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Switchable organocatalytic enantioselective sulfenocyclization of cyclohexadienes enabling chemodivergent access to chiral bicyclo[m.n.1] ring systems

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The precise control over regio- and stereoselectivity from the same substrate represents a significant challenge in organic chemistry. Herein, a switchable organocatalytic enantioselective carbosulfenylation/sulfenolactonization of cyclohexa-1,4-dienes to access the chiral bicyclo[m.n.1] ring systems, which are the critical core skeleton of many important natural products and biologically active compounds, is achieved. By simply tuning the substituent of the sulfenylating agent, a series of synthetically challenging chiral bridged bicyclo[3.3.1]nonanes and 2-oxabicyclo[3.2.1]octanes bearing three consecutive stereocenters are obtained with good yields and excellent enantioselectivities (up to 94% yield and 97% ee). Furthermore, the initial investigation of the bicyclic derivative as a chiral ligand in metal catalysis is also conducted. Our findings offer a version of switchable divergent asymmetric synthesis in which different products can be controllably generated from an identical set of substrates by simply adjusting reaction parameters.

The densely substituted bicyclo[m.n.1] systems exist ubiquitously in numerous natural products and therapeutic agents with impressive biological and medicinal properties. Generally, bridged bicyclo[m.n.1] moieties possess structural diversity with multiple stereogenic centers incorporating quaternary carbon centers at the bridgehead (Fig. 1)[1–5]. For these reasons, the straightforward construction of such complex molecules remains challenging, especially in asymmetric manners[6,7]. In the realm of the synthesis of enantioenriched bicyclo[m.n.1] skeletons, using stoichiometric amounts of optically active substrates (chiral pool) and multistep syntheses was mainly investigated[8–12]. Until recently, several elegant catalytic asymmetric methods have been devised. Among them, strategies based on transition-metal or organocatalyzed asymmetric Michael/aldol[13–15], formal [m + n] annulation[16–20], and desymmetrizing cyclizations[21–35] were established (Fig. 2a, entries 1, 2). Despite these great advances, enantioselective synthesis of functionalized bicyclo[m.n.1] derivatives with high structural diversity from identical substrates are significantly less studied (Fig. 2a, entry 3). A formidable obstacle in this research field is the scarcity of efficiency to precise control regio- and stereoselectivity from the same substrate. For this reason, the development of strategies to explore the highly regioselective synthesis of complex molecules from identical materials is in great demand.

In particular, catalytic chemodivergent synthesis has emerged as a powerful synthetic tool because it allows access to different products from an identical set of substrates by tuning the reaction parameters (catalysts, reagents, additives, solvents, and other factors)[36–39]. Considering catalytic asymmetric halogenation/chalcogenation of alkenes enables the formation of valuable chiral heterocyclic backbones[40–42], divergent cyclization strategies to surmount the regioselective bias of substrates have frequently been witnessed. For instance, Denmark[43–50],

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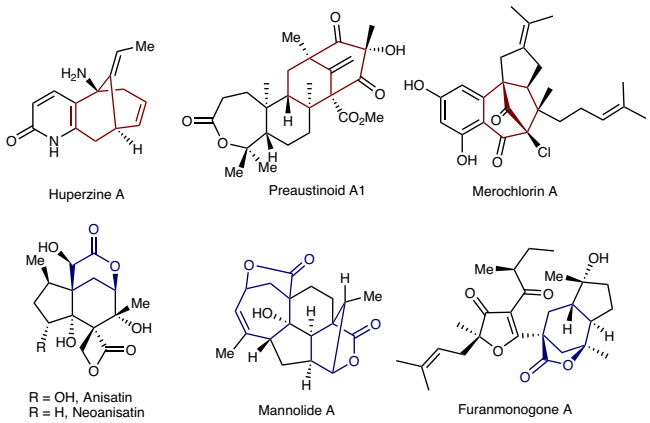

Fig. 1 | The significance of constructing chiral bicyclo[m.n.1] ring systems. Selected bicyclo[m.n.1]-containing natural products and bioactive molecules.

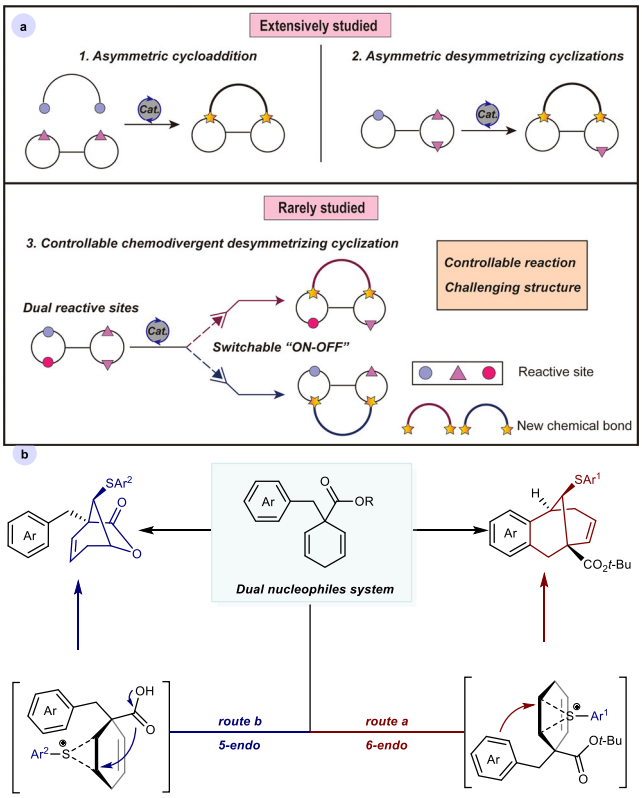

Fig. 2 | Catalytic enantioselective synthesis of bicyclo[m.n.1] ring systems. **a** Asymmetric construction of bicyclo[m.n.1] bridged bicycles. **b** Switchable synthesis of chiral bridged bicyclo[3.3.1]nonanes and oxabicyclo[3.2.1]octanes (this work).

