

Asymmetric Büchner reaction and arene cyclopropanation via copper-catalyzed controllable cyclization of diynes

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The asymmetric Büchner reaction and related arene cyclopropanations represent one type of the powerful methods for enantioselective dearomatization. However, examples of asymmetric Büchner reactions via a non-diazo approach are quite scarce, and the related arene cyclopropanation based on alkynes has not been reported. Herein, we disclose an asymmetric Büchner reaction and the related arene cyclopropanation by copper-catalyzed controllable cyclization of *N*-propargyl ynamides via vinyl cation intermediates, leading to chiral tricycle-fused cycloheptatrienes and benzenorcaradienes in high yields and enantioselectivities. Importantly, this protocol represents an asymmetric arene cyclopropanation reaction of alkynes and an asymmetric Büchner reaction based on vinyl cations.

Catalytic asymmetric dearomatization (CADA) has proven to be one of the most attractive synthetic strategies to transform aromatic compounds to three dimensional molecules^{1–8}. In the past decades, a wide range of efficient CADA reactions have been developed with a focus on the electron-rich aromatic rings, such as indoles and phenols^{1–8}. Conversely, the CADA reactions of simple benzenes and naphthalenes have been rarely reported^{9,10}, because of their intrinsic aromatic stability. Büchner reaction, as a unique type of expansive dearomatization of unactivated arenes, has become a practical strategy for the straightforward assembly of valuable functionalized cycloheptatrienes^{11–23}. In recent years, the asymmetric Büchner reaction has received extensive attention and represents a significant advance in CADA reactions, offering the great potential to build valuable chiral cycloheptatrienes (CHTs)^{24–36}. Moreover, the arene cyclopropanation product (norcaradiene, NCD), as an intermediate in the Büchner reaction, has also been widely used to prepare versatile polycyclic compounds^{13,37–42}. In 1990, McKervey and co-workers achieved an asymmetric Büchner reaction by rhodium catalysis^{24,25}, and since then, this chiral rhodium-catalyzed Büchner reaction was extensively studied by Xu and Doyle²⁶ and others^{27–29}. In

addition, chiral copper- and ruthenium-catalyzed Büchner reactions were also nicely explored by Maguire^{30–33} and Iwassa³⁴, respectively. Despite these significant advances (Fig. 1a), these protocols have to rely on the use of diazo compounds as the carbene precursors. Particularly, compared to the classical Büchner reaction, the related asymmetric arene cyclopropanation reaction is highly challenging and has been scarcely reported^{37–39,42}. Firstly, the generated norcaradienes are susceptible to isomerize into the more stable cycloheptatrienes^{11–13,28,37–42}. Secondly, the interrupted cyclopropanation products could undergo easy racemization^{11–13,26} and suffer from low regiocontrol^{11–13,39}. This also increases the difficulty in achieving the diversification of asymmetric arene Büchner reaction and cyclopropanation reaction. In 2021, Nemoto and Harada demonstrated an example of asymmetric Büchner reaction based on alkynes via a non-diazo approach (Fig. 1b)³⁵. Very recently, an asymmetric Büchner reaction by chiral rhodium-catalyzed enynone cycloisomerization⁴³ via the donor-donor Rh carbenes was elegantly studied by Zhu and co-workers³⁶. However, to our best knowledge, the asymmetric arene cyclopropanation reaction based on alkynes remains unrealized. Furthermore, direct divergent synthesis of

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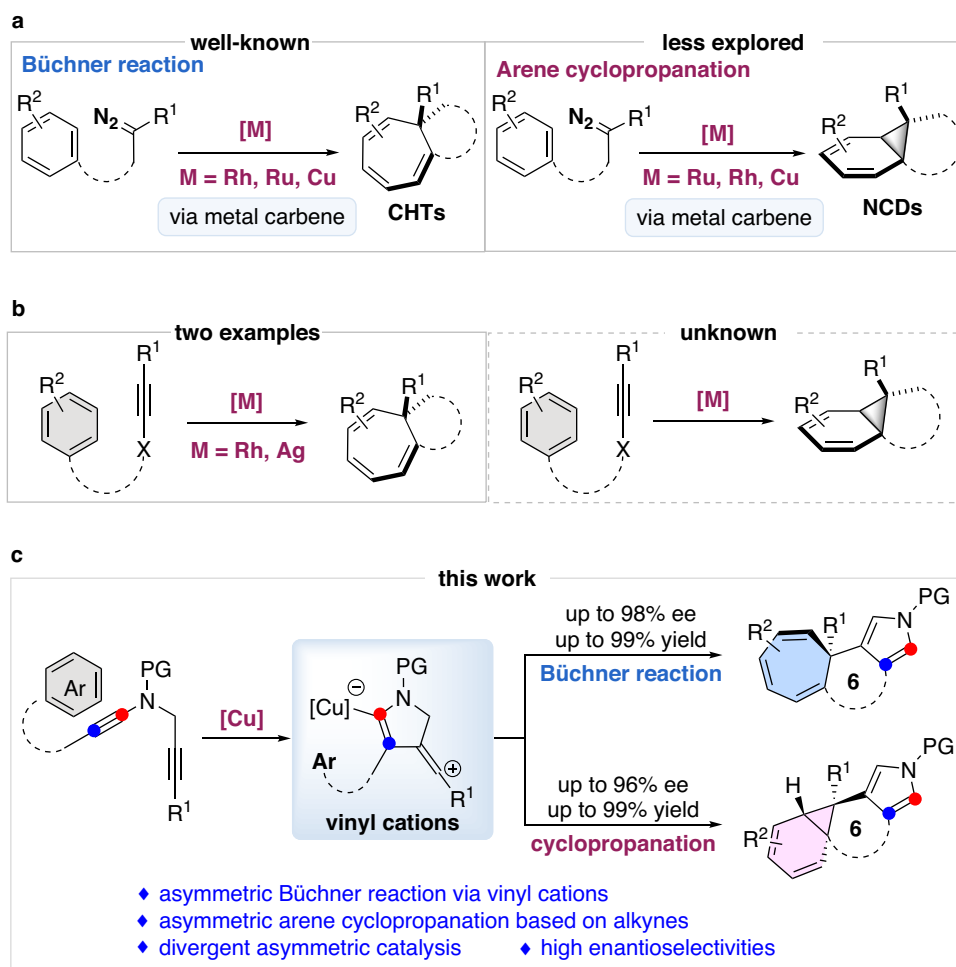


Fig. 1 | Asymmetric Büchner and arene cyclopropanation reactions. **a** Traditional asymmetric Büchner and arene cyclopropanation reactions. **b** Asymmetric Büchner and arene cyclopropanation reactions of alkynes. **c** This work: Cu-catalyzed asymmetric Büchner and arene cyclopropanation of alkynes.

chiral cycloheptatriene and benzonorcaradiene products have not yet been explored.

