EDGE ARTICLE

Check for updates

Dirhodium(II)-catalysed cycloisomerization of azaenyne: rapid assembly of centrally and axially chiral isoindazole frameworks†

Shaotong Qiu,[a] Xiang Gao[a] and Shifa Zhu ⓘ *[ab]

Described herein is a dirhodium(II)-catalyzed asymmetric cycloisomerization reaction of azaenyne through a cap-tether synergistic modulation strategy, which represents the first catalytic asymmetric cycloisomerization of azaenyne. This reaction is highly challenging because of its inherent strong background reaction leading to racemate formation and the high capability of coordination of the nitrogen atom resulting in catalyst deactivation. Varieties of centrally chiral isoindazole derivatives could be prepared in up to 99 : 1 d.r., 99 : 1 er and 99% yield and diverse enantiomerically enriched atropisomers bearing two five-membered heteroaryls have been accessed by using an oxidative central-to-axial chirality transfer strategy. The tethered nitrogen atom incorporated into the starting materials enabled easy late-modifications of the centrally and axially chiral products *via* C−H functionalizations, which further demonstrated the appealing synthetic utilities of this powerful asymmetric cyclization.

Known as one of the most significant and reliable access methods to chiral heterocycles, asymmetric cycloisomerization of conjugated enyne has caught extensive attention and interest for its wide applications in synthetic route design and mechanistic investigation.[1] Specifically, asymmetric cyclization of conjugated enynone (X = C, Z = O) has been successfully developed and applied to the rapid construction of various chiral furan-containing skeletons with high efficiency in an extremely operationally simple manner (Scheme 1a).[2] However, compared to the fruitful research with enynone, it is surprising that the analogous asymmetric version of azaenyne (Z = N–R) still remains underdeveloped.[3] In fact, no successful example of catalytic asymmetric cyclization of azaenyne has been reported in the literature despite the apparent significance of nitrogen-containing five-membered heterocycles in the synthetic and pharmaceutical community.[4] In 2004, Haley and Herges reported a detailed experimental and theoretical study of the cyclization reaction of (2-ethynylphenyl)-phenyldiazene, which is a unique azaenyne.[5] According to the DFT calculations, very close and low activation barriers for 5-*exo-dig* and 6-*endo-dig* cyclization pathways under catalyst-free conditions were found,
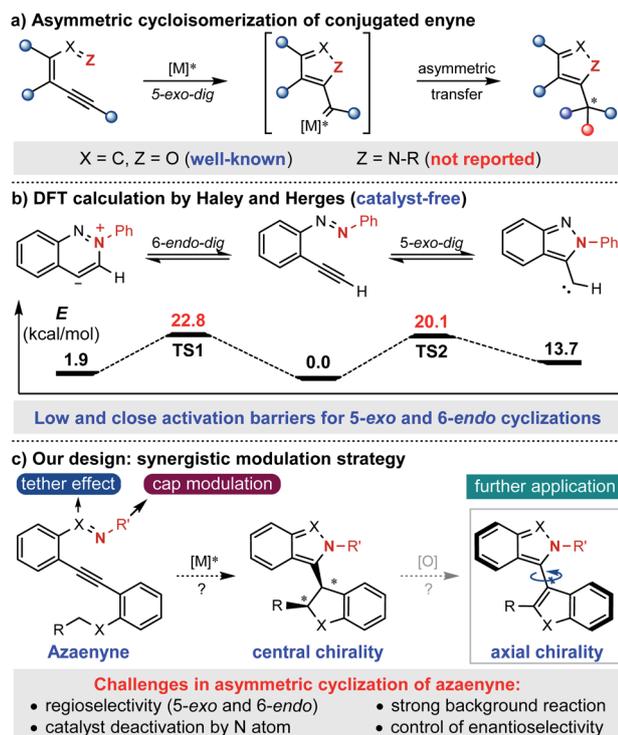
which shed light on the inherent challenges of the asymmetric reaction of azaenyne (Scheme 1b). For instance, there was usually a regioselectivity issue (5-*exo* and 6-*endo*) in the cyclization reaction of azaenyne because of their close reaction barriers where the competitive 6-*endo-dig* cyclization[3a,6] may lead to troublesome side-product formation. In addition, the low activation barrier deriving from the strong *N*-nucleophilicity of azaenyne may easily lead to self-cyclization which will cause severe background reactions to interfere with the asymmetric process. More troublingly, this transformation might suffer from catalyst deactivation arising from the high coordinating capability of the nitrogen atom in both starting materials and products, which might give more opportunities to the propagation of detrimental background reactions. In some cases, even a super-stoichiometric amount of transition metal has to be used to ensure effective conversion.[3a,7] Therefore, although many non-chiral approaches have been reported,[3,5] catalytic asymmetric cyclization of azaenyne still remains elusive due to the inherent obstacles aforementioned. With our continuous interest in alkyne chemistry,[2a,8] herein we designed a cap-tether synergistic modulation strategy to tackle these challenges, envisioning that modulation of the tethered atom and protecting cap of nitrogen in the azaenyne would intrinsically perturb and alter the reactivity of the starting material, and therefore the azaenyne motif could be effectively harnessed as a promising synthon for asymmetric transformations (Scheme 1c). It should be noted that the obtained centrally chiral product produced from intramolecular C–H insertion of donor-type metal carbene[9] might be potentially converted into the axially chiral molecule *via* a central-to-axial chirality conversion strategy.

Scheme 1 Development of the asymmetric cyclization reaction of conjugated azaenyne.

Scheme 2 Typical substrate investigation.