Chen[51–54], Zhao[55–59] and others[60,61] developed efficient approaches for divergent enantioselective cyclization using electrophilic sulfur (SAr) and trifluoromethylthiolation (SCF_3) regents. The aforementioned successful examples realized divergent transformations via regioselective cyclization of the double bond with the same nucleophile, mostly controlled the divergent reactions by tuning the alkene substituents, length of the alkyl chain, and were generally limited to building monocyclic compounds. By comparison, starting materials equipped with two potential nucleophiles have the ability to create more structurally different types of products bearing more than two stereocenters, yet to the best of our knowledge, divergent enantioselective halogenation/chalcogenation of such alkenes to construct bridged bicyclo[m.n.1] system is surprisingly underexplored (Fig. 2a, entry 3). As a continuation of our ongoing effort in the catalytic enantioselective cyclization of alkenes[62,63] and the powerfulness of the catalytic enantioselective desymmetrization reactions in the construction of all-carbon quaternary stereocenters[64,65], we envisioned that a suitable dual-nucleophile system could be identified to deliver complex cyclic architectures with high structural diversity under readily modulated catalytic conditions. Herein, we report a switchable asymmetric regioselective sulfenocyclization of cyclohexa-1,4-dienes bearing two potential nucleophilic sites (aryl and carboxylic acid). By tuning the sulfenylating reagents, a series of functionalized bicyclo[3.3.1]nonane and 2-oxabicyclo[3.2.1]octane containing three new stereogenic centers, including an all-carbon quaternary bridgehead center, were produced in high diastereo- and enantioselectivity (Fig. 2b).

Results

Reaction optimization

To validate whether the dual nucleophile system could implement the regioselective cyclization, cyclohexa-1,4-diene derivatives **1** were selected as model substrates employing sulfenylating reagent (1.2 equiv.) and chiral catalyst (10 mol%) in hexafluoroisopropanol (HFIP) at 0 °C. Initially, different ester groups were tested in the presence of readily accessible (*R*)-BINAP monosulfide (BINAP(S)) **C1** and sulfenylating reagent **S1** (Table 1, entries 1-5). Indeed, substrates **1** bearing methyl (Me), ethyl (Et), isopropyl (*i*-Pr), or phenyl (Ph) ester delivered corresponding bicyclo[3.3.1]nonane derivatives in moderate to high yields and ee values (Table 1, entries 1-4). Accordingly, *tert*-butyl (*t*-Bu) ester was proved to be the most promising substrate to enhance the ee value of product **2a** to 90% (Table 1, entry 5). Next, several sulfenylating reagents with different activities were screened (see the Supplementary Information for more details). Replacing regent **S1** with 5,5-dimethyl-3-(phenylthio)−2,4-imidazolidinedione **S2** completely shut down the transformation (Table 1, entry 6). Evaluation of *N*-(arylthio)-succinimides revealed the bicyclo[3.3.1]nonane **2a** was obtained with improved yield and ee value by using reagent **S3** (Table 1, entry 7). To our delight, *N*-[(4-bromophenyl)]-succinimide **S4** could further increase the yield of **2a** to 92% with excellent enantioselectivity (95% ee) (Table 1, entry 8). When the sulfenylating agent **S5** bearing diisopropyl group was used, product **2a** was barely observed, but triggered the 5-*endo* sulfenolactonization product **3a** in 17% yield and 60% ee, thus supporting our hypothesis on the enantioselective chemodivergent synthesis (Table 1, entry 9). Because previous reports revealed Lewis base catalysis plays a vital role in electrophilic alkene functionalization, a survey of various chiral Lewis base catalysts was conducted (Table 1, entries 10-13). For example, (*R*)-BINAP(S) derivative **C2** gave **2a** in excellent yield (94%) and enantioselectivity (94% ee) (Table 1, entry 10). In comparison, (*R*)-BINAP disulfide derivatives **C3** and **C4** generally delivered **2a** in slightly lower ee values (Table 1, entries 11, 12). To our surprise, the chiral BINAM-based selenophosphoramide **C5** developed by the Denmark group has been widely used for enantioselective sulfenocyclization of alkenes, yet showed rather sluggish for this transformation (Table 1, entry 13). In addition, (*R*)-BINAP, (*R*)-BINAP monoxide and dioxide were totally ineffective for this reaction, suggesting that the P = S moiety of the catalyst is a critical factor for achieving high reactivity and enantioselectivity (see the Supplementary Information for more details). Then, we next turned our attention to investigating the reaction conditions of switchable access to 2-oxabicyclo[3.2.1]octane **3a** (Table 1, entries 14-19). To improve the activity and site-selectivity control for the *5-endo* sulfenolactonization, the tunability of the carbonyl group and sulfenylating agents were exploited. Switching the ester moiety to more reactive carboxylic acid could specifically deliver the targeted *5-endo* product **3a** in 37% yield and 78% ee (Table 1, entry 14). On the other hand,