As a versatile intermediate in organic synthesis, vinyl cations have gained particular attention for their unique carbene-like reactivity in the past decade^{44,45}. However, the exploitation of an asymmetric catalysis based on vinyl cation intermediates remains elusive but highly desirable⁴⁶. In the past several years, our group has developed a facile copper-catalyzed diyne cyclization for the generation of vinyl cations. By using this strategy, a variety of useful asymmetric transformations have been established via a remote control of enantioselectivity^{47–54}, including intramolecular aromatic C(sp²)-H functionalization⁴⁷, vinylic C(sp²)-H functionalization⁴⁹, unactivated C(sp³)-H functionalization⁵⁴, cyclopropanation⁴⁷, and [1,2]-Stevens-type rearrangement⁵⁰, and intermolecular annulations with styrenes⁴⁸ and ketones⁵¹, and atroposelective cyclization^{52,53}. Inspired by these results and by our recent studies on the ynamide chemistry for N-heterocycle synthesis^{55–61}, we envisaged that intramolecular arene moieties might capture the vinyl cations generated from the diyne cyclization and eventually lead to the dearomatized products (Fig. 1c).

Herein, we report the successful implementation of this mechanistic design to a highly enantioselective synthesis of a wide range of tricycle-fused cycloheptatrienes by Büchner reaction via the copper-catalyzed cyclization of phenyl-substituted *N*-propargyl ynamides. Interestingly, such a copper-catalyzed cyclization of naphthyl-substituted *N*-propargyl ynamides allows the formation of chiral benzonorcaradienes by interrupted arene cyclopropanation. Thus, by utilizing alkynes as precursors, this method leads to practical and

divergent synthesis of enantioenriched cycloheptatrienes and benzonorcaradienes. Importantly, this protocol not only represents an asymmetric arene cyclopropanation reaction of alkynes, but also constitutes an asymmetric Büchner-type reaction based on vinyl cations. Of note, chiral fused bicyclo[5.4.0] rings and benzonorcaradienes are important structural motifs found in various natural products and bioactive molecules (Fig. 2)^{36,62–70}.

Results

Screening of conditions on the asymmetric Büchner reaction

At the outset, *N*-propargyl ynamide **1a** bearing an electronically deactivated arene moiety was used as the model substrate^{35,36} to explore the asymmetric Büchner reaction based on our previous copper-catalyzed diyne cyclization^{47–54}, and selected results are summarized in Table 1 (see the Supplementary Materials, Table S1). In the presence of 10 mol % Cu(MeCN)₄PF₆ as the catalyst and 12 mol % NaBARF₄ as the additive in DCM at 35 °C, we were pleased to find that the expected chiral pyrrole-fused cycloheptatriene **2a** was obtained in high yields (>80%) with moderate enantioselectivities by using bisphosphine ligands **L1** and **L2** as chiral ligands, and no background aromatic C–H insertion product was observed⁴⁷ (Table 1, entries 1 and 2). Then, various bisoxazoline (BOX) ligands **L3–L9** (12 mol %) were screened. It was found that poor enantioselectivities were achieved when typical BOX ligands such as **L3** and **L4** were employed as chiral ligands (Table 1, entries 3 and 4). In addition, the use of BOX ligand **L5** also led to low enantioselectivity (Table 1, entry 5, 42% ee). Subsequently, Tang's side-armed bisoxazoline (SaBOX) ligands⁷¹ were investigated on the basis of our previous

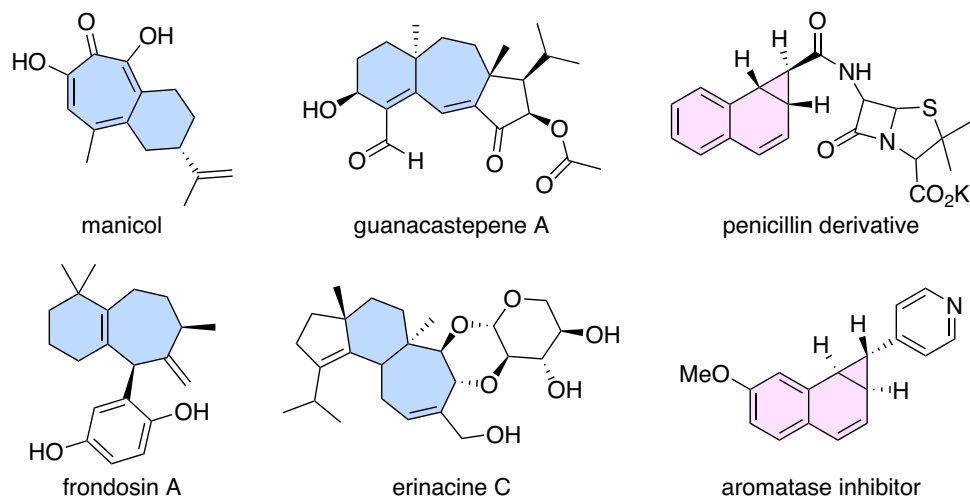


Fig. 2 | Selected natural products and bioactive molecules containing fused bicyclo[5,4,0] ring and benzonorcaradiene motif. Some of representative molecules are listed.

studies^{47–54}. Gratifyingly, the desired chiral product **2a** could be obtained in 94% yield with 79% ee by using the dibenzyl-substituted SaBOX ligand **L6** (Table 1, entry 6). Further screening of other SaBOX ligands **L7–L9** (Table 1, entries 7–9) revealed that the use of **L9** allowed the formation of the desired **2a** in 95% yield with 81% ee (Table 1, entry 9). Next, we screened some other typical solvents such as DCE, toluene and THF (Table 1, entries 10–12), and found that the use of toluene as solvent could further improve the enantioselectivity (Table 1, entry 11). To our delight, a significant temperature effect was observed (Table 1, entries 13 and 14), and the chiral product **2a** was formed in 95% yield with 96% ee when the temperature was lowered to $-20\text{ }^{\circ}\text{C}$ (Table 1, entry 14).

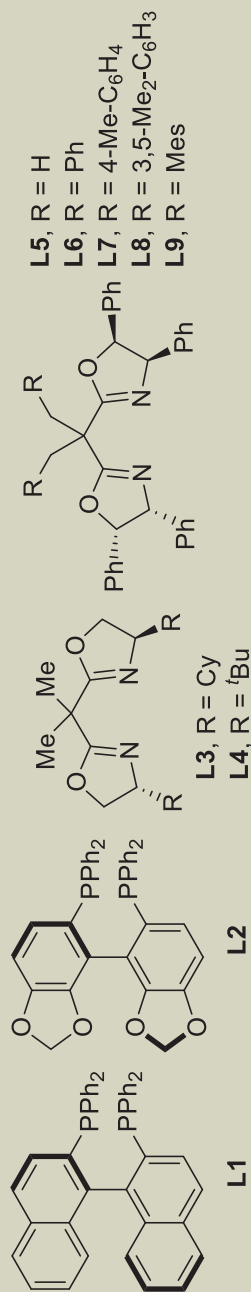
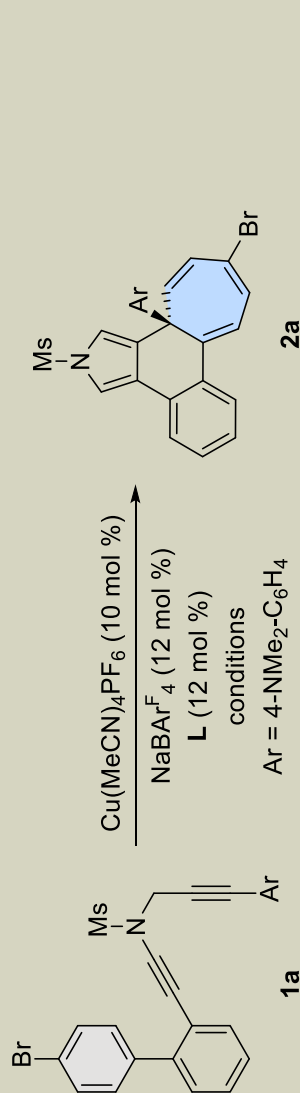
Reaction scope study on the asymmetric Büchner reaction

