

Cite this: *Chem. Sci.*, 2023, 14, 7291

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Cobalt-catalyzed enantioselective C–H/N–H annulation of aryl sulfonamides with allenes or alkynes: facile access to C–N axially chiral sultams†

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Herein we report a cobalt-catalyzed enantioselective C–H/N–H annulation of aryl sulfonamides with allenes and alkynes, using either chemical or electrochemical oxidation. By using O₂ as the oxidant, the annulation with allenes proceeds efficiently with a low catalyst/ligand loading of 5 mol% and tolerates a wide range of allenes, including 2,3-butadienoate, allenylphosphonate, and phenylallene, resulting in C–N axially chiral sultams with high enantio-, regio-, and position selectivities. The annulation with alkynes also exhibits excellent enantiocontrol (up to >99% ee) with a variety of functional aryl sulfonamides, and internal and terminal alkynes. Furthermore, electrochemical oxidative C–H/N–H annulation with alkynes is achieved in a simple undivided cell, demonstrating the versatility and robustness of the cobalt/Salox system. The gram-scale synthesis and asymmetric catalysis further highlight the practical utility of this method.

Received 6th April 2023

Accepted 8th June 2023

DOI: 10.1039/d3sc01787g

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Introduction

Atropisomerism, a type of chirality arising from sterically hindered rotation around a single sigma bond, has become an interesting and cutting-edge field due to its intriguing characteristics.¹ In this context, the enantioselective assembly of C–N axially chiral skeletons, which possess appealing agricultural and medicinal activities^{2,3} (Fig. 1a), has received considerable attention in recent years.^{4–9} While numerous methods have been developed for the synthesis of C–N axially chiral anilides,^{10–13} the straightforward construction of C–N axially chiral sulfonamide continues to be underdeveloped despite its promising applications in the treatment of pain.¹⁴ Currently, the known method remains predominantly confined to the atroposelective N–H functionalization of sulfonamides by employing organic or transition-metal catalysts,^{15–20} pioneered by Taguchi²¹ and Curran,²² for Pd-catalyzed enantioselective *N*-allylation. Therefore, given the importance of chiral sulfonamides and their limited synthetic methods, the development of efficient and practical strategies to access enantioenriched C–N axially chiral sulfonamides is highly desirable.

Transition metal-catalyzed enantioselective C–H functionalization is a powerful tool for accessing valuable chiral molecules in a straightforward and atom-economic manner.^{23–29} Among the first-row 3d transition metals, cobalt-catalyzed enantioselective C–H activation has gained increasing attention due to its abundant reserves, low toxicity, and unique reactivity.^{30–36} The Ackermann,³⁷ Shi,^{38–40} Cramer,^{41–43} Yoshino and Matsunaga^{44–47} groups have made significant advances by using a high-valent Cp^XCo^{III} catalyst with the carboxylic acid (CCA) ligand. The Lautens,⁴⁸ Yoshikai,^{49,50} and Wencel-Delord⁵¹ groups developed asymmetric low-valent cobalt-catalyzed systems. Recently, growing attention has been turned to the use of readily available cobalt salt catalysts and flexibly tunable chiral ligands (such as, salicyl-oxazoline, Salox). In 2022, the Shi group^{52–56} and our group^{57–59} have independently developed cobalt/Salox-catalyzed asymmetric C–H functionalization to assemble axially chiral, *C*- and *P*-stereogenic frameworks, using carboxylic amides or arylphosphinamides as substrates (Fig. 1b). Recently, the Shi,^{55,56} Ackermann,^{60–62} and Ling⁶³ groups have accomplished these transformations under electrochemical conditions. However, the direct activation of sulfonamide derivatives to construct enantioenriched sultam derivatives has not been reported yet.