With this design in mind, different types of azaenynes bearing typical tethering atoms and capping groups were chosen to test our hypothesis and representative results are shown in Scheme 2. First, *t*Bu-capping imine (X = C, R = *t*Bu) was selected as a substrate to test our hypothesis.[6a] It was found that the imine exhibited low reactivity and the reaction temperature has to be elevated to 100 °C to initiate the transformation with or without catalyst. Unfortunately, the desired 5-*exo-dig* cyclization product was not detected, but isoquinoline from 6-*endo-dig* cyclization was obtained instead (Scheme 2a). To further regulate and control the regioselectivity and reactivity, triazene (X = N, R = *N*-piperidyl) was then investigated. Similarly, this substrate also showed low reactivity and it is still required to be heated at 100 °C for conversion. In the absence of a metal catalyst, an unexpected alkyne, deriving from the fragmentation of the triazene moiety, was produced in 41% yield. When 2 mol% Rh₂(OPiv)₄ was added as a catalyst, the side reaction could be efficiently suppressed and the reaction selectivity was apparently reversed. In this case, the target C–H insertion dihydrofuran was furnished as the major product in 30% yield but still accompanied by concomitant formation of 12% yield of undesired alkyne (Scheme 2b). The above investigations showed neither the imine nor triazene was an ideal substrate for the asymmetric reaction. Thus, we moved our attention to the diazene substrate (X = N, R = aryl). As demonstrated by Haley's and Herges' pioneering work, *ortho*-alkynyl diazene, compared with imine and triazene, was more unstable and tended to self-cyclization even at room temperature.[5a] As shown in Scheme 2c, the *ortho*-alkynyl diazene
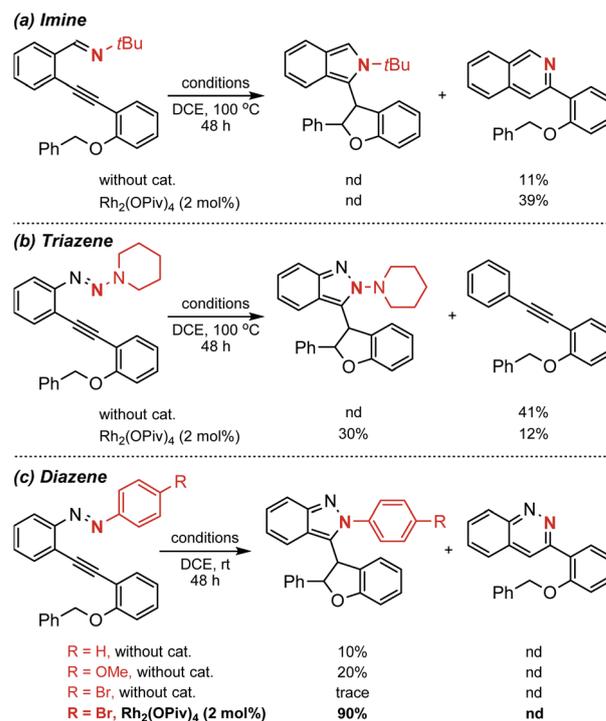
degrades and 5-*exo-dig* cyclization products could be observed even in DCE solvent without any catalyst at room temperature. When the phenyl capping group was installed in the substrate, the reaction furnished 10% yield of isoindazole derivative. The uncatalyzed self-cyclization reaction was obviously accelerated when an electron-rich capping group (4-MeO–C₆H₄–) was introduced, affording the corresponding product in 20% yield. Inspired by these findings, we assumed that installation of an electron deficient group on the capping phenyl would reduce the nucleophilicity of the nitrogen atom and thus the troublesome self-cyclization reaction might be effectively inhibited. To our delight, when a bromo-substituent was introduced onto the phenyl cap, the undesired self-cyclization was almost suppressed. When Rh₂(OPiv)₄ was added as a catalyst, the desired carbene-involved C–H insertion product was furnished in 90% yield at room temperature. Worthy of note was the total absence of any cinnoline formation from 6-*endo-dig* cyclization.[3a,6b] In short, the synthetic challenges associated with regioselectivity (5-*exo-dig* and 6-*endo-dig*), strong background reaction and catalyst deactivation could be successfully regulated and controlled *via* a tether-cap synergistic modulation strategy.

Encouraged by the above findings, *ortho*-alkynyl bromodiazene **1a** was chosen as a model substrate and different types of chiral dirhodium catalysts[10] were screened in DCE at room temperature for 48 h. As shown in Table 1, excellent diastereoselectivities (>99 : 1 d.r.) were observed in all these attempts with varied yields and enantioselectivities (16–98%, 50 : 50–98 : 2 er). First, the desired product **2a** could be obtained in 56% yield and 29 : 71 er when dirhodium *N*-sulfonylprolinate Rh₂(*S*-DOSP)₄ was used as the chiral catalyst (entry 1). Dirhodium carboxamide Rh₂(5*S*-MEPY)₄ exhibited poorer catalytic activity