After establishing the optimal reaction conditions (Table 1, entry 14), we then exploited the generality of this catalytic asymmetric Büchner reaction. As illustrated in Fig. 3, the Büchner reactions of various *N*-protected ynamides **1a–1f** were first carried out to afford the desired chiral pyrrole-fused cycloheptatrienes **2a–2f** in 95–99% yields with excellent enantioselectivities (91–96% ees). Then, *N*-propargyl ynamides **1g** and **1h** with *para*-halogen-substituents (R^2) on the aromatic ring were found to be suitable substrates, furnishing the corresponding products **2g** and **2h** in excellent yields and enantioselectivities. However, the use of diyne **1i** possessing a *meta*-halogen-substituent at the biaryl moiety led to the desired **2i** with excellent enantioselectivity (98% ee) but in decreased yield³⁵, and significant formation of arene cyclopropanation product (49%) was observed (see the Supplementary Materials, Figs. S1, S2). Besides, the variation of aryl substituents of *N*-propargyl ynamides was studied, such as substrates **1j–1p** containing different substituents at the 4-position of the aromatic ring, and the expected products **2j–2p** were formed in 85–99% yields with 80–96% ees. We also examined diynes with the piperonyl group (**1q**) and disubstituted aromatic group (**1r**), and found that the reaction could efficiently generate the corresponding chiral cycloheptatrienes **2q** (99%, 92% ee) and **2r** (99%, 81% ee), respectively. In addition to the aryl-substituted diynes, the heteroaryl-substituted *N*-propargyl ynamide **1s** was also suitable for this reaction, and the desired product was obtained in 95% yield and 95% ee. Next, a wide range of ynamides containing different R^1 substituents were screened, leading to products **2t–2y** in excellent yields (91–99%) and enantioselectivities (90–95% ees). Notably, the reaction was also extended to diyne substrates bearing no electron-withdrawing groups to produce the

desired **2z** (98%, 91% ee) and **2aa** (99%, 83% ee) at $30\text{ }^{\circ}\text{C}$ in DCM. Interestingly, the reaction also proceeded smoothly with the cyclohexenyl-linked aryl-diyne, yielding the corresponding product **2ab** in 85% yield with 96% ee. Of note, in cases of the diyne substrates **1ac–1ad** with non-electron-rich groups, higher temperature was required ($50\text{ }^{\circ}\text{C}$) and low enantioselectivities ($<10\%$ ees) were observed (see the Supplementary Materials, Fig. S3), which is similar to the previous protocols^{47–54}. Our attempts to extend the reaction to Cy-substituted diyne **1ae** failed to obtain the corresponding Büchner product, and instead a hydroarylation product was formed in 69% yield (see the Supplementary Materials, Fig. S4). In addition, this asymmetric Büchner reaction could proceed smoothly with the heterocycle-linked diynes **1af–1ag** and the alkyl-linked aryl diynes **1ah–1ai**, but only gave the corresponding cycloheptatriene products **2af–2ai** with moderate enantioselectivities (40–53% ees) under the optimized reaction conditions (see the Supplementary Materials, Fig. S5). Attempts to extend the reaction to the cyclopropyl-linked aryl diyne **1aj** only led to the formation of the corresponding cyclopropane **4aj** in 38% yield with 20% ee (see the Supplementary Materials, Fig. S6). Importantly, almost no arene cyclopropanation product (except substrate **1i**) and no C–H insertion product were detected in all these cases. The absolute configuration of product **2b** was confirmed by X-ray crystallographic analysis. Thus, this protocol constitutes a chiral copper-catalyzed asymmetric Büchner reaction of alkynes.

Screening of conditions on the asymmetric cyclopropanation

Interestingly, during the substrate scope study of the above Büchner reaction, it was found that when the naphthyl-substituted diyne was employed as substrate, the corresponding arene cyclopropanation product was obtained instead and no formation of the seven-membered Büchner cyclization product was observed. Inspired by this dearomatized cyclopropanation reaction, we then chose the naphthalene ring-substituted *N*-propargyl ynamide **3a** as the model substrate to investigate this asymmetric arene cyclopropanation, and some of the results are displayed in Table 2 (see the Supplementary Materials, Table S2). In the presence of $\text{Cu}(\text{MeCN})_4\text{PF}_6$ (10 mol %), NaBAR_4 (12 mol %) and bisphosphine ligand **L1** or **L2** as chiral ligand in DCM at $35\text{ }^{\circ}\text{C}$, we were delighted to find that the desired tricycle-fused benzonorcaradiene **4a** bearing three chiral centers could be generated in excellent yields with moderate enantioselectivities (Table 2, entries 1 and 2). Further screening of various BOX ligands **L3–L6** and **L10–L12** (Table 2, entries 3–9)

Table 1 | Optimization of reaction conditions for asymmetric Büchner reaction of *N*-propargyl ynamide **1a**

Entry	L	Reaction conditions	Yield (%) ^a	Ee (%) ^b
1	L1	DCM, 35 °C, 0.5 h	86	49
2	L2	DCM, 35 °C, 0.5 h	83	55
3	L3	DCM, 35 °C, 0.5 h	71	<5
4	L4	DCM, 35 °C, 0.5 h	79	11
5	L5	DCM, 35 °C, 0.5 h	90	42
6	L6	DCM, 35 °C, 0.5 h	94	79
7	L7	DCM, 35 °C, 0.5 h	93	41
8	L8	DCM, 35 °C, 0.5 h	86	51
9	L9	DCM, 35 °C, 0.5 h	95	81
10	L9	DCE, 35 °C, 0.5 h	94	84
11	L9	toluene, 35 °C, 0.5 h	94	85
12	L9	THF, 35 °C, 0.5 h	95	70
13	L9	toluene, 0 °C, 8 h	93	87
14	L9	toluene, -20 °C, 40 h	95	96

Reaction conditions: **1a** (0.05 mmol), $\text{Cu}(\text{MeCN})_4\text{PF}_6$ (0.005 mmol), **L** (0.006 mmol), NaBAF_4 (0.006 mmol), solvent (1 mL), in Schlenk tubes.

^aMeasured by ¹H NMR using diethyl phthalate as internal standard.

^bDetermined by HPLC analysis. Mes = mesityl. NaBAF_4 = sodium tetrakis[3,5-bis(trifluoromethyl)phenoxy]borate. DCM = dichloromethane, DCE = 1,2-dichloroethane, THF = tetrahydrofuran.