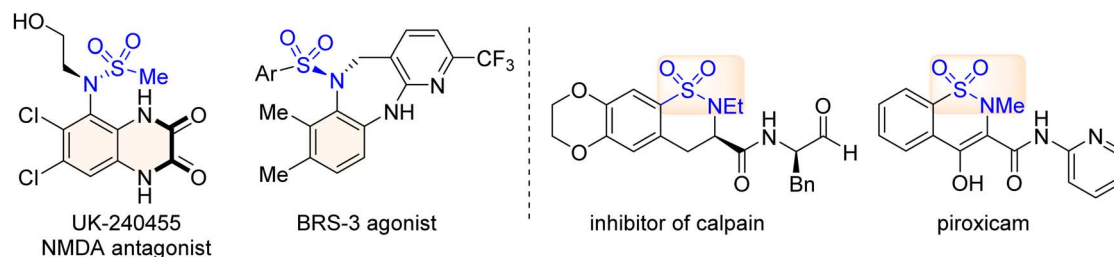
Inspired by the pioneering achiral cobalt-catalyzed C–H activation/annulation reported by Ribas,⁶⁴ Rao,⁶⁵ Volla,⁶⁶ Lei⁶⁷ and Zhang,⁶⁸ herein we aimed to develop a Co^{II}/Salox catalyzed enantioselective C–H annulation of 8-aminoquinoline-directed^{69,70} aryl sulfonamides with allenes or alkynes, for the construction of C–N axially chiral sultam-based scaffolds,^{71,72} which are promising motifs in agrochemicals, pharmaceuticals (e.g. piroxicam) and biologically active molecules.^{73–75} Nevertheless, this asymmetric system faces several challenges: (1) the non-

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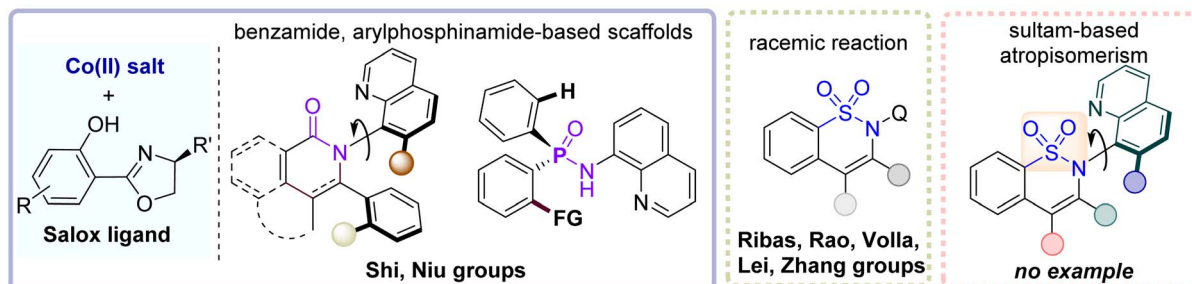
† Electronic supplementary information (ESI) available: General information, experimental section, X-ray crystallographic data, compound characterization, and NMR spectra (PDF). CCDC 2241825 (for 4aa) and 2248260 (for 5aa). For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3sc01787g>

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a) Representative chiral sulfonamides or sultams in medicine



b) Previous cobalt-catalyzed asymmetric and achiral C-H functionalization



c) This work: cobalt-catalyzed chemo- or electro-oxidative asymmetric C-H activation/annulation of aryl sulfonamides

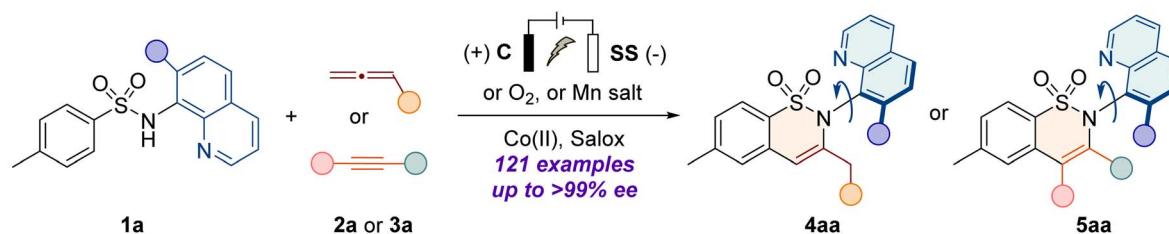


Fig. 1 Background and project synopsis.