Table 1 Optimization of reaction conditions[a]
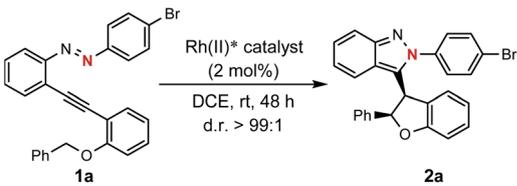
| Entry	Rh(II)*	Solvent	Yield[b] [%]	er[c]
1	Rh$_2$(R-DOSP)$_4$	DCE	56	29 : 71
2	Rh$_2$(5S-MEPY)$_4$	DCE	17	50 : 50
3	Rh$_2$(S-BTPCP)$_4$	DCE	61	8 : 92
4	Rh$_2$(S-PTPA)$_4$	DCE	91	91 : 9
5	Rh$_2$(S-PTTL)$_4$	DCE	86	97 : 3
6	Rh$_2$(S-PTAD)$_4$	DCE	93	94 : 6
7	Rh$_2$(S-NTTL)$_4$	DCE	92	96 : 4
8	Rh$_2$(S-TCPTTL)$_4$	DCE	95	98 : 2
9	**Rh$_2$(S-TFPTTL)$_4$**	**DCE**	**98**[d]	**98 : 2**
10	Rh$_2$(S-TFPTTL)$_4$	DCM	88	98 : 2
11	Rh$_2$(S-TFPTTL)$_4$	Toluene	92	98 : 2
12	Rh$_2$(S-TFPTTL)$_4$	MeCN	16	92 : 8
13	Rh$_2$(S-TFPTTL)$_4$	n-Hexane	96	98 : 2
14[e]	Rh$_2$(S-TFPTTL)$_4$	DCE	65[f]	96 : 4
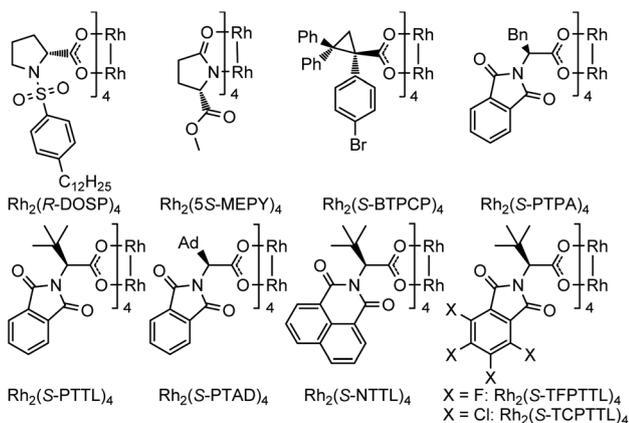
[a] Unless otherwise noted, reactions were performed at 0.1 M in DCE using 0.20 mmol substrate and catalyst (2 mol%) under a N$_2$ atmosphere. [b] Determined by ^{1}H NMR spectroscopy. [c] The er value of **2a** was determined by HPLC using a chiral stationary phase. [d] Isolated yields. [e] 1 mol% catalyst was used. [f] 25% starting material was recovered.

with no enantioselectivity (entry 2). Dirhodium triarylcyclopropane carboxylate Rh$_2$(S-BTPCP)$_4$ led to an improved enantioselectivity (8 : 92 er), but only gave moderate yield (entry 3). To our delight, phthalimide-based dirhodium complexes proved to be better choices for this reaction, affording the target product **2a** in obviously higher yields (86–98%) with effective control of enantioselectivities (91 : 9–98 : 2 er) (entries 4–9). For example, when Rh$_2$(S-PTPA)$_4$ was utilized as the catalyst, the desired product **2a** could be obtained in 91% yield with 91 : 9 er (entry 4). The enantioselectivity could be further improved to 97 : 3 er by using a bulkier dirhodium catalyst Rh$_2$(S-PTTL)$_4$ (entry 5). When sterically more crowded Rh$_2$(S-PTAD)$_4$ and Rh$_2$(S-NTTL)$_4$ were tested, marginal improvement of yields (93% and 92%) was observed but with slight reduction in

enantioselectivity (94 : 6 er and 96 : 4) (entries 6–7). Furthermore, electron-deficient dirhodium catalysts Rh$_2$(S-TCPTTL)$_4$ and Rh$_2$(S-TFPTTL)$_4$ were also examined (entries 8–9), where Rh$_2$(S-TFPTTL)$_4$ gave the best yield of 98% with the best enantioselectivity of 98 : 2 er (entry 9). In the tested solvents, DCE proved to be the optimal one (entries 10–13). Reduced catalyst loading provided less satisfactory results with 25% starting material recovered (entry 14).