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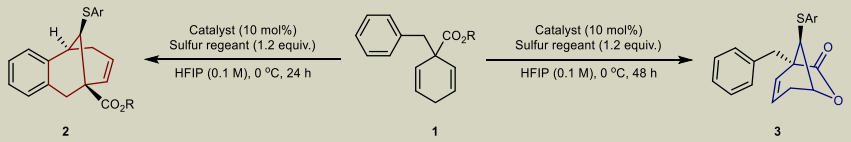
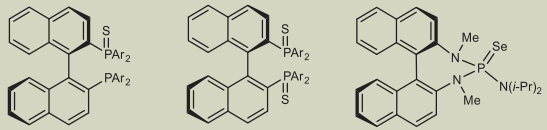
Table 1 | Optimization of the reaction conditions[a]



2 1 3

Catalyst:

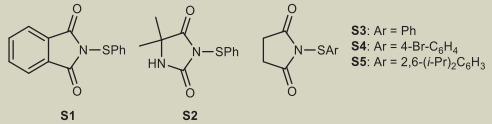


C1: Ar = Ph
C2: Ar = 3,5-$(CH_3)_2C_6H_3$

C3: Ar = Ph
C4: Ar = 3,5-$(CH_3)_2C_6H_3$

C_5

Sulfur regeant:



S1 S2

S3: Ar = Ph
S4: Ar = 4-Br-C_6H_4
S5: Ar = 2,6-(*i*-Pr)$_2C_6H_3$

Entry	R	Catalyst	Sulfur reagent	2		3	
				Yield (%)[b]	ee (%)[c]	Yield (%)	ee (%)
1	Me	**C1**	**S1**	60	69	–	–
2	Et	**C1**	**S1**	63	65	–	–
3	*i*-Pr	**C1**	**S1**	80	85	–	–
4	Ph	**C1**	**S1**	60	73	–	–
5	*t*-Bu	**C1**	**S1**	79	90	–	–
6	*t*-Bu	**C1**	**S2**	trace	–	–	–
7	*t*-Bu	**C1**	**S3**	81	91	–	–
8	*t*-Bu	**C1**	**S4**	92	95	–	–
9	*t*-Bu	**C1**	**S5**	trace	–	17	60
10	*t*-Bu	**C2**	**S4**	94	94	–	–
11	*t*-Bu	**C3**	**S4**	83	90	–	–
12	*t*-Bu	**C4**	**S4**	94	87	–	–
13	*t*-Bu	**C5**	**S4**	trace	–	–	–
14	H	**C1**	**S5**	–	–	37	78
15	H	**C1**	**S3**	–	–	40	20
16	H	**C1**	**S4**	–	–	35	34
17	H	**C2**	**S5**	–	–	54	91
18	H	**C3**	**S5**	–	–	64	78
19	H	**C4**	**S5**	–	–	44	88
20[d]	H	**C2**	**S5**	–	–	69	91

[a]All the reactions were performed on 0.1 mmol scales. [b]Isolated yield. [c]Determined by HPLC using a chiral stationary phase. [d]Reaction was performed with **S5** (0.15 mmol) in HFIP (0.5 mL).

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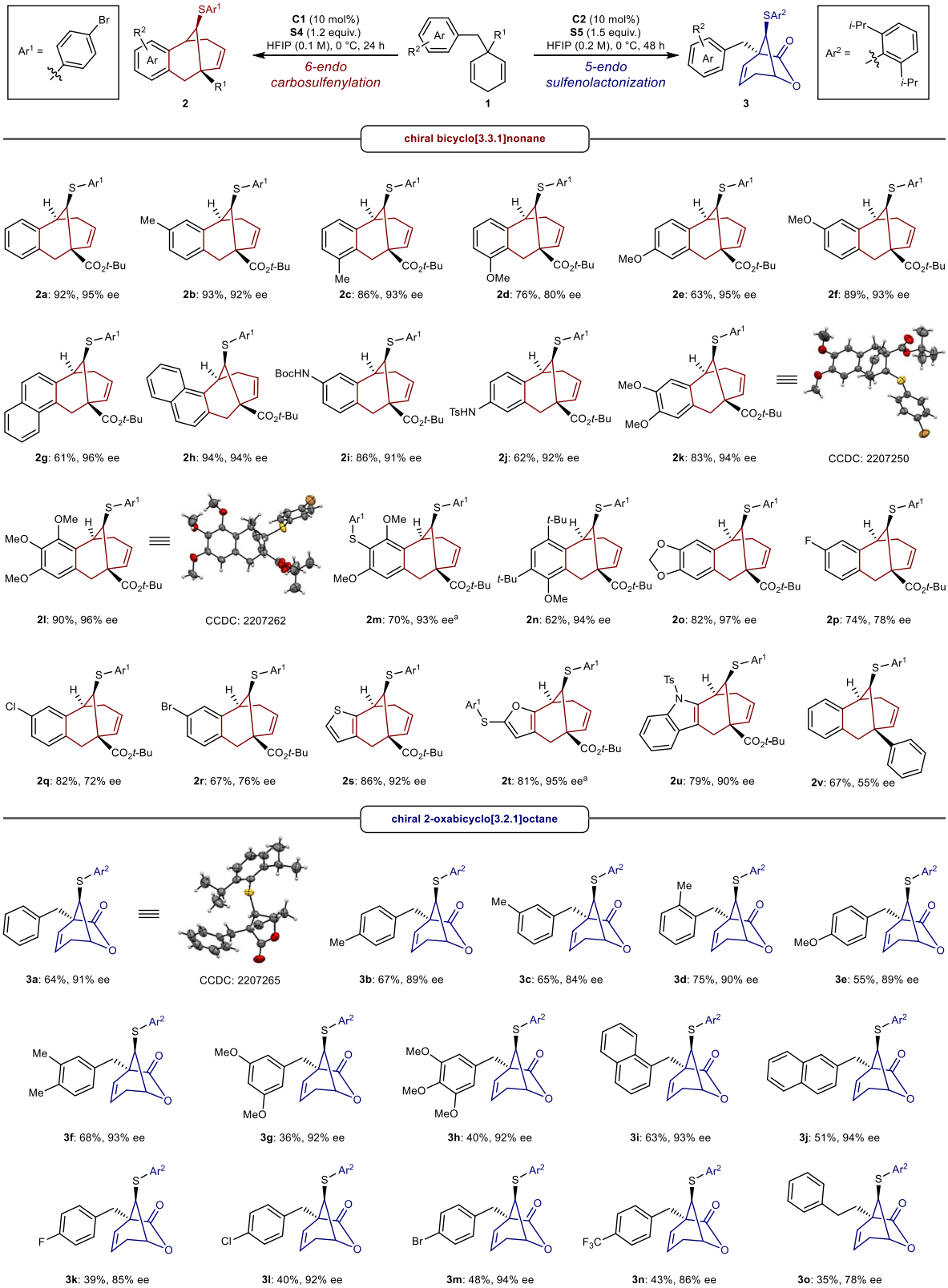

