyclization process (Scheme 6).



Scheme 6 The geometries and relative free energies (Δ*G*, in kcal mol^{-1}) of the transition state **[CuL8]-*R* TS$_B$** and **[CuL8]-*S* TS$_B$** with the chiral ligand **L8** in the *trans*-formation of intermediate **B** to **C** with different orientations of hydrogen atom. Calculations at SMD(toluene)-M06-D3/Def2tzvp//M06/6-31G(d,p)/LANL2DZ level. Key bond lengths are shown in bold (unit: Å).

Finally, we should mention that similar vinyl cation-involving mechanism supported by DFT computations[19] also accounts for the copper-catalyzed diyne cyclizations reported previously.[10]

Conclusions

In summary, we have developed a novel copper-catalyzed asymmetric cyclization of alkenyl *N*-propargyl ynamides involving a vinylic C(sp^2)–H functionalization, representing the first asymmetric such a vinylic C(sp^2)–H functionalization through cyclopentannulation. This method enables the practical and atom-economical construction of a diverse array of valuable chiral dicyclic- and polycyclic-pyrroles in moderate to excellent yields with wide substrate compatibility and high enantioselectivities (up to 99% ee) under mild conditions. Significantly, based on detailed mechanistic studies including control experiments and DFT calculations, a revised mechanism involving a novel type of endocyclic copper carbenes, which constitutes the first generation of electron-rich heteroatom-substituted metal carbenes (CAAC type) from alkynes, and a remote control of enantioselectivity is proposed, Thus, this protocol provides new mechanistic insight into the copper-catalyzed asymmetric diyne cyclization and represents a new chiral control pattern in asymmetric catalysis based on remote-stereocontrol and vinyl cations. To our best knowledge, examples of the direct catalytic asymmetric reactions of vinyl cations have not been reported. We envision that the findings described in this paper will open up new horizons in the field of asymmetric diyne cyclizations, and catalytic asymmetric reactions involving metal carbenes, vinyl cations and remote-stereocontrol.

Data availability

Data for the crystal structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under the deposition numbers CCDC 2046032 (**2s**), 2046033 (**3pc**). All other data supporting the findings of this study, including experimental procedures and compound characterization, are available within the paper and its supplementary information files, or from the corresponding authors on request.

Author contributions

X.-Q. Z., Y.-X. Z., Y.-Y. Z., F.-L. H. performed experiments. P. H., X. L. performed DFT calculations. L.-W. Y. conceived and directed the project and wrote the paper. All authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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