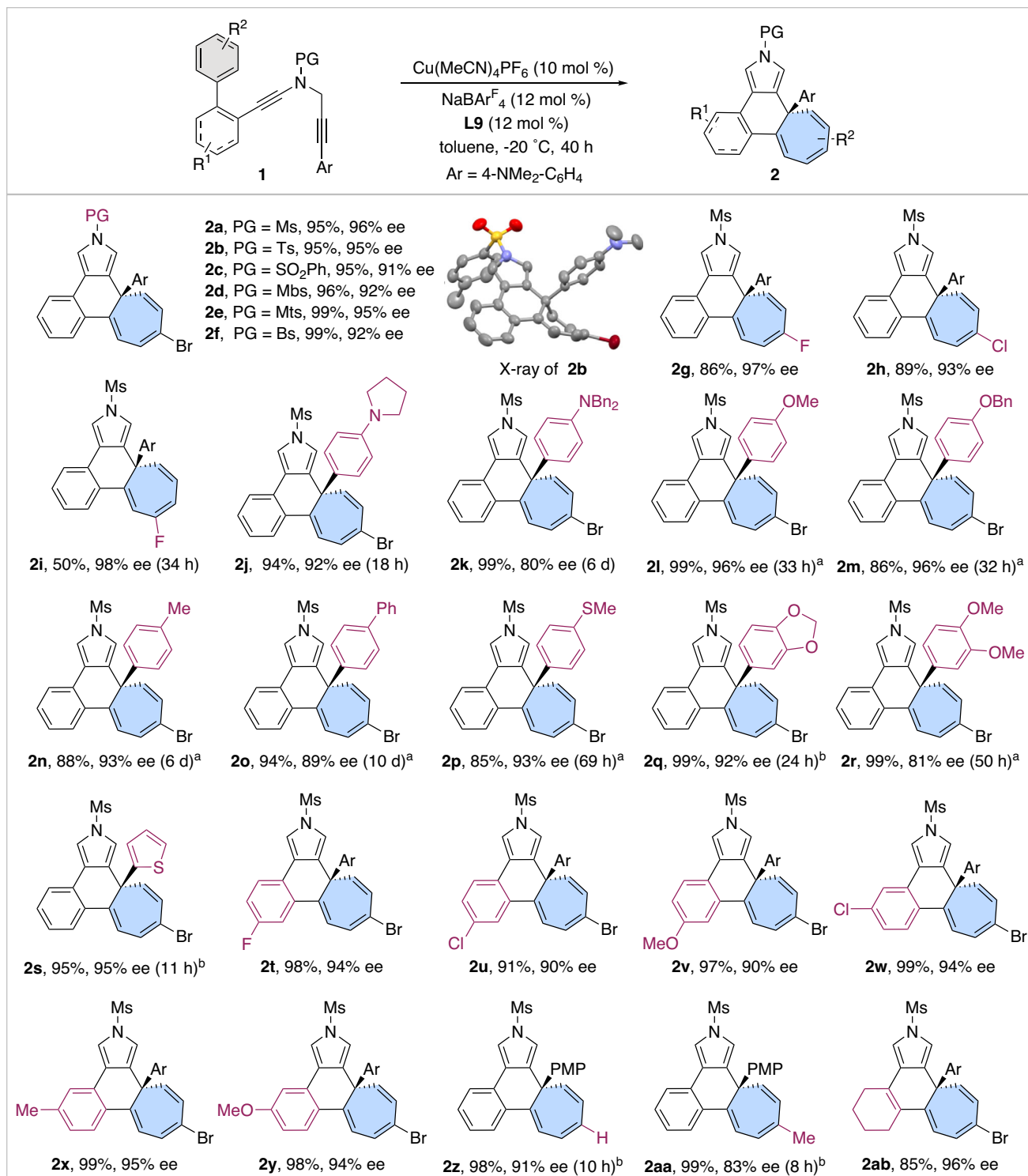


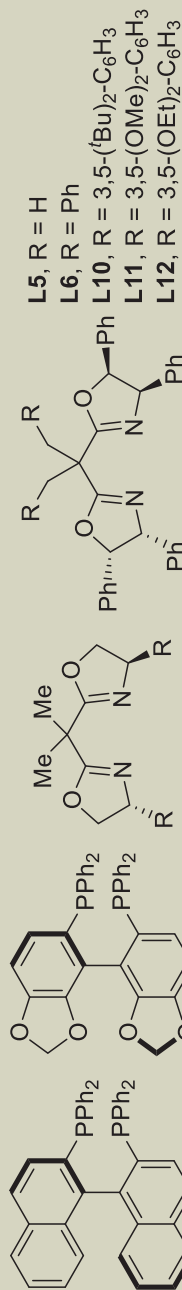
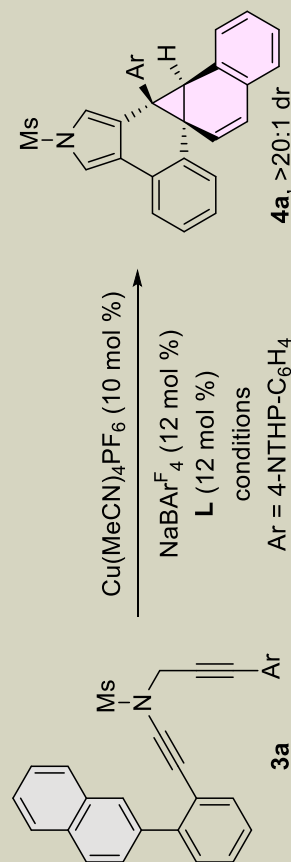
Fig. 3 | Scope of asymmetric Büchner reaction of *N*-propargyl ynamides 1. Reaction conditions: **1** (0.1 mmol), $\text{Cu}(\text{MeCN})_4\text{PF}_6$ (0.01 mmol), **L9** (0.012 mmol), NaBARF_4 (0.012 mmol), toluene (2 mL), -20°C , in vials; yields are those for the

isolated products; ees are determined by HPLC analysis. ^aDCM (2 mL), 20°C ; ^bDCM (2 mL), 30°C . Ts = *p*-toluenesulfonyl, Mbs = 4-methoxybenzenesulfonyl, Mts = 2-mesitylenesulfonyl, Bs = 4-bromobenzenesulfonyl, PMP = 4-methoxyphenyl.

revealed that the use of SaBOX ligand **L12** led to the expected chiral benzonorcaradiene **4a** in 93% yield with 92% ee (Table 2, entry 9). Subsequently, the effect of solvent was explored (Table 2, entries 10–12), and slightly improved yield and enantioselectivity could be achieved by using 2-MeTHF as the solvent (Table 2, entry 12). Finally, it was found that lowering the reaction temperature to 0°C allowed the formation of the desired cyclopropane product **4a** in 95% yield with 96% ee (Table 2, entry 13).

Reaction scope study on the asymmetric cyclopropanation

With the optimal reaction conditions in hand (Table 2, entry 13), the substrate scope of this asymmetric arene cyclopropanation was investigated. As shown in Fig. 4, diynes with various *N*-protecting groups were first explored to provide the expected chiral tricyclic-fused benzonorcaradienes **4a–4e** in generally excellent yields with high enantioselectivities (90–96% ees). We then examined the substitutions of the parent ring of substrates **3f–3m** with different

Table 2 | Optimization of reaction conditions for asymmetric cyclopropanation of *N*-propargyl ynamides **3a**

Entry	L	Reaction conditions	Yield (%) ^a	Ee (%) ^b
1	L1	DCM, 35 °C, 0.5 h	88	68
2	L2	DCM, 35 °C, 0.5 h	90	54
3	L3	DCM, 35 °C, 0.5 h	61	<5
4	L4	DCM, 35 °C, 0.5 h	63	33
5	L5	DCM, 35 °C, 0.5 h	88	83
6	L6	DCM, 35 °C, 0.5 h	92	90
7	L10	DCM, 35 °C, 0.5 h	78	82
8	L11	DCM, 35 °C, 0.5 h	80	90
9	L12	DCM, 35 °C, 0.5 h	93	92
10	L12	toluene, 35 °C, 0.5 h	85	93
11	L12	THF, 35 °C, 0.5 h	94	93
12	L12	2-MeTHF, 35 °C, 3 h	95	94
13	L12	2-MeTHF, 0 °C, 40 h	95	96

Reaction conditions: **3a** (0.05 mmol), $\text{Cu}(\text{MeCN})_4\text{PF}_6$ (0.005 mmol), **L** (0.006 mmol), NaBARF_4 (0.006 mmol), solvent (1 mL), in Schlenk tubes

^aMeasured by ¹H NMR using diethyl phthalate as internal standard.