Fig. 3 | Substrate scope. General reaction conditions for *6-endo* carbosulfenylation: **1** (0.10 mmol), **C1** (0.01 mmol), **S4** (0.12 mmol) in HFIP (1.0 mL) at 0 °C for 24 h. General reaction conditions for *5-endo* sulfenolactonization: **1** (0.10 mmol), **C2** (0.01 mmol), **S5** (0.15 mmol) in HFIP (0.5 mL) at 0 °C for 48 h. Isolated yields. The ee values were determined by HPLC analysis on a chiral stationary phase. [a], **S4** (0.25 mmol) was used.

replacing **S5** with other sulfenylating agents such as **S3** and **S4** dramatically affected the enantioselectivity (Table 1, entries 15-16). After carefully screening the catalysts (see the Supplementary Information for more details), we identified that (*R*)-DM-BINAP monosulfide **C2** could promote the sulfenolactonization of the carboxylic acid substrate with a good yield (54%) in 91% ee (Table 1, entry 17). However, (*R*)-BINAP disulfide derivatives **C3** and **C4** led to inferior results in terms of enantioselectivities (Table 1, entries 18, 19). Subsequently, the

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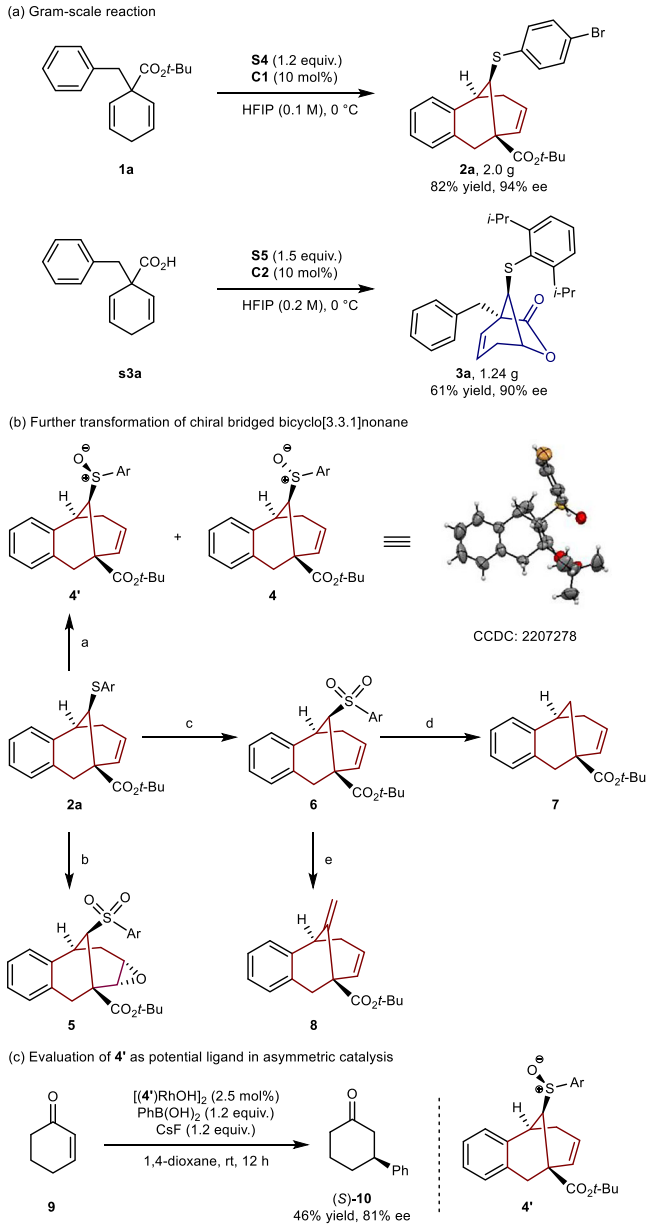

Fig. 4 | Gram-scale reaction, further transformation and application of chiral bridged bicyclo[3.3.1]nonane. a Gram-scale reactions. **b** Further transformation of chiral bridged bicyclo[3.3.1]nonane. Reaction conditions: a) H_2O_2 (1.8 equiv.), HFIP, 25 °C, 18 h, 62%, 4:1 dr, 94% ee. b) *m*-CPBA (6.0 equiv.), CH_2Cl_2, 42%, 94% ee. c) *m*-CPBA (2.5 equiv.), CH_2Cl_2, 60%, 94% ee. d) Mg, MeOH, 25 °C, 24 h, 99%, 94% ee. e) (i) *n*-BuLi (1.2 equiv.), Et_2O (0.1 M), 0 °C; (ii) ICH_2Cl (3.0 equiv.), *i*-PrMgCl (3.0 equiv.), THF, −78 °C, 45 min then −60 °C, 12 h. 25% for two steps, 96% ee. **c** Evaluation of **4'** as potential ligand in asymmetric catalysis.

stoichiometry of **S5** and reaction concentration were evaluated, yielding compound **3a** at 69% yield and 91% ee (Table 1, entry 20).