With the optimized reaction conditions in hand (Table 1, entry 9), the substrate scope of this asymmetric cyclization was then examined. As shown in Scheme 3, the catalytic process could be successfully applied to azaenynes **1** bearing different ether side chains. For example, in addition to **1a**, various azaenyne derivatives containing benzylic ethers could be efficiently converted into the desired products **2b–i** with excellent diastereoselectivities and enantioselectivities (>99 : 1 d.r., 97:3–99 : 1 er). The yields were typically higher than 90% for most substrates. Satisfyingly, the substrates with bulkier aryl groups were well-tolerated to afford the isoindazole products **2j–m** in good yields with excellent diastereo- and enantiocontrol (>97 : 3 d.r., > 95 : 5 er). In addition to azaenynes with arylmethyl ether, this protocol was also successfully applied to substrates with allylic ether, propargyl ether and even aliphatic ether to furnish the cyclization products **2n–u** in good yields with decent diastereo- and enantioselectivities (>93 : 7 d.r., > 90 : 10 er). In the cases of allylic and propargyl ether, only C–H insertion products (**2n–p**) were observed though cyclopropanation or cyclopropenation often took place competitively when using the allylic or propargyl substrate to trap the carbene intermediate.[11] It was noted that the azaenynes with aliphatic ether, which represent challenging substrates[2a] in the asymmetric carbene transfer reactions, also showed good reactivities to afford the corresponding chiral dihydrobenzofurans (**2q–u**) with excellent diastereoselectivities (>93 : 7 d.r.) and enantioselectivities (>98 : 2 er). Interestingly, when phenyl and methoxyphenyl capping azaenynes, which potentially suffered from the undesired background reactions, were subjected to the standard conditions, chiral products (**2v–w**) could be obtained with high optical purity (>99 : 1 d.r., > 96 : 4 er) as well. These results might be attributed to the high catalytic activity of Rh$_2$(S-TFPTTL)$_4$ in the asymmetric cyclization process, which eventually led to complete suppression of the uncatalyzed self-cyclization. The scopes with respect to the group R^1 on the fused phenyl ring were further investigated. Both electron-rich and -deficient substituents R^1 were well accommodated, with the product yields ranging from 80% to 99%, enantiomeric ratios ranging from 95 : 5 to 97 : 3 and diastereomeric ratios higher than 99 : 1 (**2x–z**). In addition, azaenyne substituted with an alkyl side chain at the alkynyl carbon atom was also tested, giving tetrahydrofuran (**2aa**) with excellent diastereoselectivity (>99 : 1 d.r.), good enantioselectivity (90 : 10 er) and moderate yield (43%). In addition to the side chain of ether, this asymmetric protocol could even be extended to the more challenging nitrogen- and thio-tethered analogues, albeit with somewhat lower reactivities (46–65% yields) but good stereoselectivities (93 : 7 er and 84 : 16 d.r. for **2ab**; 81 : 19 er and >99 : 1 d.r. for
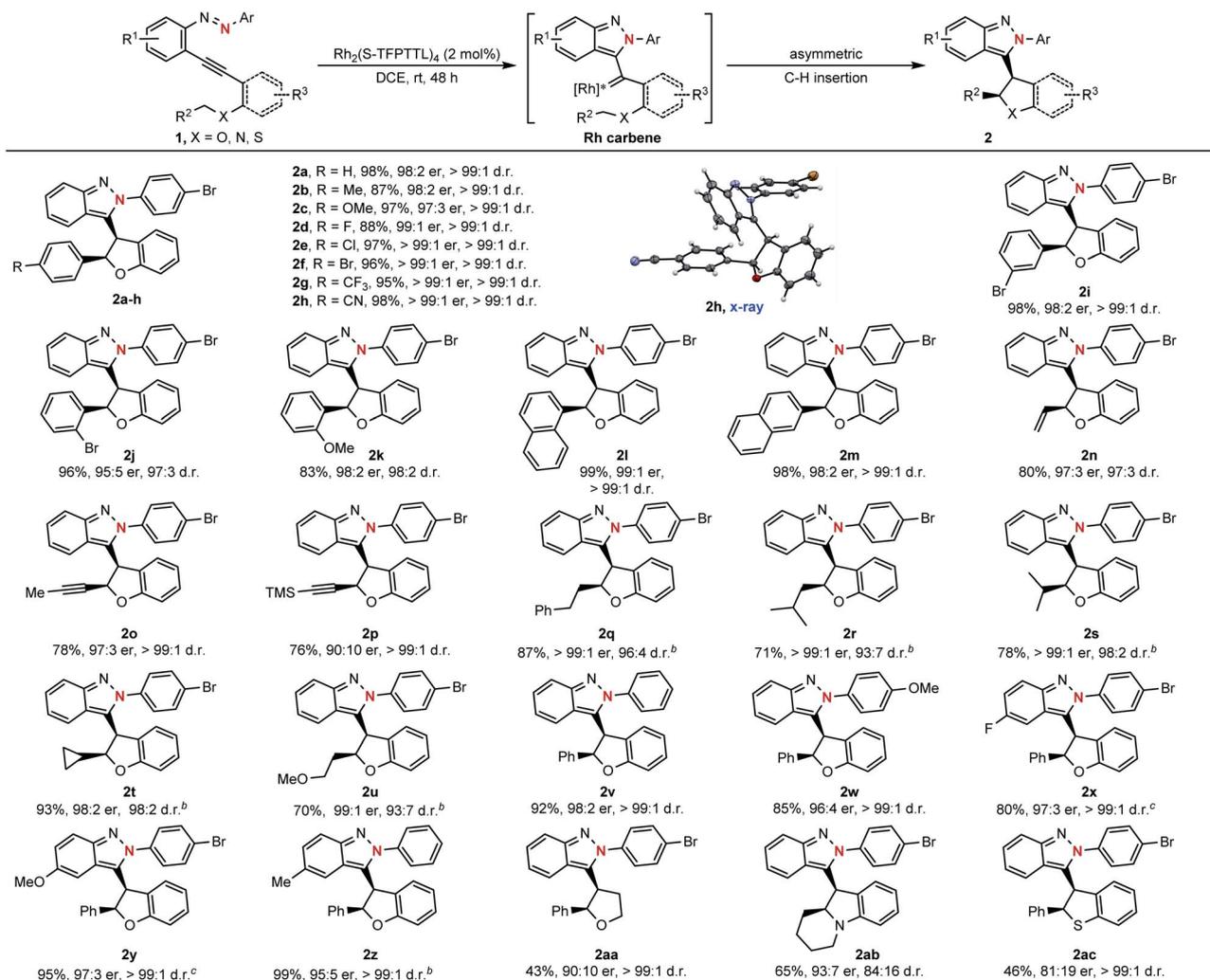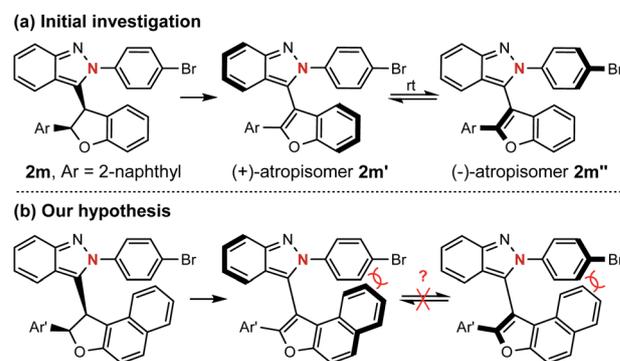
Scheme 3 [a]Unless otherwise noted, the reactions were performed under standard conditions for 48 h or monitored by TLC until the starting material disappeared. [b]5 mol% catalyst was used. [c]Reactions were performed in n-hexane, using 2 mol% Rh₂(S-TCPTTL)₄ as the catalyst.