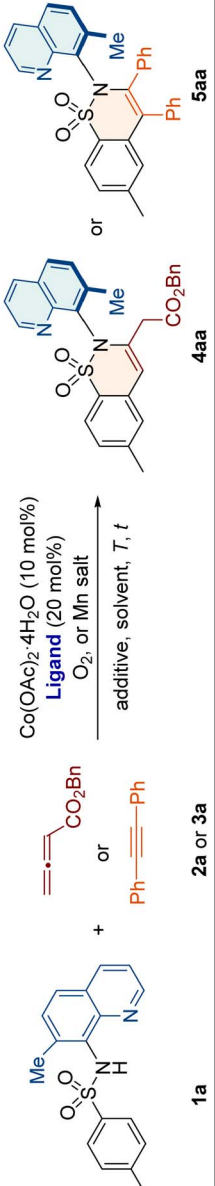
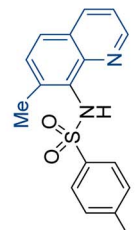
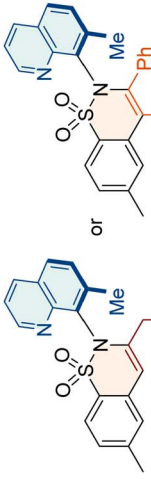
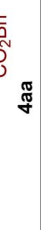
aromatic nature and the flexibility of sultam frameworks make the construction of axial chirality more challenging; (2) the regioselective annulation across two different C=C double bonds of allenes⁷⁶ can lead to the feasible synthesis of either C-stereogenic or C-N axially chiral scaffolds. Controlling both the regio- and enantio-selectivity is therefore crucial. For example, the Volla and Maiti group reported that the variation of the electronic nature of allenes resulted in the change of the annulation pattern for cobalt catalysis.⁷⁷ (3) Simultaneous compatibility of both allene and alkyne coupling partners in one protocol is appealing yet challenging. Herein, we report an efficient cobalt catalyzed enantioselective C-H/N-H activation/annulation of aryl sulfonamides with allenes and alkynes to access C-N axially chiral sultams (Fig. 1c). The reaction proceeded smoothly with cheap cobalt(II) salt as the catalyst, and environmental green O₂ or commercial Mn salts as the oxidant. The annulation with alkynes was also achieved under constant-current electrolysis (CCE) conditions with high efficiency and enantiocontrol. Typically, a broad class of electron-poor and electron-rich allenes (e.g. 2,3-butadienoate, allenylphosphonate, and phenylallene), and internal or terminal alkynes were well tolerated to deliver C-N axially chiral sultams with high enantio-, regio- and position selectivities (121 examples, up to >99% ee).