Substrate scope

With the optimized conditions in hand, the generality of enantioselective 6-*endo* carbosulfenylation was assessed. As illustrated in Fig. 3, a broad range of substituted cyclohexa-1,4-dienes were first tested to produce optically pure bicyclo[3.3.1]nonanes. The starting materials bearing electron-donating groups (Me, OMe) on the different positions of the phenyl ring delivered the desired products **2b-2f** in good yields (63-93%) with high enantioselectivities (80-95% ee). Naphthyl derivatives **1g** and **1h** proceeded smoothly to provide the corresponding bicyclo[3.3.1]nonanes in excellent ee values (94-96%). Pleasingly, *N*-Boc and *N*-Tosyl protected substrates could be successfully converted into products **2i** and **2j** in 91% and 92% ee, providing additional versatility for the products.

With multiple electron-donating substituents in the *ortho*, *meta* and *para* position of the phenyl ring have less effect on the yields and enantioselectivities (**2k-2o**, 62-90% yields, 93–97% ee). Noteworthily, the absolute configuration of **2k** and **2l** were unambiguously confirmed as *5R*, *9S*, *11R* by X-ray single crystal diffraction analysis. In addition, weakly deactivating halogen (fluoro, chloro, bromo) substituted substrates were also applicable to furnish the anticipated compounds **2p-2r** in good yields (67-82%) and ee values (72-78%). Substrates bearing heteroaromatic rings, including thiophene, furan, and indole moieties, were also reactive under these conditions, yielding exclusive products **2s**–**2u** in high yields (79–86%) with excellent enantioselectivities (90–95%). Notably, the furan moiety underwent further sulfenylation at the α-position, affording the final product **2t** with an aryl sulfide segment. Replacing the ester group with a phenyl group was also evaluated in the catalytic system, yielding the corresponding **2v** in 67% yield with a significantly reduced enantioselectivity (55% ee).

Next, the feasibility of switchable divergent synthesis of 2-oxabicyclo[3.2.1]octane was further explored (Fig. 3). Notably, the structure of **3a** was assigned as *1S, 5S, 8R* by X-ray crystallographic analysis. Electron-donating substituents (Me, OMe) on the phenyl ring had no significant effect on the reaction, furnishing the desired products **3b-3e** in moderate to good yields (55-75%) with high enantioselectivities (84-90% ee). Multiply-substituted starting materials were also well-tolerated to deliver **3f-3h** in up to 68% yield and 93% ee value. Sterically demanding 1- and 2-naphthyl derivatives reacted well to give products **3i** and **3j** in moderate to good yields (63% and 51%) and excellent ee values (93% and 94%). Correspondingly, the starting materials bearing halophenyl also led to **3k-3m** with high enantioselectivities (85-94% ee), albeit relatively low yields were observed (39-48%). In the presence of the strong electron-withdrawing group (CF_3), the reaction proceeded well with reasonable control of the enantioselectivity (**3n**, 86% ee). It is important to stress that the phenethyl-substituted product **3o** was also isolated in 35% yield and 78% ee. To enhance the yields of certain low-yielding reactions, such as **3g, 3k**, and **3o**, we investigated the addition of one equivalent of acid, including MsOH, TfOH, TFA, and $BF_3{\cdot}OEt_2$, as an additive. However, this strategy completely inhibited the reaction and instead resulted in the decarboxylation and aromatization of the starting materials.

Synthetic transformation of the products and synthetic utility

Based on the versatility of phenylthiol moiety, several additional transformations of chiral bridged bicyclo[3.3.1]nonane were conducted (Fig. 4). Notably, a gram-scale synthesis of **2a** and **3a** was achieved with decent yield while maintaining enantioselectivity (Fig. 4a). As shown in Fig. 4b, starting from **2a** with 94% ee value, the phenylthiol moiety could be oxidized using hydrogen peroxide (H_2O_2) to deliver the sulfoxide **4** with 4:1 dr and 94% ee (confirmed by X-ray crystallographic analysis). On the other hand, oxidation of **2a** in the presence of 6.0 equiv. *meta*-chloroperoxybenzoic acid (*m*-CPBA) led to epoxide **5** in 42% yield and 94% ee. Switching to 2.5 equiv. *m*-CPBA could selectively oxidize the phenylthiol moiety to sulfone and afforded product **6** in 60% yield. Additionally, reductive desulfonylation of **6** occurred effectively to establish bicyclo[3.3.1]nonane **7** in excellent yield and ee value. Upon the strong leaving group ability of the sulfonyl group, the sulfone **6** was transformed into the terminal olefin **8** in 96% ee after two steps. To evaluate the synthetic utility of the resulting bicyclo[3.3.1]nonane derivative, the isolated sulfoxide isomer **4'** (94% ee) was employed as an efficient chiral sulfoxide alkene ligand (Fig. 4c). From commercially available $[Rh(coe)_2Cl]_2$, the desired $[(\mathbf{4'})RhOH]_2$ catalyst was prepared in situ under mild conditions. Encouragingly, the