2ac). Structures of the resulting products were confirmed by X-ray crystallographic analysis of their analogue **2h**.
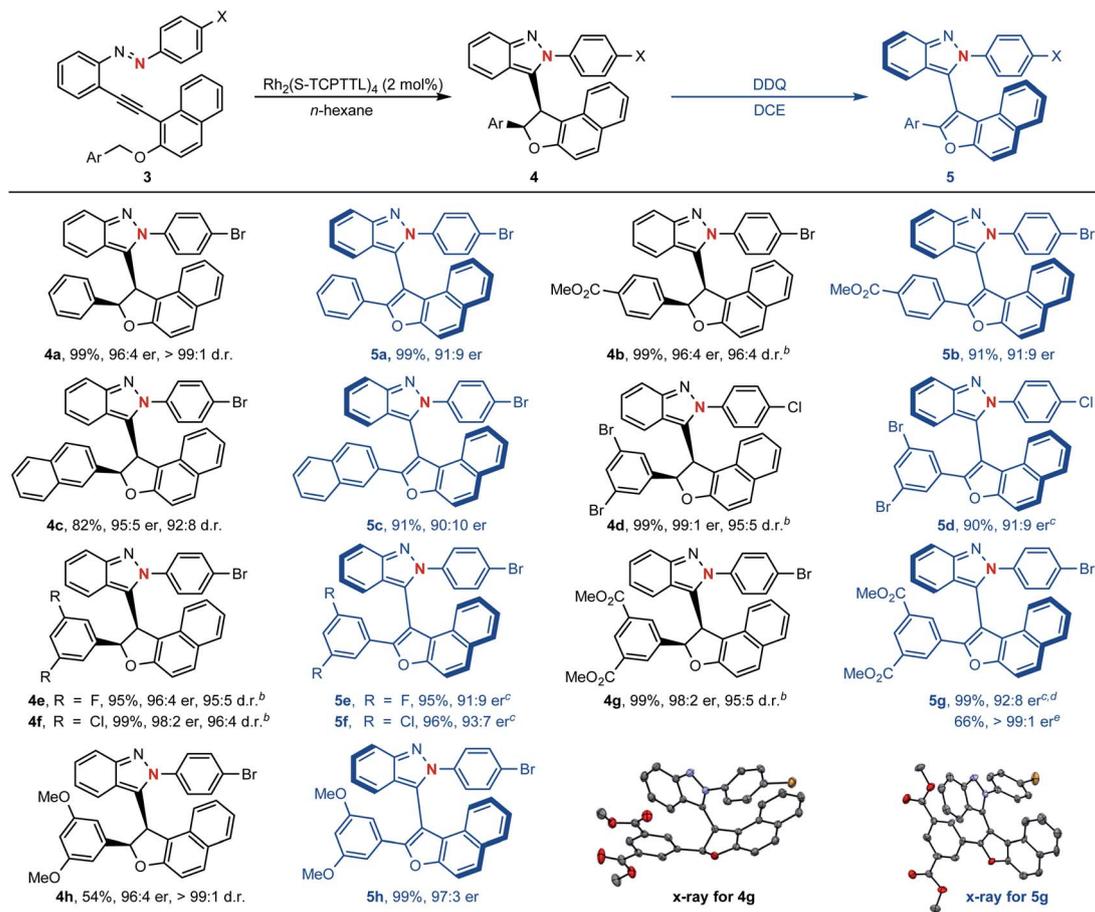
The successful preparation of centrally chiral isoindazole through the asymmetric cyclization reaction prompted us to explore the further applications of this protocol. Axially chiral biaryl skeletons are undoubtedly regarded as one of the most prominent structural motifs for their ubiquity in natural products, pharmaceuticals and useful chiral ligands in asymmetric catalysis.[12] Due to the lower rotational barrier, there are only limited examples of the enantioselective synthesis of axially chiral atropisomers featuring a five-membered ring, especially those bearing two pentatomic aromatics.[13] Compared with the furan analogue, the extending cap in the isoindazole scaffold provides additional *ortho* steric hindrance making these molecules possible candidates for the preparation of five-five-membered biaryl atropisomers. Considering the unique chiral skeleton of dihydrofuranyl isoindazole **2**, we began to explore their potential application in chiral atropisomer synthesis *via* a central-to-axial chirality transfer strategy. As shown in Scheme 4, oxidative aromatization of representative dihydrofuran

candidate **2m** furnished two configurationally unstable atropisomers, which might be attributed to their relatively low rotational barriers as five-membered atropisomers especially when the furan ring was incorporated (see ESI† for details). Therefore, it was hypothesized that extending the fused phenyl

Scheme 4 Investigation of central-to-axial chirality transfer.