Results and discussion

Optimization of the reaction conditions

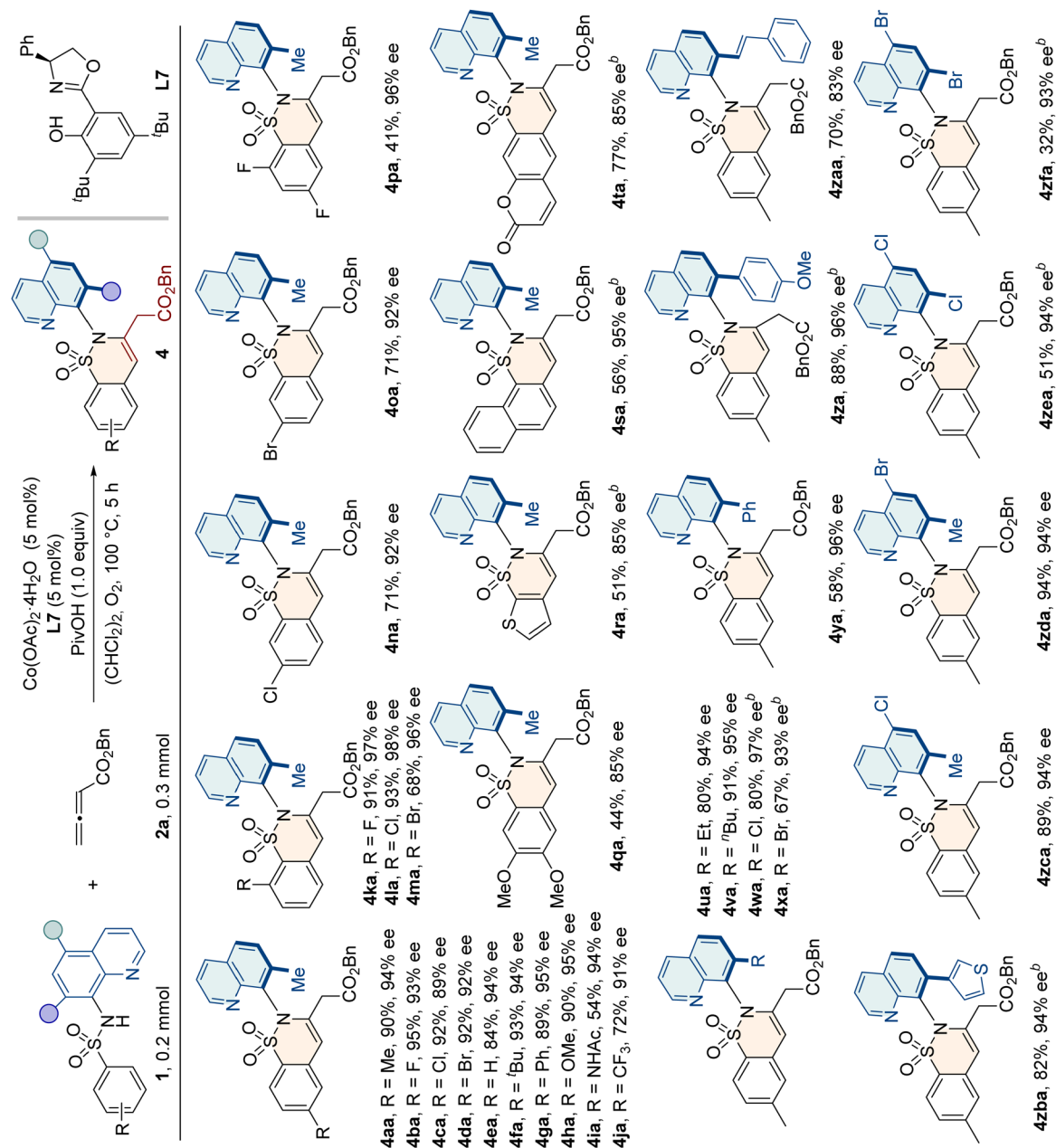
The reaction was initiated using sulfonamide **1a** and ester-substituted allene **2a**, with Co(OAc)₂·4H₂O as the catalyst and O₂ as the oxidant (Table 1). When the chiral ligand salicyloxazoline **L1** was used, the desired C-N axially chiral sultam **4aa** was obtained as a single regioisomeric product with 90% yield and 70% ee. Further evaluation of the Salox ligand showed that **L7**, bearing bulky *tert*-butyl substituents on the phenol-ring, gave a promising enantioselectivity of 95% ee. Moreover, after screening solvents, additives, and catalyst/ligand loadings, the desired **4aa** was obtained in 90% yield and 94% ee with a low catalyst loading of 5 mol% and O₂ as the oxidant. When alkyne **3a** was employed as the coupling partner, the C-N axially chiral product **5aa** was formed with 91% yield and 98% ee under optimized conditions, with **L7** as the chiral ligand and Mn(OAc)₃·2H₂O as the oxidant. The absolute configurations of **4aa** and **5aa** were confirmed as *R_a* by X-ray crystallography. Control experiments suggest that the methyl group at the C7 position of the quinoline ring is crucial for improving efficiency and meanwhile generating the axial chirality in the transformation (Scheme S1 in the ESI†).