^bdetermined by HPLC analysis. NTHP = 1-pyrrolidinyl, 2-MeTHF = 2-methyltetrahydrofuran.

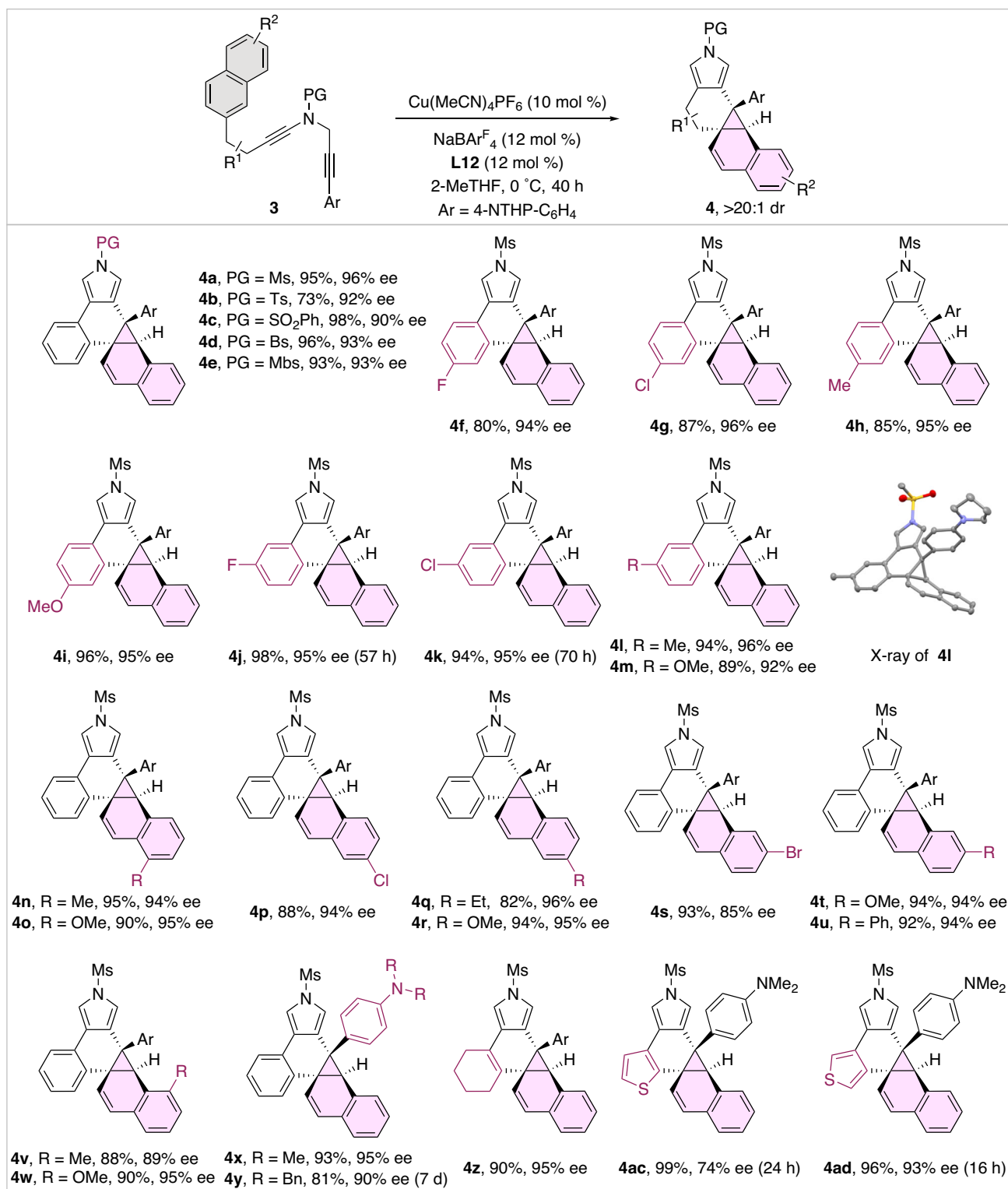


Fig. 4 | Scope of asymmetric cyclopropanation of *N*-propargyl ynamides **3**. Reaction conditions: **3** (0.15 mmol), Cu(MeCN)₄PF₆ (0.015 mmol), **L12** (0.018 mmol), NaBAR₄^F (0.018 mmol), 2-MeTHF (3 mL), 0 °C, in vials; yields are those for the isolated products; ees are determined by HPLC analysis.

electron-donating and -withdrawing substituents in 4- and 5-positions, and found that the desired benzonorcaradienes **4f–4m** were furnished in 80–98% yields with 92–96% ees. In addition, diynes containing different naphthalene moieties were appropriate substrates to afford the corresponding enantioenriched cyclopropanes **4n–4w** in high yields with the ees of 85–96%. Moreover, this cyclopropanation reaction could also proceed smoothly in case of diynes bearing different nitrogen-substituted aromatic rings (**3x** and **3y**). Similarly, the

cyclohexenyl-linked *N*-propargyl ynamide **3z** was also suitable for this reaction, yielding the desired chiral cyclopropane product **4z** in 90% yield and 95% ee. However, the reaction of 1-naphthyl- and PMP-substituted diynes **3aa–3ab** afforded the desired products **4aa** (64% ee) and **4ab** (66% ee) with moderate enantioselectivities, and the formation of the Büchner cyclization product was observed in the latter case (see the Supplementary Materials, Figs. S7, S8). We speculate that the moderate enantiomeric excess value in the former case may be