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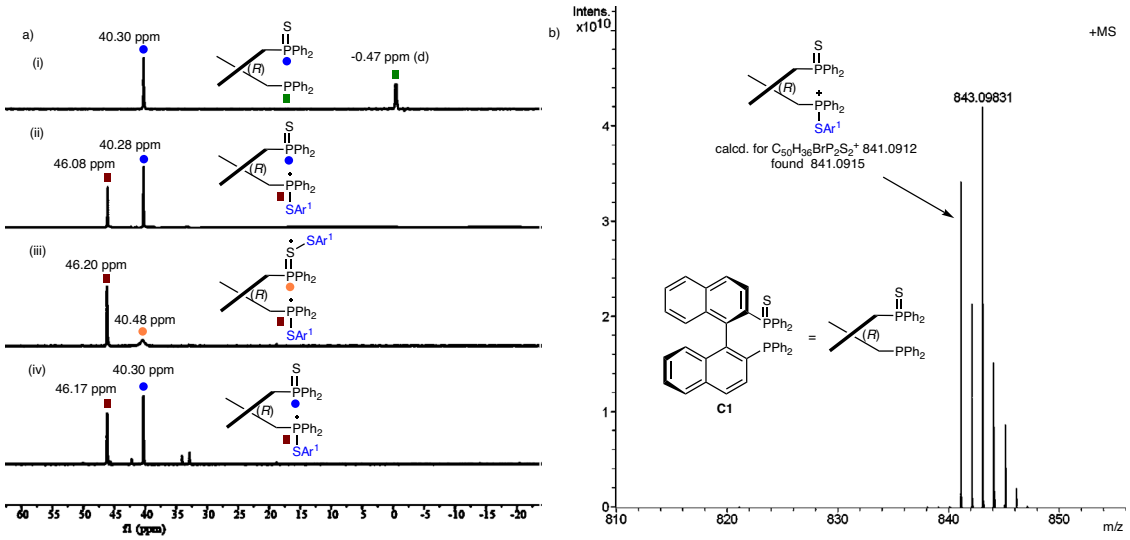

Fig. 5 | Mechanism study. a, ^{31}P NMR spectra: (i) (*R*)-BINAP(S) **C1**, (ii) (*R*)-BINAP(S) **C1**/**S4** = 1:1, (iii) (*R*)-BINAP(S) **C1**/**S4** = 1:6, (iv) (*R*)-BINAP(S) **C1**/**S4**/**1a** = 1:6:5. **b**, Sample preparation: (*R*)-BINAP(S) **C1**/**S4** = 1:6 in HFIP, then diluted with methanol.

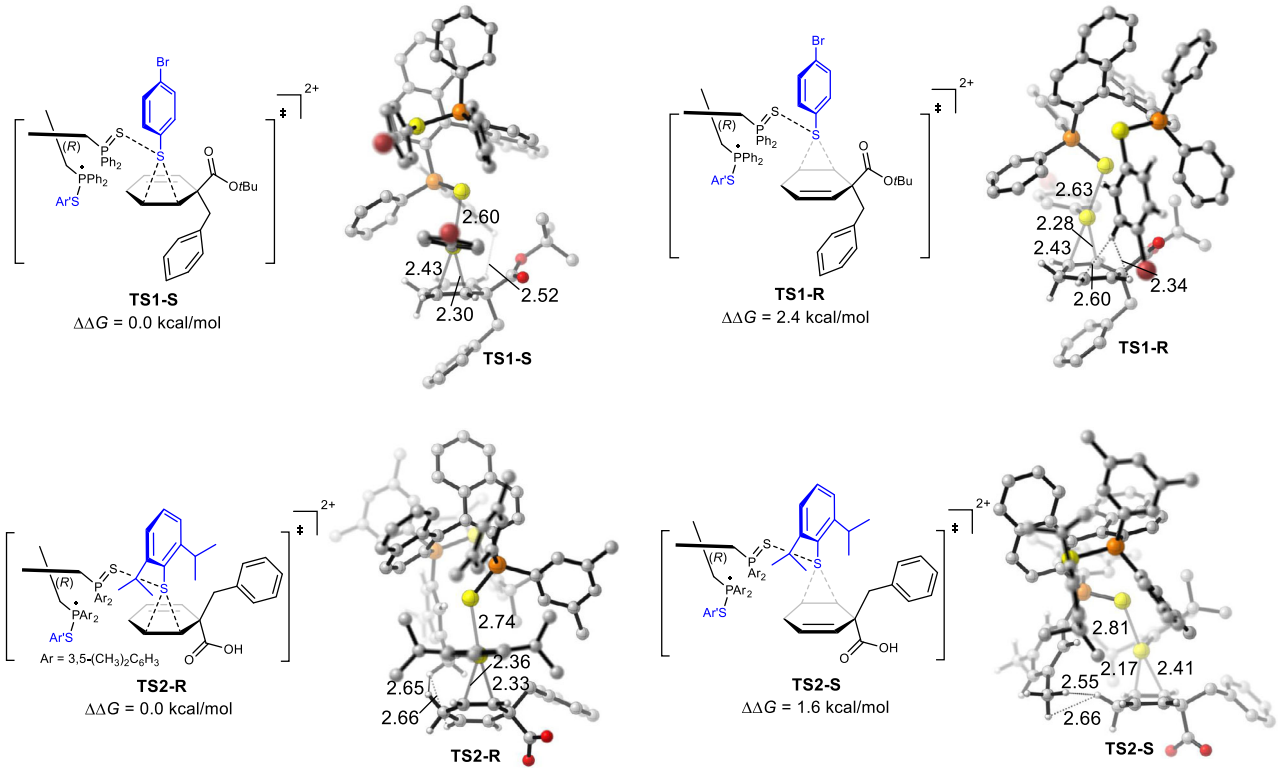

Fig. 6 | DFT calculations of the electrophilic addition transition states. The geometries and free energy profiles of the four transition states, **TS1-S, TS1-R, TS2-R**, and **TS2-S**, leading to the formation of chiral thiiranium ions. All hydrogen atoms are omitted for clarity, except those used to indicate interatomic distances. Bond distances are given in angstroms.