Table 1 Optimization studies^a

		2a or 3a	
1a	5aa	4aa	5aa
			
L1	L5	L4	L5
4aa, 90%, 70% ee	4aa, 31%, 31% ee	4aa, trace	4aa, 31%, 31% ee
5aa, 26%, 96% ee	4aa, 15%, 81% ee	5aa, trace	4aa, 15%, 81% ee
L2	L3	L3	L3
4aa, 65%, 4% ee	4aa, 34%, 15% ee	4aa, 34%, 15% ee	4aa, 34%, 15% ee
5aa, 8%, 75% ee	5aa, 8%, 66% ee	5aa, 8%, 66% ee	5aa, 8%, 66% ee
L6	L7	L7	L7
4aa, 25%, 75% ee	4aa, 19%, 95% ee	4aa, 19%, 95% ee	4aa, 19%, 95% ee
5aa, 34%, 95% ee	5aa, 41%, 99% ee	5aa, 41%, 99% ee	5aa, 41%, 99% ee
L8	L9	L9	L9
4aa, 85%, 72% ee	4aa, 85%, 71% ee	4aa, 85%, 71% ee	4aa, 85%, 71% ee
5aa, 25%, 95% ee	5aa, 23%, 95% ee	5aa, 23%, 95% ee	5aa, 23%, 95% ee
L10	L10	L10	L10
4aa, 53%, 44% ee	4aa, 53%, 44% ee	4aa, 53%, 44% ee	4aa, 53%, 44% ee
5aa, 39%, 97% ee	5aa, 39%, 97% ee	5aa, 39%, 97% ee	5aa, 39%, 97% ee