4a, 99%, 96:4 er, > 99:1 d.r.

5a, 99%, 91:9 er

4b, 99%, 96:4 er, 96:4 d.r.[b]

5b, 91%, 91:9 er

4c, 82%, 95:5 er, 92:8 d.r.

5c, 91%, 90:10 er

4d, 99%, 99:1 er, 95:5 d.r.[b]

5d, 90%, 91:9 er[c]

4e, R = F, 95%, 96:4 er, 95:5 d.r.[b]
4f, R = Cl, 99%, 98:2 er, 96:4 d.r.[b]

5e, R = F, 95%, 91:9 er[c]
5f, R = Cl, 96%, 93:7 er[c]

4g, 99%, 98:2 er, 95:5 d.r.[b]

5g, 99%, 92:8 er[c,d]
66%, > 99:1 er[e]

4h, 54%, 96:4 er, > 99:1 d.r.

5h, 99%, 97:3 er

x-ray for 4g

x-ray for 5g

Scheme 5 [a]Conditions for cyclization of azaenyne: Rh₂(S-TCPTTL)₄ (2 mol%), n-hexane, rt for 48 h or monitored by TLC until the starting material disappeared; conditions for oxidative chirality transfer: DDQ (2 equiv.), DCE, −20 °C for 48 h or monitored by TLC until the starting material disappeared. [b]45 °C. [c]DDQ (5 equiv.). [d]Room temperature. [e]After one recrystallization.

to naphthyl might afford stable atropisomers by enhancing the *ortho* steric hindrance (Scheme 4b).

To our delight, as shown in Scheme 5, naphthyl-fused dihydrofurans **4** could be easily accessed through the above established dirhodium-catalyzed cyclization process and configurationally stable atropisomers **5** could be generated *via* further oxidative dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant (see ESI† for the proposed mechanism). For example, asymmetric cyclization reactions proceeded smoothly to give the centrally chiral compounds **4** in good yields (54–99%) with excellent diastereoselectivities (92 : 8–99 : 1 d.r.) and enantioselectivities (95 : 5–99 : 1 er) under slightly modified reaction conditions. This reaction was compatible with a variety of arylmethyl side chains in azaenynes and well-accommodated with various functional groups (F, Cl, Br, OMe, and –CO₂Me). Additionally, oxidative dehydrogenation of chiral candidates **4** with DDQ smoothly resulted in the formation of axially chiral atropisomers **5** in 90–99% yields with only slight loss of chiral integrity (90 : 10–97 : 3 er). An enantiomerically pure atropisomer could be obtained through a simple recrystallization procedure as exemplified by compound **5g**. The structure and absolute configuration of

isoindazole **4g** and atropisomer **5g** were confirmed by their single-crystal X-ray diffraction analysis.

With centrally and axial chiral molecules in hand, further transformations of these compounds were also explored. The tethered nitrogen atom in azaenynes not only showed a synergetic effect with the capping group on promoting asymmetric cyclization but also served as an innate directing group for late-stage modifications *via* C–H functionalization. As shown in Scheme 6, a variety of functional groups could be directly introduced onto the capping aromatic rings, allowing for rapid build-up of molecular complexity. For example, synthetically valuable alkenyl,[14] allyl[15] and alkynyl[16] groups could be easily incorporated into the final structures, which had wide potential applications in organic synthesis (**6a–c**). Furthermore, C–H alkylation,[17] amidation[18] and selenylation[19] were performed smoothly to afford the desired products **6d–g**. It is noteworthy that unique chiral chelation backbones were constructed by amidation and selenylation of the isoindazole moiety (**6e–g**). In addition to centrally chiral compounds, axial chiral atropisomers **5** themselves could be efficiently converted to their functionalized scaffolds as well (**6h–i**) through a similar directed C–H functionalization process.
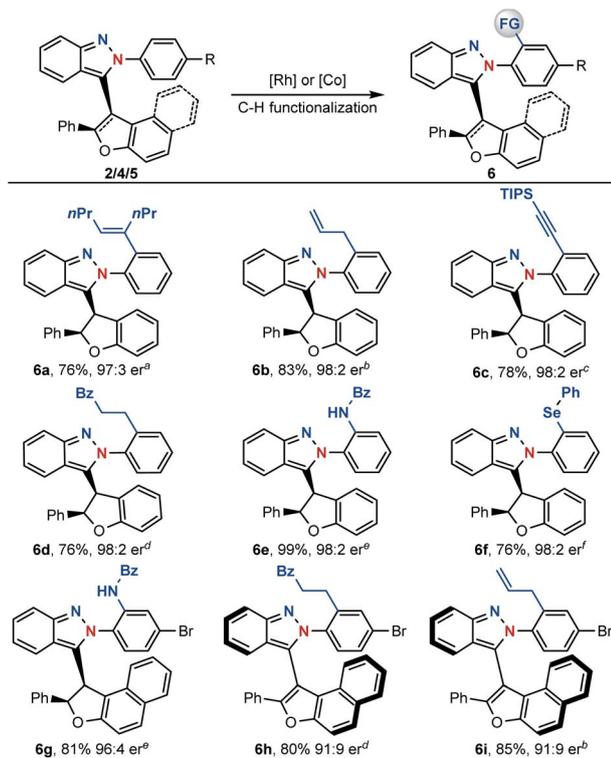
Scheme 6 Late-stage modification of chiral isoindazoles. Reaction conditions: [a] 4-octyne, [Rh(Cp*Cl₂)]₂, AgSbF₆, Cu(OAc)₂, DCE, 80 °C. [b] Allyl carbonate, [Rh(Cp*Cl₂)]₂, AgSbF₆, PivOH, PhCl, 40 °C. [c] Hypervalent iodine-alkyne, [Rh(Cp*Cl₂)]₂, Zn(OTf)₂, DCE, 80 °C. [d] Alkene, [Rh(Cp*Cl₂)]₂, AgSbF₆, AcOH, 1,4-dioxane, 50 °C. [e] 3-Phenyl-1,4,2-dioxazol-5-one, [Cp*Co(MeCN)₃](SbF₆)₂, DCE, 80 °C. [f] PhSeCl, [Rh(Cp*Cl₂)]₂, AgSbF₆, THF, 60 °C.