[(**4'**)RhOH]$_2$-catalyzed asymmetric 1,4-addition of phenylboronic acid to cyclic enone **9** proceeded smoothly to furnish the product **10** in 46% yield and 81% ee, indicating the chiral sulfoxides could be utilized as promising ligands in metal-catalyzed asymmetric reactions[66,67].

Mechanistic investigations

To gain insight into the reaction mechanism, we conducted the mechanistic studies through ^{31}P NMR measurement of the catalytically active species generated from the reaction participants (Fig. 5)[68]. The original two peaks at −0.47 and +40.30 ppm of (*R*)-BINAP(S) belong to phosphine (III) and phosphine sulfide (V) moieties (Fig. 5a (i)). After 1.0 equiv. sulfenylating agent **S4** was reacted with (*R*)-BINAP(S), the signal of phosphine (III) disappeared, and a new signal was observed at +46.08 ppm, which suggested that the formation of an unsymmetrical and electron-deficient phosphorus species (Fig. 5a (ii)). When the amount of **S4** was increased to 6.0 equiv., the signal of the P = S (V) group vanished, and a broad, weak peak at +40.48 ppm was newly observed. We postulate that *P* = S (V) group act as a soft Lewis base that could interact with excess **S4** to form the putative P = S$^+$——SAr^1 as active chemical species (Fig. 5a (iii)). Interestingly, when (*R*)-BINAP(S)

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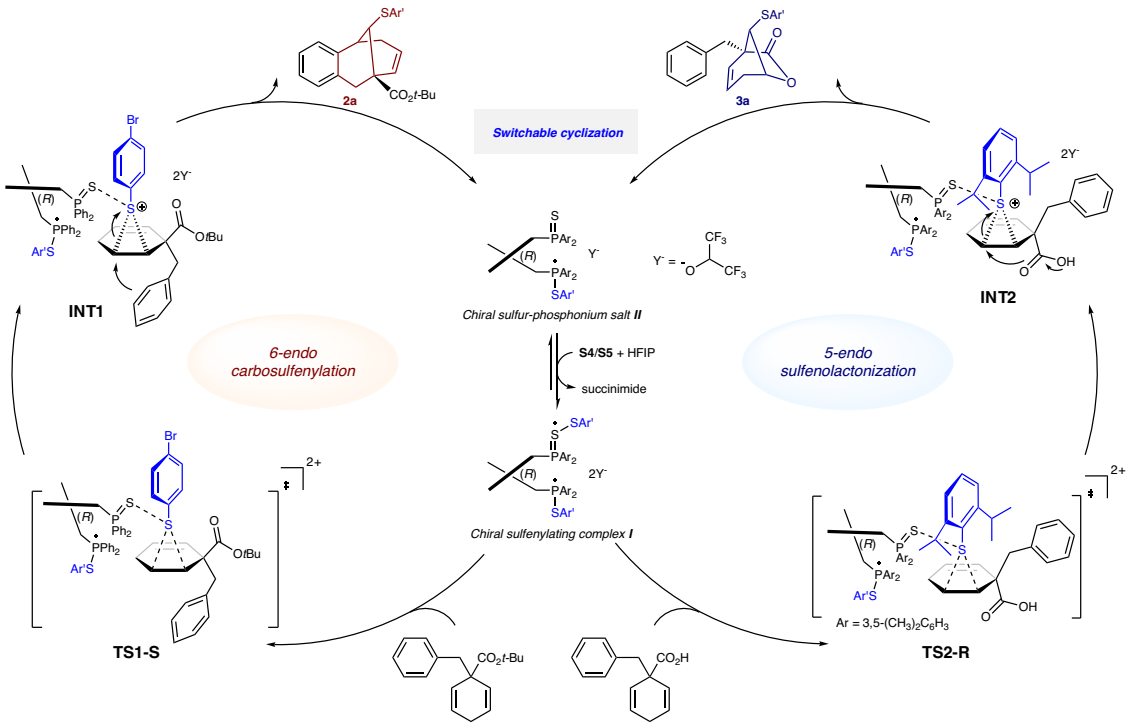

Fig. 7 | Proposed mechanism. A plausible reaction mechanism for the switchable organocatalytic enantioselective carbosulfenylation/sulfenolactonization of cyclohexa-1,4-dienes to access chiral bridged bicyclo[3.3.1]nonanes and 2-oxabicyclo[3.2.1]octanes.

was treated with excess reagent **S4** and substrate **1a** (Fig. 5a (iv)), the ^{31}P NMR spectroscopic property exactly corresponds with the unsymmetrical phosphorus compound in Fig. 5a (ii). Considering the above results showed (*R*)-BINAP could not catalyze the reaction, while (*R*)-BINAP monosulfide efficiently promote the transformation, we speculate the moiety P = S$^+$——SAr^1 species in Fig. 5a (iii) serve as the actual $^+$SAr^1 transfer agent, not the P$^+$——SAr^1 group of the species in Fig. 5a (ii). To confirm the validity of the catalytically active species, an ESI-HRMS analysis of the mixture of (*R*)-BINAP(S) with excess reagent **S4** was performed. As illustrated in Fig. 5b, the transient species in Fig. 5a (ii) was successfully captured. However, the intermediate Fig. 5a (iii) was not detected might be due to its instability in methanol.