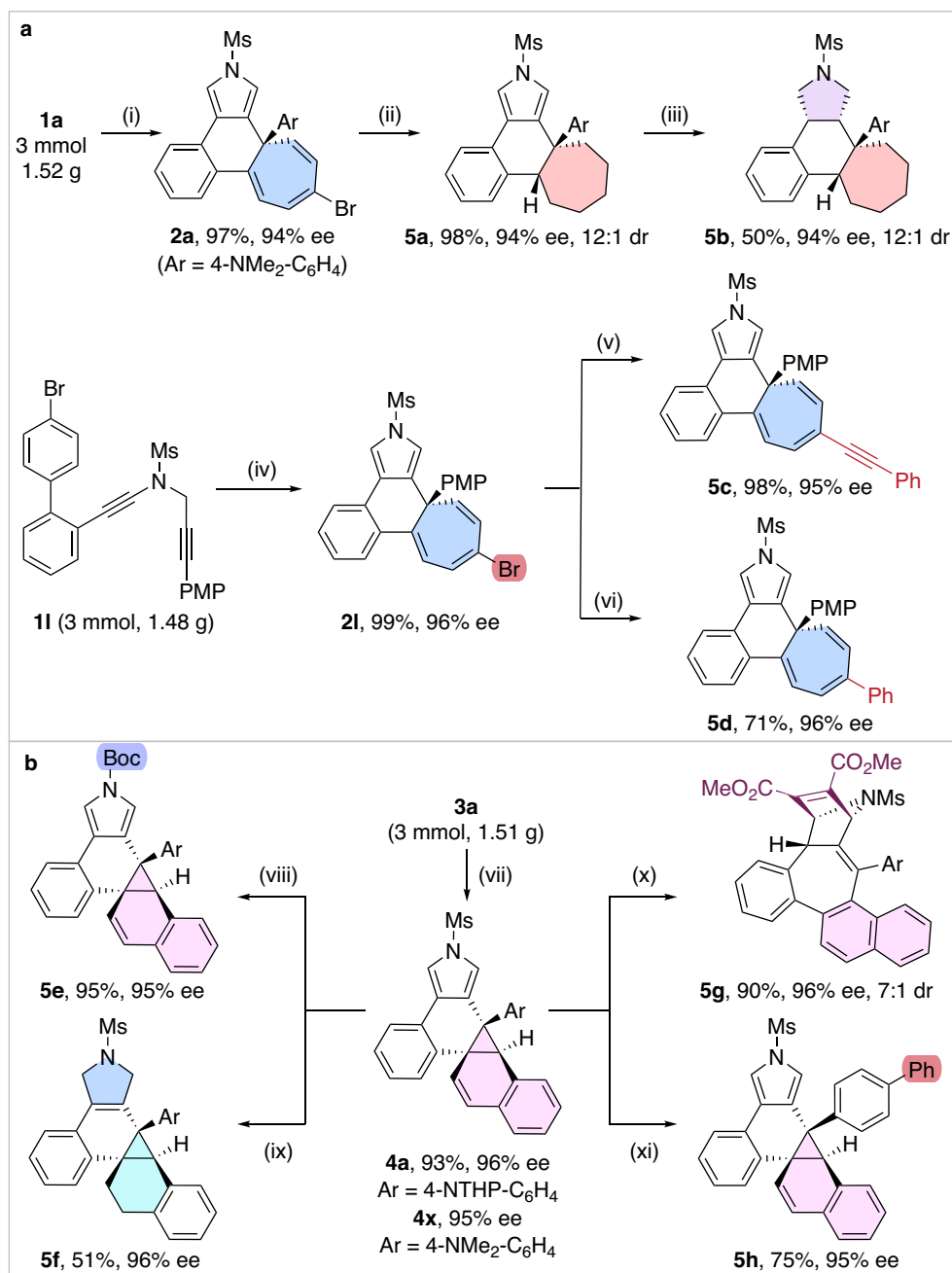


Fig. 5 | Scale-up reaction and product elaborations. a Preparative-scale reaction of **1a** and synthetic applications. **b** Preparative-scale reaction of **3a** and synthetic applications. Reagents and conditions: (i) Cu(MeCN)₄PF₆ (5 mol %), NaBAR^F₄ (6 mol %), **L9** (6 mol %), toluene, -20 °C, 9 d. (ii) Pd/C (10 mol %), H₂ (1 atm), MeOH, rt, 12 h. (iii) Pd(OH)₂/C (10 mol %), H₂ (8 MPa), AcOH:EA = 1:1, 80 °C, 72 h. (iv) Cu(MeCN)₄PF₆ (10 mol %), NaBAR^F₄ (12 mol %), **L9** (12 mol %), DCM, 20 °C, 4 d. (v) Phenylacetylene (4 equiv), Pd(PPh₃)₄ (5 mol %), CuI (10 mol %), THF:Et₃N = 3:1, 50 °C, 1 h. (vi)

PhB(OH)₂ (3.5 equiv), Pd(PPh₃)₄ (10 mol %), CsF (2.5 equiv), DME, 50 °C, 8 h. (vii) Cu(MeCN)₄PF₆ (5 mol %), NaBAR^F₄ (6 mol %), **L12** (6 mol %), 2-MeTHF, 0 °C, 51 h. (viii) KOH (10 equiv), THF:MeOH = 1:1, 50 °C, 1.5 h, then DMAP (20 mol %), (Boc)₂O (3 equiv), Et₃N (4 equiv), DCM, rt, 2 h. (ix) NaBH₃CN (5 equiv), DCM:TFA = 10:1, rt, 1 h; Pd/C (10 mol %), H₂ (1 atm), AcOH, 60 °C, 12 h. (x) DMAD (20 equiv), toluene, 60 °C, 12 h. (xi) MeOTf (10 equiv), Et₂O, 0 °C to rt, 2 h; Pd(PPh₃)₂Cl₂ (5 mol %), PhMgBr (2 equiv), THF, rt, 2 h.

attributed to the steric hindrance between the bridging benzene ring and the dearomatized naphthalene ring of the obtained product. Interestingly, this arene cyclopropanation proceeded smoothly with the heterocycle-linked diynes **3ac** and **3ad**, furnishing the corresponding cyclopropanes **4ac** (99%, 74% ee) and **4ad** (96%, 93% ee), respectively. Finally, it was found that the use of the alkyl-linked naphthyl-diyne **3ae** only led to the desired **4ae** in 90% yield with 42% ee under the optimized reaction conditions (see the Supplementary Materials, Fig. S9). Of note, neither Büchner cyclization product nor C–H insertion product was observed in all cases. Importantly, four

rings containing three stereocenters with high stereospecificity are assembled in one step under mild conditions. The absolute configuration of product **4i** was confirmed by X-ray crystallographic analysis.

Synthetic applications

To showcase the synthetic utility of this method, the gram-scale reactions and further product elaborations were explored (Fig. 5). The gram-scale synthesis of chiral cycloheptatriene **2a** was first explored, and the desired product was obtained in 97% yield with a slightly decreased