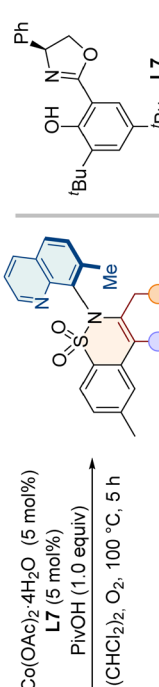
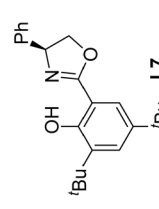
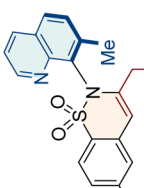
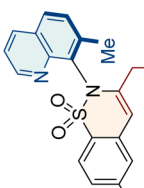
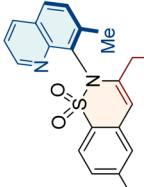
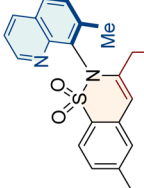
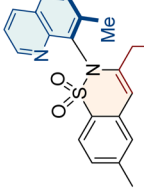
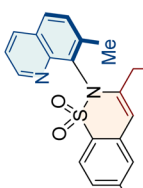
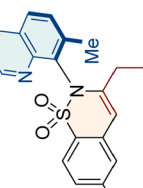
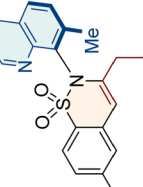
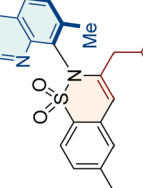
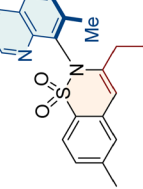
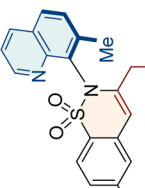
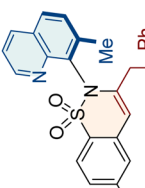
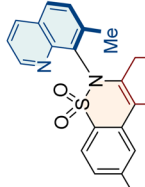
^a Reaction conditions for 4aa: 1a (0.1 mmol), 2a (0.3 mmol), Co(OAc)₂·4H₂O (10 mol%), L (20 mol%), dioxane (1.0 mL), O₂, 100 °C, and 5 h; reaction conditions for 5aa: 1a (0.1 mmol), 3a (0.2 mmol), Co(OAc)₂·4H₂O (10 mol%), L (20 mol%), Mn(OAc)₃·2H₂O (0.1 mmol), MeOH (1 mL), air, 100 °C, and 6 h. Isolated yields. ^b 1a (0.2 mmol), Co(OAc)₂·4H₂O (5 mol%), L (5 mol%), PivOH (1.0 equiv.), (CHCl₃)₂ (2.0 mL), O₂, 100 °C, and 5 h. ^c 1a (0.2 mmol), Co(OAc)₂·4H₂O (10 mol%), L (20 mol%), Mn(OAc)₃·2H₂O (1.0 equiv.), NaOPiv (1.0 equiv.), MeOH (2 mL), air, 100 °C, and 36 h. The ee values were determined by chiral HPLC analysis.



Table 2 Scope of aryl sulfonamides for the annulation with allenes^a

^a Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), Co(OAc)₂·4H₂O (5 mol%), L7 (5 mol%), PivOH (1.0 equiv.), (CHCl₃)₂ (2 mL), O₂, 100 °C, 5 h, and isolated yields. ^b Co(OAc)₂·4H₂O (10 mol%), L7 (10 mol%), and 10 h.

Table 3 Scope of allenes^a

			
1a, 0.2 mmol	2, 0.3 mmol		
		4ab, 86%, 97% ee	
		4ac, 86%, 92% ee	
		4ad, 93%, 90% ee	
		4ae, 86%, 90% ee	
		4af, 52%, 91% ee	
		4ag, 60%, 93% ee ^b	
		4ah, 55%, 92% ee ^b	
		4ai, 72%, 91% ee ^b	
		4aj, 62%, 92% ee ^b	
		4ak, 62%, 90% ee ^b	
		4al, 64%, 84% ee ^b	
		4am, 50%, 77% ee ^b	
		4an, 35%, 91% ee	

^a Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), Co(OAc)₂·4H₂O (5 mol%), L7 (5 mol%), and PivOH (1.0 equiv.) in (CHCl₂)₂ (2 mL) under O₂ at 100 °C for 5 h. ^b Co(OAc)₂·4H₂O (10 mol%), L7 (20 mol%), and 5 h.