Density Functional Theory (DFT) calculations were conducted on the transition states of electrophilic addition to further elucidate the origins of enantioselectivity (see the Supplementary Data 1). As shown in Fig. 6, the calculated free energy of transition state **TS1-R** is 2.4 kcal/mol higher than that of **TS1-S** for the cyclohexa-1,4-diene substrate bearing a *tert*-butyl group, which aligns with the observed high enantioselectivity. Structural analysis indicates that steric repulsion between cyclohexa-1,4-diene and (*R*)-BINAP(S) **C1** is less pronounced in **TS1-S** than in **TS1-R**, as evidenced by the closest hydrogen-to-hydrogen (H···H) distance of 2.52 Å in **TS1-S** compared to 2.34 Å in **TS1-R**. Furthermore, Fig. 6 shows that when the ester moiety is replaced with a more reactive carboxylic acid, the calculated free energy of **TS2-R** is 1.6 kcal/mol lower than that of **TS2-S**. Structural analysis further suggests that steric repulsion between cyclohexa-1,4-diene and (*R*)-BINAP(S) **C2** is reduced in **TS2-R** relative to **TS2-S**, with an H···H distance of 2.65 Å in **TS2-R** versus 2.55 Å in **TS2-S**. These findings indicate that steric repulsion plays a crucial role in determining the enantioselectivity of these reactions.

Based on these studies and previous reports, a possible catalytic cycle for this reaction is proposed in Fig. 7. HFIP may act as a hydrogen-bonding donor to activate sulfenylating agent **S4** or **S5** to react with (*R*)-BINAP(S) **C1** or **C2** to generate chiral sulfenylating complex **I**. The sulfenocyclization of cyclohexadienes then proceeds in a stepwise manner. The sulfenylating complex **I** undergoes electrophilic addition to the double bond of cyclohexa-1,4-dienes via transition states **TS1-S** and **TS2-R**, respectively, leading to the formation of chiral thiiranium ions **INT1** and **INT2**. The electrophilic addition steps (**TS1-S** and **TS2-R**) are identified as the enantioselectivity-determining steps and are also proposed to be crucial for chemoselectivity. Subsequently, *6-endo* carbosulfenylation or *5-endo* sulfenolactonization selectively occurs. The switchable cyclization diverges into the corresponding chiral bicyclo[3.3.1]nonane **2a** or 2-oxabicyclo[3.2.1]octane **3a**, simultaneously releasing species **II** and regenerating complex **I** for the next catalytic reaction cycle.

Discussion

In summary, we have developed a switchable organocatalytic enantioselective desymmetrizing sulfenocyclization of cyclohexa-1,4-dienes. The readily accessible (*R*)-BINAP monosulfide derivatives were proved as reliable catalysts in this transformation, which provided access to various architecturally challenging chiral bridged bicyclic skeletons bearing three consecutive stereocenters with an all-carbon quaternary bridgehead stereocenter. By manipulating the nucleophilic component of the cyclohexa-1,4-diene substrates, the regioselective transformation was controlled by tuning the sulfenylating agents, affording bicyclo[3.3.1]nonanes or 2-oxabicyclo[3.2.1]octanes in good yields and good to excellent enantioselectivities. Further derivatizations and application as the chiral ligand of the cyclic systems lead to a series of synthetically useful and valuable molecules without loss of stereochemical integrity. Additional applications of this protocol and mechanistic details are currently under investigation by our group.

Methods

General procedure for the asymmetric carbosulfenylation

To a flame-dried vial was added (*R*)-BINAP(S) **C1** (6.5 mg, 0.01 mmol), sulfur agent **S4** (34 mg, 0.12 mmol, 1.2 equiv.) and HFIP (0.5 mL), the mixture was stirred at 0 °C for 5 min., then the solution of the ester substrate (0.10 mmol) in HFIP (0.5 mL) was added. The reaction was stirred at 0 °C for 24 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and the volatiles were removed by rotary

evaporation to afford crude product. The residue was purified by flash column chromatography (petro ether/EtOAc = 100/1) to afford the product **2**.

General procedure for the asymmetric sulfenolactonization

To a flame-dried vial was added **C2** (7.7 mg, 0.01 mmol), sulfur agent **S5** (43.7 mg, 0.15 mmol, 1.5 equiv.) and HFIP (0.25 mL), the mixture was stirred at 0 °C for 5 min., then the solution of the carboxylic acid substrate (0.10 mmol) in HFIP (0.25 mL) was added. The reaction was stirred at 0 °C for 48 h. Upon completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and the volatiles were removed by rotary evaporation to afford crude product. The residue was purified by flash column chromatography (petro ether/EtOAc = 50/1) to afford the product **3**.

Data availability

The crystallographic data generated in this study have been deposited in the Cambridge Crystallographic Data Center, with the deposition numbers 2207250 (for **2k**), 2207262 (for **2 l**), 2207265 (for **3a**), and 2207278 (for **4**), respectively. The data can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/getstructures. All Cartesian coordinates are available as separate Supplementary Data 1. All other data generated in this manuscript are available within the Article and its Supplementary Information. Data supporting the findings of this manuscript are also available from the corresponding author upon request.

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Author contributions

J.D. designed and directed the project. B.-Q.Z. and L.C. performed the optimization studies, substrate scope analysis and mechanistic studies. W.-Y.X. conducted some of the synthetic experiments and collect some

experimental data. J.D., Y.-L.L., and Y.L. wrote the manuscript. All authors discussed the results and commented on the manuscript.

Competing interests
The authors declare no competing interests.

Additional information
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