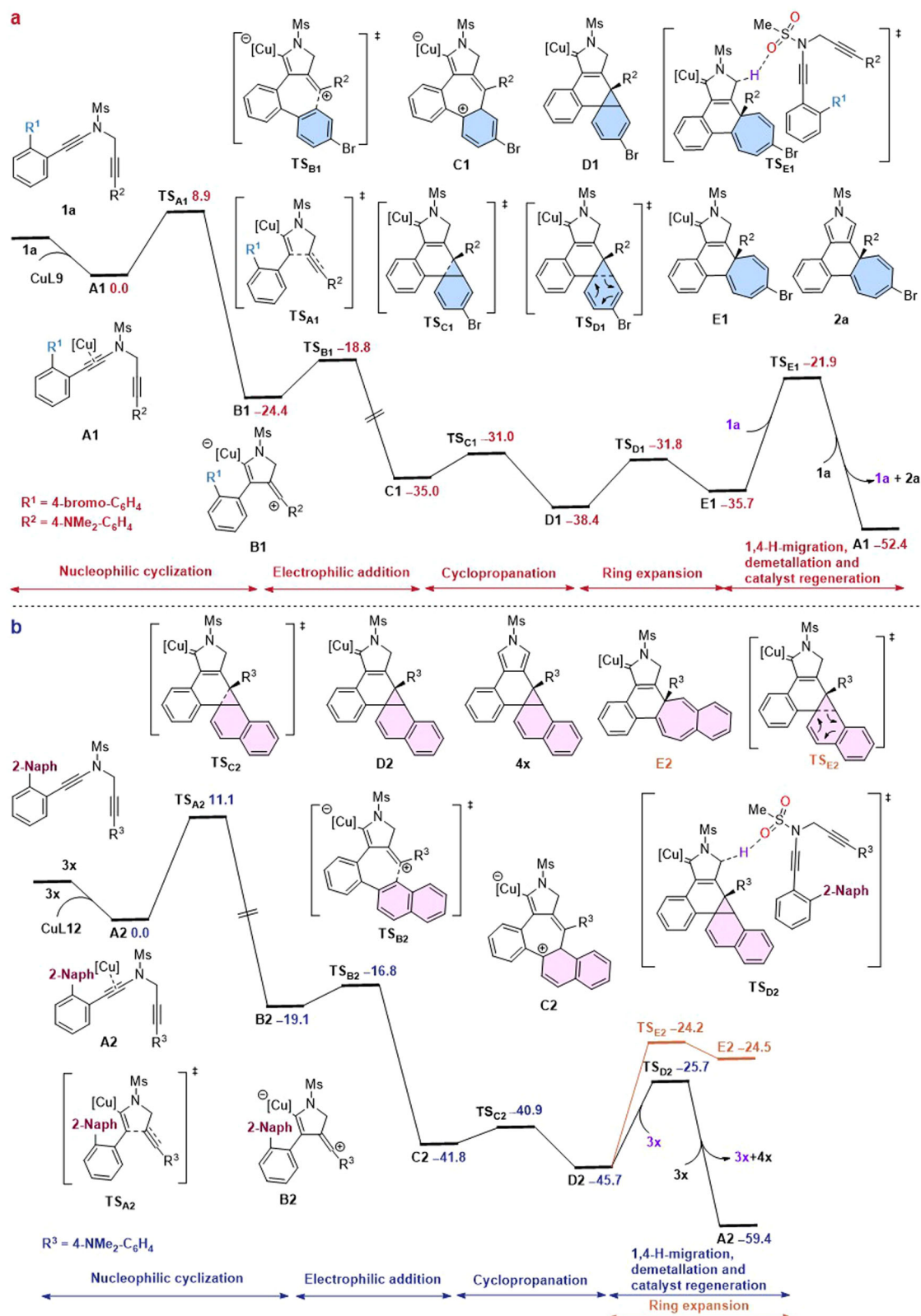


Fig. 6 | DFT-computed free energy diagram for the Büchner and arene cyclopropanation reactions. Relative free energies (ΔG , in kcal/mol) were computed at: **a** (PCM, solvent = toluene)-PBE0-D3/6-311++G(d,p)-SDD//B3LYP-D3/6-31G(d)-LANL2DZ level of theory. **b** (PCM, solvent = 2-MeTHF)-PBE0-D3/6-311++G(d,p)-SDD//B3LYP-D3/6-31G(d)-LANL2DZ level of theory.

LANL2DZ level of theory. **b** (PCM, solvent = 2-MeTHF)-PBE0-D3/6-311++G(d,p)-SDD//B3LYP-D3/6-31G(d)-LANL2DZ level of theory.

enantioselectivity (94% ee) under 5 mol % of chiral copper catalyst, as shown in Fig. 5a. Next, selective hydrogenation of the double bond of cycloheptatriene moiety of **2a** with Pd/C generated the debromination product **5a** in 98% yield with 12:1 dr. Further hydrogenation of the

pyrrole moiety with Pd(OH)₂/C under a H₂ atmosphere (8 MPa) could lead to the formation of pyrrolidine-fused product **5b** in 50% yield with excellent dr. In addition, further transformation of cycloheptatriene **21**, which was synthesized on a preparative-scale in 99% yield with 96% ee,

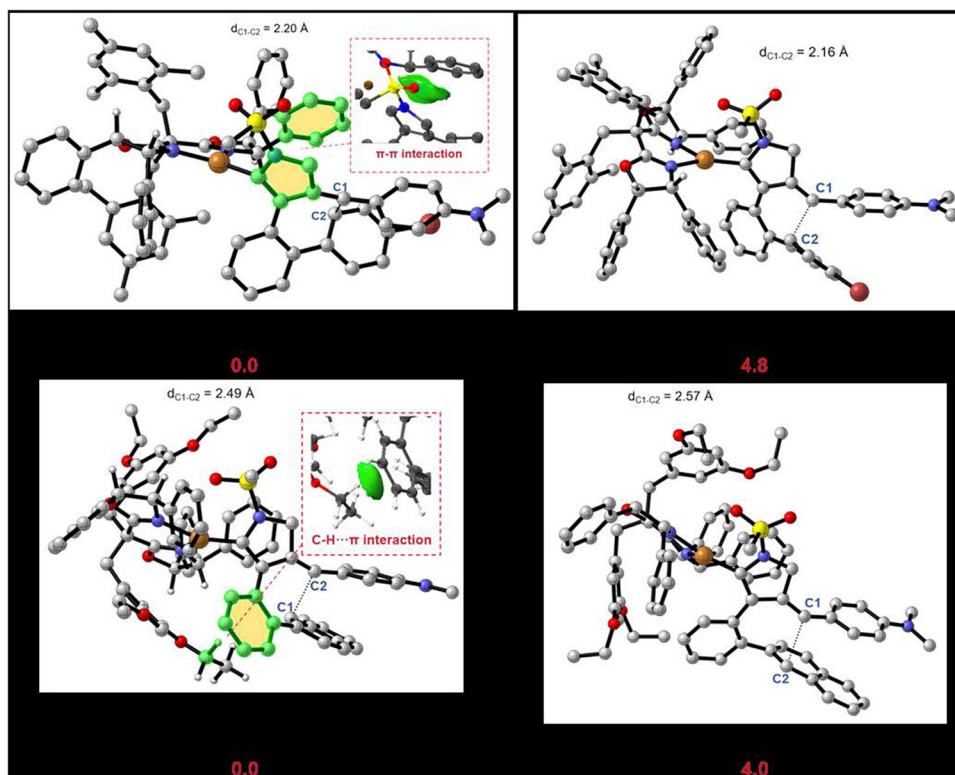


Fig. 7 | The geometries and relative free energies ($\Delta\Delta G$, in kcal/mol) of the transition states **CuL9-(S)-TS_{B1}/**CuL9-(R)-TS_{B1}** and **CuL12-(S)-TS_{B2}**/**CuL12-(R)-TS_{B2}** with the chiral ligand **L9** and **L12**. All hydrogen atoms are omitted for clarity except for those involved in critical interactions. Relative free energies ($\Delta\Delta G$, in**

kcal/mol) were computed at the PCM(toluene)-PBE0-D3/6-311++G(d,p)-SDD//B3LYP-D3/6-31G(d)-LANL2DZ level of theory and PCM(2-MeTHF)-PBE0-D3/6-311++G(d,p)-SDD//B3LYP-D3/6-31G(d)-LANL2DZ level of theory. Color code: red = O; white = H; gray = C; yellow = S; blue = N; brown = Cu.