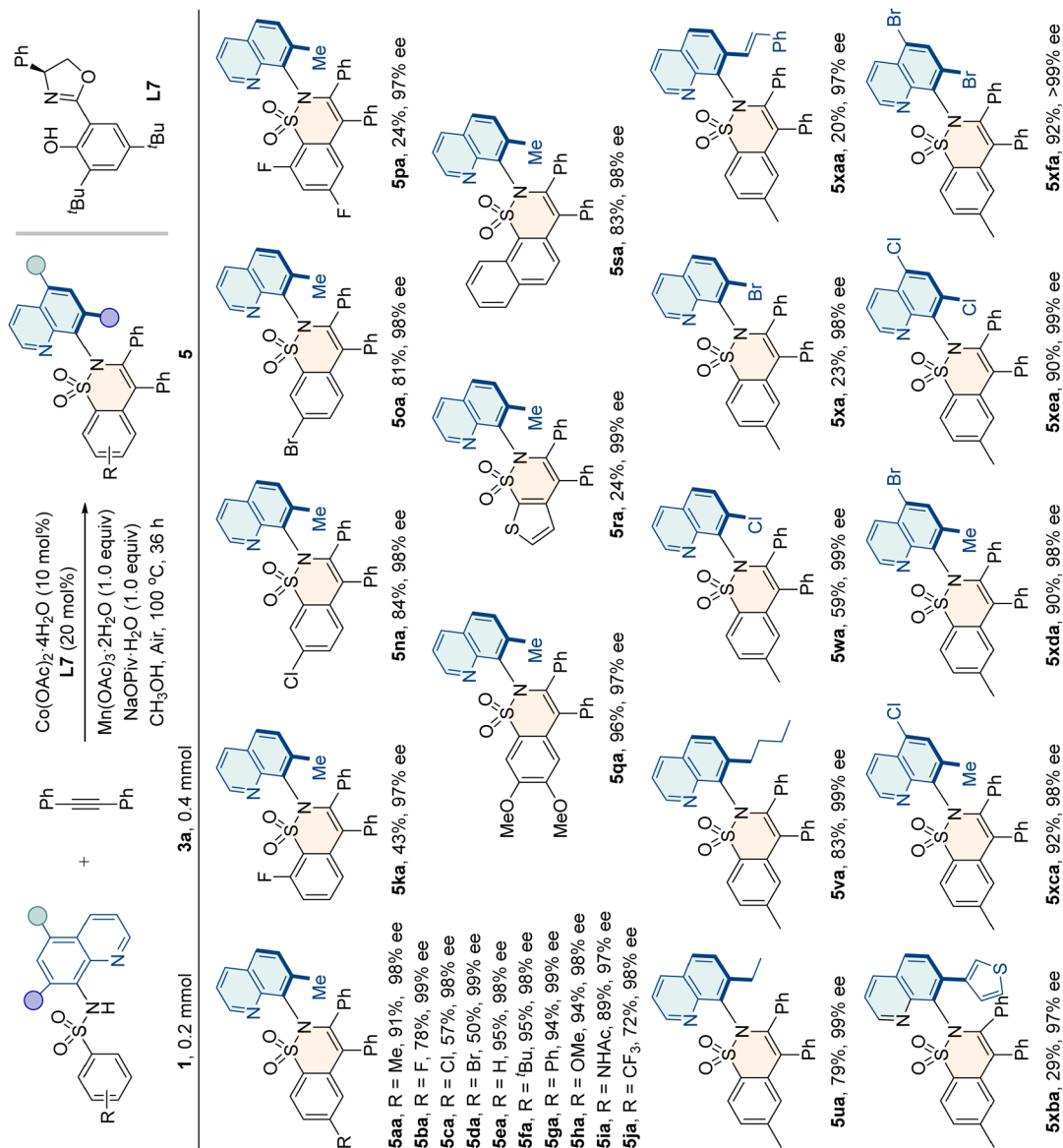
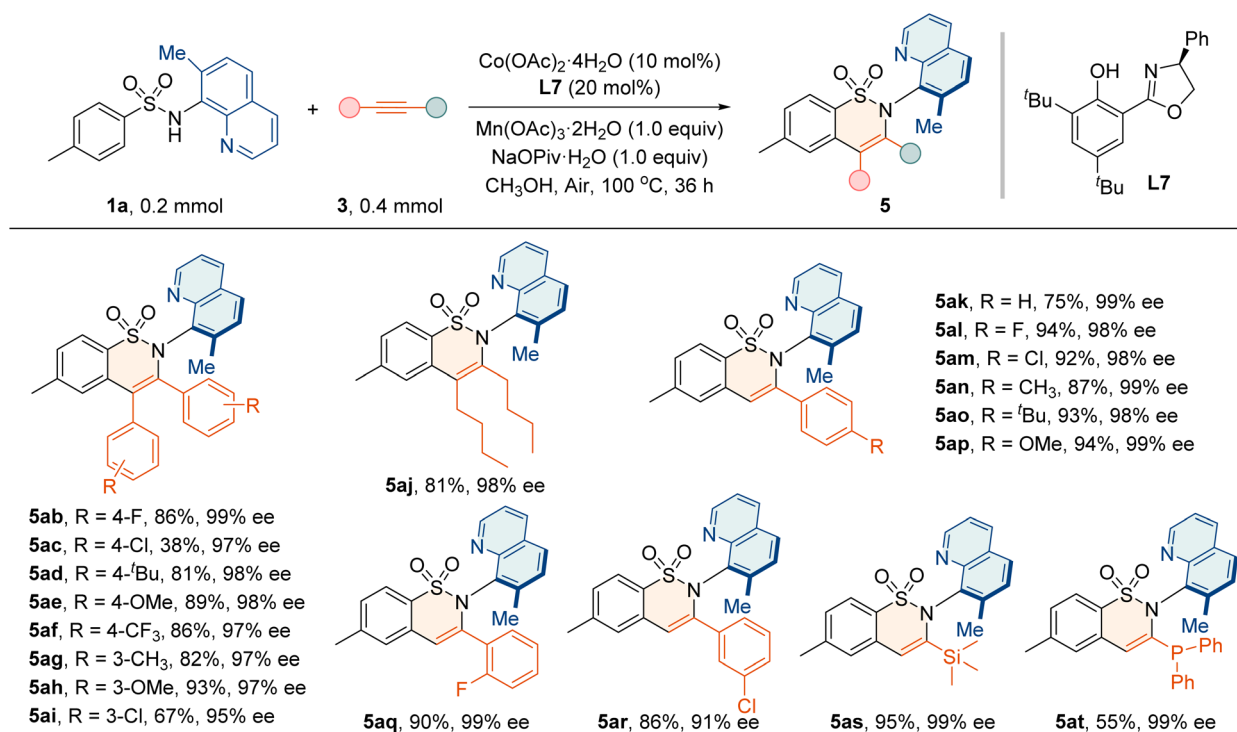
Table 4 Scope of aryl sulfonamides for annulation with alkynes^a^a Reaction conditions: **1** (0.2 mmol), **3a** (0.4 mmol), $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (10 mol%), **L7** (20 mol%), $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (0.2 mmol), and $\text{NaOPiv} \cdot \text{H}_2\text{O}$ (0.2 mmol) in MeOH (2 mL) at 100 °C for 36 h.