Conclusions

In summary, a dirhodium-catalyzed asymmetric cyclization reaction of azaenyne has been developed through a cap-tether synergistic modulation strategy. Benefiting from this strategy, a diverse array of centrally chiral isoindazole derivatives could be prepared in up to 99 : 1 d.r., 99 : 1 er and 99% yield in an efficient and practical manner. This reaction is highly challenging due to its inherent strong background reaction leading to racemate formation and the high capability of coordination of the nitrogen atom resulting in catalyst deactivation. Compared with the well-established enynone system, this work represents a significant advance in the asymmetric cyclization of conjugated enyne motifs where the introduction of the nitrogen tether atom and capping group provided strategic advantages in both reactivity regulation of reactants and further applications of the products. On one hand, this cycloisomerization of azaenyne features an additional cap in the formed heterocycle, which enables access to varieties of enantiomerically enriched atropisomers bearing five–five-membered heteroaryls *via* an oxidative central-to-axial chirality transfer strategy. On the other hand, the tethered nitrogen atom incorporated in the azaenyne served as an innate directing group of the product for late-stage modifications *via* transition metal catalyzed C–H functionalization. Various important functional groups were introduced into the centrally and axially chiral frameworks, demonstrating the appealing synthetic utilities of this powerful asymmetric cyclization.

Data availability

All the data have been included in the ESI.†

Author contributions

S. Qiu and X. Gao performed all the experiments. S. Qiu and S. Zhu contributed to the conception of the experiments, discussion of the results and preparation of manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1 For selected reviews on conjugated enynes, see: (a) H. Wang, Y. Kuang and J. Wu, *Asian J. Org. Chem.*, 2012, **1**, 302–312; (b) A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084–3213; (c) A. L. S. Kumari, A. S. Reddy and K. C. K. Swamy, *Org. Biomol. Chem.*, 2016, **14**, 6651–6671; (d) J. Ma, L. Zhang and S. Zhu, *Curr. Org. Chem.*, 2016, **20**, 102–118; (e) L. Li, D. Huang, C. Shi and G. Yan, *Adv. Synth. Catal.*, 2019, **361**, 1958–1984.

2 For selected reports on asymmetric cyclization reactions of enynone, see: (a) D. Zhu, J. Ma, K. Luo, H. Fu, L. Zhang and S. Zhu, *Angew. Chem., Int. Ed.*, 2016, **55**, 8452–8456; (b) J. Yang, Z. Li, M. Li, Q. He, S. Zhu and Q. Zhou, *J. Am. Chem. Soc.*, 2017, **139**, 3784–3789; (c) M. Huang, J. Yang, Y. Zhao and S. Zhu, *ACS Catal.*, 2019, **9**, 5353–5357; (d) K. Wang, Z. Liu, G. Xu, Y. Shao, S. Tang, P. Chen, X. Zhang and J. Sun, *Angew. Chem., Int. Ed.*, 2021, **60**, 16942–16946.

3 For selected nonchiral reports on cyclization reactions of azaeyne see: (a) D. B. Kimball, R. Herges and M. M. Haley, *J. Am. Chem. Soc.*, 2002, **124**, 1572–1573; (b) F. Nishino, K. Miki, Y. Kato, K. Ohe and S. Uemura, *Org. Lett.*, 2003, **5**, 2615–2617; (c) H. Shen, C. Li and R. Liu, *Tetrahedron Lett.*, 2004, **45**, 9245–9247; (d) C. Zhu, C. Feng and M. Yamane, *Chem. Commun.*, 2017, **53**, 2606–2609; (e) W. Wei, X. Li, M. Gu, H. Yao and A. Lin, *Org. Biomol. Chem.*, 2017, **15**, 8458–8462.

4 (a) H. Cerecetto, A. Gerpe, M. González, V. J. Arán and C. O. de Ocáriz, *Mini-Rev. Med. Chem.*, 2005, **5**, 869–878; (b) M. D. Angelis, F. Stossi, K. A. Carlson,

B. S. Katzenellenbogen and J. A. Katzenellenbogen, *J. Med. Chem.*, 2005, **48**, 1132–1144.

5 For selected reviews on this type of cyclization reaction, see:(*a*) L. D. Shirtcliff, T. J. R. Weakley and M. M. Haley, *J. Org. Chem.*, 2004, **69**, 6979–6985; (*b*) L. D. Shirtcliff, S. P. McClintock and M. M. Haley, *Chem. Soc. Rev.*, 2008, **37**, 343–364; (*c*) B. S. Young, R. Herges and M. M. Haley, *Chem. Commun.*, 2012, **48**, 9441–9455.