was also investigated. It was found that facile Sonagashira coupling and Suzuki coupling afforded the corresponding products **5c** (98%, 95% ee) and **5d** (71%, 96% ee), respectively. Subsequently, the gram-scale synthesis and synthetic applications of the cyclopropane products **4** were demonstrated, as depicted in Fig. 5b. In the presence of 5 mol % of chiral copper catalyst, the preparative reaction of **3a** resulted in the formation of the desired product **4a** in 93% yield and 96% ee. Interestingly, the Ms protecting group was readily removed by treating with KOH and protected again by the Boc group, furnishing the corresponding **5e** in 95% yield with 95% ee (two steps). Additionally, the two-step reduction reactions of **4a** with NaBH₃CN and Pd/C/H₂, respectively, could lead to the dihydropyrrole product **5f** in 51% yield (two steps). Then, the Diels-Alder reaction was also tested by the use of DMAD reagent, and the unexpected ring-expansion product **5g** was formed in 90% yield and 96% ee. The relative configuration of the product **5g** was confirmed by X-ray crystallographic analysis. Moreover, the NMe₂ group of the cyclopropane product **4x** could be further converted into the aryl group by Pd-catalyzed cross-coupling with an aryl Grignard reagent, delivering the corresponding **5h** in 75% yield. Significantly, almost no erosion of the enantiopurity of the compounds was observed in all these elaborations.

Mechanistic investigations

On the basis of the aforementioned experimental observations, our previous studies^{47–54}, and comprehensive computational analysis (see the Supplementary Materials, Tables S6–9), a plausible vinyl cation-involved mechanism from **1a** to **2a** and **3x** to **4x** is exhibited in Fig. 6. The reaction is initialized via a preferential coordination of the Cu^I catalyst to activate the electron-rich amide-tethered C≡C bond of **1a** and **3x** to produce the precursor **A1** and **A2**, followed by an intramolecular cyclization to afford the vinyl cation intermediate **B1** and **B2** with a free energy barrier of 8.9 kcal/mol and 11.1 kcal/mol, respectively.

Nevertheless, the reaction deviates upon reaching the intermediate **B**. Upon the generation of the vinyl cation intermediate **B1**, the vinyl cation undergoes an electrophilic addition to the aryl group connected to the side chain, conquering a free energy barrier of 5.6 kcal/mol, forming a dearomatized carbon cation intermediate **C1**. Then, within intermediate **C1**, an electrophilic addition and cyclopropanation process occurs to afford the cyclopropane-tethered copper carbenoid intermediate **D1**, undergoing **TS_{C1}** with a slight barrier height of only 4.0 kcal/mol. Subsequently, the cyclopropane structure undergoes a ring-expansion process, resulting in Büchner-type copper carbenoid intermediate **E1**. Finally, the Büchner-type product **2a** is obtained through a rate-determining Lewis base (**1a**)-assisted 1,4-H migration process similar to our previous studies^{49–54}, with a barrier height of 13.8 kcal/mol (Fig. 6a). While in the reaction pathway starting from intermediate **B2**, after going through the same process and forming a cyclopropane-type copper carbenoid intermediate **D2**, instead of the same ring-expansion process as is mentioned above, which undergoes a higher free energy barrier in the subsequent steps, the cyclopropane-type product **4x** is much more thermodynamically favorable right after the same rate-determining Lewis base (**3x**)-assisted 1,4-H migration process from intermediate **D2**, undergoing a free energy barrier of 20.1 kcal/mol (Fig. 6b). All above, under the provided reaction conditions, this reaction can proceed smoothly, with the Lewis base-assisted 1,4-H migration process being the rate-determining step.

The enantio-determining step in the synthesis of chiral products **2a** and **4x** was also computationally investigated employing the chiral ligand **L9** and **L12** coordinated to the Cu^I center in the irreversible enantio-determining electrophilic addition step (Fig. 7). Upon further observation of structures of these enantio-determining transition states, it is found that in **CuL9-(S)-TS_{B1}**, there is a significant $\pi \cdots \pi$ interaction between the substrate and the branched phenyl group of **L9**, which stabilizes the transition state. Above factor results in the free

energy difference of 4.8 kcal/mol between the two enantio-determining transition states, ultimately leading to the enantioselectivity of the Büchner-type product. Similarly, in **CuL12-(S)-TS_{B2}**, there is a fairly strong C-H... π interaction between the substrate and the branched phenyl group of **L12**, stabilizing the transition state, accounting for the energy difference of 4.0 kcal/mol between the two enantio-determining transition states, finally leading to the enantioselectivity of the cyclopropane-type product.

Discussion

In summary, we have developed an asymmetric Büchner reaction and the related arene cyclopropanation through copper-catalyzed controllable cyclization of *N*-propargyl ynamides via vinyl cations, enabling divergent and atom-economic synthesis of a wide range of chiral tricyclo-fused cycloheptatrienes and benzonorcaradienes in generally excellent yields and enantioselectivities. Significantly, this protocol not only represents an asymmetric arene cyclopropanation reaction of alkynes, but also constitutes an asymmetric Büchner-type reaction based on vinyl cations. Moreover, theoretical calculations further support the mechanism of vinyl cation-involved dearomatized cyclization and elucidate the origin of enantioselectivity. We believe that these findings will offer further perspectives and explorations in the field of asymmetric catalysis based on dearomatization reaction and vinyl cation chemistry.

Methods

General

For ¹H, ¹³C, and ¹⁹F nuclear magnetic resonance (NMR) spectra of compounds in this manuscript and details of the synthetic procedures as well as more reaction condition screening, see Supplementary Information.

General procedure for the synthesis of chiral cycloheptatrienes **2**

To an oven-dried Schlenk tube with a stir bar were sequentially added Cu(MeCN)₄PF₆ (0.01 mmol, 3.8 mg), **L9** (0.012 mmol, 8.8 mg) and NaBAR^F₄ (0.012 mmol, 10.6 mg, white crystal) under argon atmosphere. After injecting toluene (1 mL) into the Schlenk tube, the mixture was stirred at 25 °C for 2 h. Then the mixture reaction was cooled to -20 °C, and *N*-propargyl ynamide **1** (0.1 mmol) in toluene (1 mL) was added into the reaction mixture dropwise. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was directly purified by column chromatography on silica gel (eluent: PE/EtOAc) to afford the desired chiral cycloheptatriene **2**.

General procedure for the synthesis of chiral tetracyclopropanes **4**

To an oven-dried Schlenk tube with a stir bar were sequentially added Cu(MeCN)₄PF₆ (0.015 mmol, 5.7 mg), **L12** (0.018 mmol, 15.0 mg) and NaBAR^F₄ (0.0018 mmol, 16.2 mg, white crystal) under argon atmosphere. After injecting 2-MeTHF (1.5 mL) into the Schlenk tube, the mixture was stirred at 25 °C for 2 h. Then the mixture reaction was cooled to 0 °C, and *N*-propargyl ynamide **3** (0.15 mmol) in 2-MeTHF (1.5 mL) was added into the reaction mixture dropwise. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: PE/EtOAc) to afford the desired chiral benzonorcaradiene **4**.

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 2301623 (**2b**), 2301624 (for **4I**) and 2301659 (for **5g**). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. 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. The coordinates of the optimized structures in this study are provided in the Source Data file. Source data are provided with this paper.

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Author contributions

Y.X.Z., T.Q.H., X.Li. and B.Z. performed experiments. X.H. and X.Lu. designed the DFT calculations. L.G.L. performed the DFT calculations. L.W.Y. and Z.X. conceived and directed the project and wrote the paper. All authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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