6 For selected reports on 6-*endo-dig* cyclization of azaenyne, see: (*a*) Q. Huang, J. A. Hunter and R. C. Larock, *Org. Lett.*, 2001, **3**, 2973–2976; (*b*) X. Fang, J. Cao, W. Ding, H. Jin, X. Yu and S. Wang, *Org. Lett.*, 2021, **23**, 1228–1233.

7 Y. Fang, C. Wang, S. Su, H. Yu and Y. Huang, *Org. Biomol. Chem.*, 2014, **12**, 1061–1071.

8 (*a*) L. Chen, K. Chen and S. Zhu, *Chem*, 2018, **4**, 1208–1262; (*b*) R. Wu, J. Lu, T. Cao, J. Ma, K. Chen and S. Zhu, *J. Am. Chem. Soc.*, 2021, **143**, 14916–14925.

9 For selected reviews on donor-donor carbenes, see: (*a*) D. Zhu, L. Chen, H. Fan, Q. Yao and S. Zhu, *Chem. Soc. Rev.*, 2020, **49**, 908–950; (*b*) B. D. Bergstrom, L. A. Nickerson, J. T. Shaw and L. W. Souza, *Angew. Chem., Int. Ed.*, 2021, **60**, 6864–6878, for selected reports, see references 2 and:; (*c*) J. Barluenga, L. Riesgo, R. Vicente, L. A. Llpez and M. Tomás, *J. Am. Chem. Soc.*, 2008, **130**, 13528–13529; (*d*) Y. Xia, S. Qu, Q. Xiao, Z. Wang, P. Qu, L. Chen, Z. Liu, L. Tian, Z. Huang, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 13502–13511; (*e*) J. González, J. González, C. Pérez-Calleja, L. A. López and R. Vicente, *Angew. Chem., Int. Ed.*, 2013, **52**, 5853–5857; (*f*) C. Soldi, K. N. Lamb, R. A. Squitieri, M. González-López, M. J. D. Maso and J. T. Shaw, *J. Am. Chem. Soc.*, 2014, **136**, 15142–15145; (*g*) H. Jin, B. Tian, X. Song, J. Xie, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2016, **55**, 12688–12692; (*h*) R. L. Sahani and R. Liu, *Angew. Chem., Int. Ed.*, 2017, **56**, 1026–1030; (*i*) F. Hong, Z. Wang, D. Wei, T. Zhai, G. Deng, X. Lu, R. Liu and L. Ye, *J. Am. Chem. Soc.*, 2019, **141**, 16961–16970; (*j*) L. Yang, D. Evans, B. Xu, W. Li, M. Li, S. Zhu, K. N. Houk and Q. Zhou, *J. Am. Chem. Soc.*, 2020, **142**, 12394–12399; (*k*) J. R. Jagannathan, J. C. Fettinger, J. T. Shaw and A. K. Franz, *J. Am. Chem. Soc.*, 2020, **142**, 11674–11679; (*l*) K. Dong, X. Fan, C. Pei, Y. Zheng, S. Chang, J. Cai, L. Qiu, Z. Yu and X. Xu, *Nat. Commun.*, 2020, **11**, 2363.

10 For selected reviews on the dirhodium (II) catalysed asymmetric C–H insertion reaction of metal carbenes, see: (*a*) H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861–2904; (*b*) M. P. Doyle, *J. Org. Chem.*, 2006, **71**, 9253–9260; (*c*) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704–724; (*d*) H. M. L. Davies and K. Liao, *Nat. Rev. Chem.*, 2019, **3**, 347–360.

11 (*a*) S. Ishii, S. Zhao, G. Mehta, C. J. Knors and P. Helquist, *J. Org. Chem.*, 2001, **66**, 3449–3458; (*b*) M. Honma and M. Nakada, *Tetrahedron Lett.*, 2003, **44**, 9007–9011.

12 For selected reviews, see: (*a*) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*; Wiley, New York, 1994; (*b*) M. C. Kozlowski, B. J. Morgan and E. C. Linton, *Chem. Soc. Rev.*, 2009, **38**, 3193–3207; (*c*) G. Bring-mann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563–639; (*d*) *Privileged Chiral Ligands and Catalysts*, ed. Q. Zhou, Wiley-VCH, Weinheim, Germany, 2011; (*e*) J. E. Smyth, N. M. Butler and P. A. Keller, *Nat. Prod. Rep.*, 2015, **32**, 1562–1583.

13 (*a*) D. Bonne and J. Rodriguez, *Chem. Commun.*, 2017, **53**, 12385–12393; (*b*) D. Bonne and J. Rodriguez, *Eur. J. Org. Chem.*, 2018, 2417–2431; (*c*) S. Zhang, Q. Yao, G. Liao, X. Li, H. Li, H. Chen, X. Hong and B. Shi, *ACS Catal.*, 2019, **9**, 1956–1961.

14 D. L. Davies, C. E. Ellul, S. A. Macgregor, C. L. McMullin and K. Singh, *J. Am. Chem. Soc.*, 2015, **137**, 9659–9669.

15 H. Wang, N. Schrçder and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 5386–5389.

16 F. Xie, Z. Qi, S. Yu and X. Li, *J. Am. Chem. Soc.*, 2014, **136**, 4780–4787.

17 J. A. Boerth, J. R. Hummel and J. A. Ellman, *Angew. Chem., Int. Ed.*, 2016, **55**, 12650–12654.

18 Y. Liang, Y. Liang, C. Tang, Y. Yuan and N. Jiao, *Chem.–Eur. J.*, 2015, **21**, 16395–16399.

19 S. Yu, B. Wan and X. Li, *Org. Lett.*, 2015, **17**, 58–61.