Table 5 Scope of alkynes^a

^a Reaction conditions: **1a** (0.2 mmol), **3** (0.4 mmol), Co(OAc)₂·4H₂O (10 mol%), **L7** (20 mol%), Mn(OAc)₃·2H₂O (0.2 mmol), and NaOPiv·H₂O (0.2 mmol) in MeOH (2 mL) at 100 °C for 36 h.

Scope of the substrates

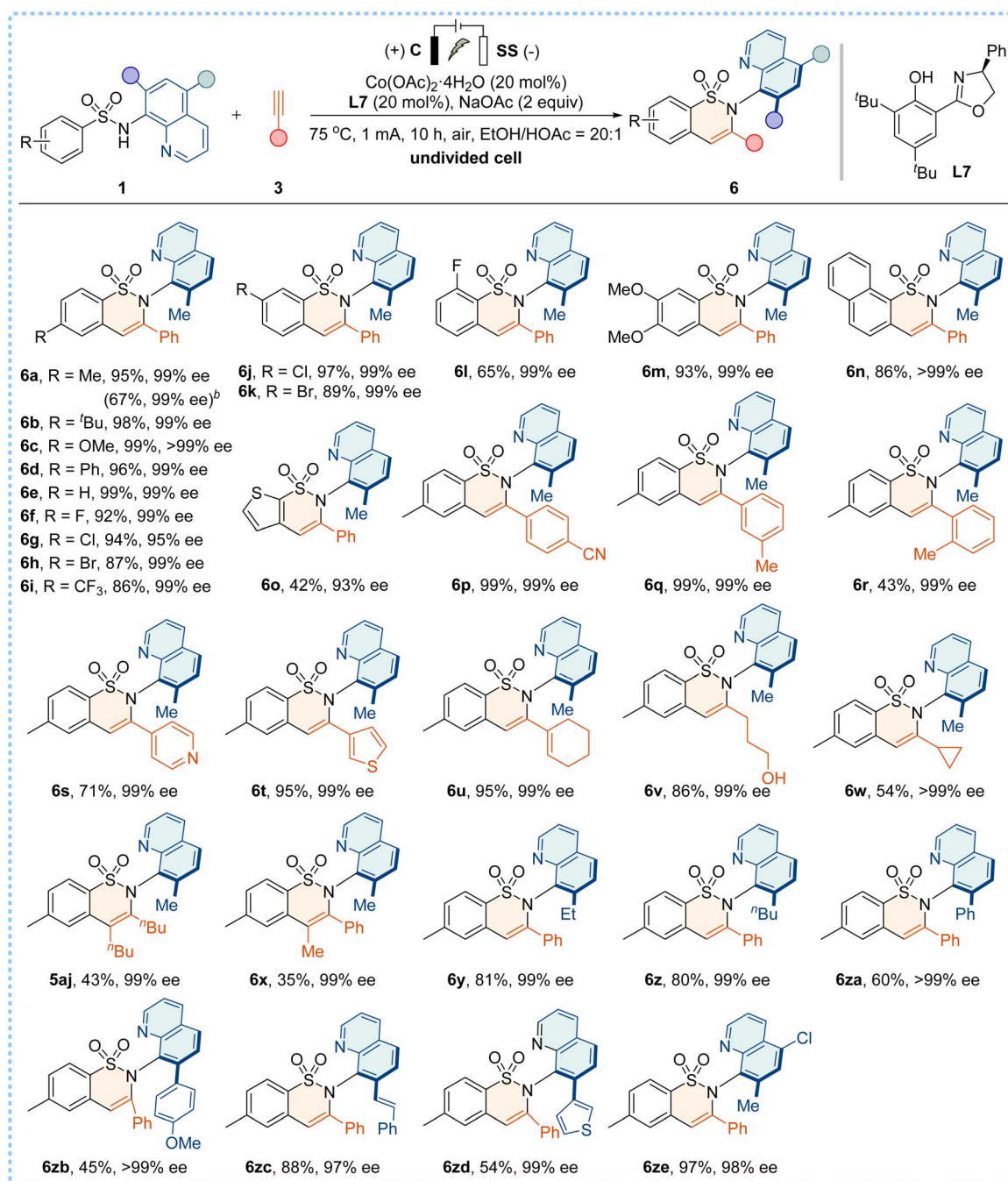
With the optimized conditions in hand, we evaluated the potential of sulfonamide substrates for annulation with allenes (Table 2). A variety of functional groups, including electron-donating (–alkyl, –Ph, –OMe, and –NHAc) or electron-withdrawing (–F, –Cl, –Br, and –CF₃) groups at the *para*-position of the aryl ring, were well tolerated, and the resulting products **4aa–4ja** were obtained with good yields and enantioselectivities. *Ortho*-substituted sulfonamides **1k–1m** also reacted smoothly, delivering **4ka–4ma** with excellent enantiopurities of 96–98% ee. Substitution on the *meta*-position allowed the reaction to occur exclusively on the less hindered position, giving products **4na** and **4oa** with 71% yields and 92% ee values. Additionally, disubstituted sulfonamides were applicable to deliver the products with good efficiency. Generally, the protocol was also compatible with naphthyl, heterocyclic, and coumarin sulfonamides, producing the desired **4ra–4ta** with good yields and enantioselectivities. To further investigate the method's applicability, we evaluated sulfonamide substrates with diverse groups at the C5 or C7 position of the quinoline ring. We were pleased to find that substrates bearing alkyl (–Et and –*n*-Bu) or halogen groups (–Cl and –Br) at the C7 position of the quinoline ring reacted smoothly, giving the C–N axially chiral products **4ua–4xa** with good yields (67–91%) and excellent enantioselectivities (93–97% ee). The introduction of bulky substituents, such as phenyl, 4-methoxyphenyl, styryl, and thienyl groups, also gave the

desired products **4ya–4zba** with comparable efficiency. Furthermore, substrates with functional groups (–Cl and –Br) at the C5 position or at both C5 and C7 positions of the quinoline ring were also applicable in this protocol, with a high level of enantioselectivities (**4zca–4zfa**, 93–94% ee).

We proceeded to evaluate the scope of allenes, as shown in Table 3. When the benzyl group was replaced with other alkyl groups, such as methyl, ethyl, isopropyl, *n*-butyl and *t*-butyl, the products were obtained in good yields (52–93%) and high enantioselectivities (90–97% ee). Notably, in addition to ester-substituted allenes, electron-rich allenes were also examined in this protocol. Phenylallenes **2g** and **2h–2k** bearing electron-withdrawing or donating groups all reacted smoothly under slightly modified conditions to give products **4ag–4ak** with high enantiopurities of 90–93% ee. Benzyl-substituted allene **2l** was also compatible in this reaction. Additionally, other electron deficient allene partners, such as allenyl phosphonate **2m**, underwent annulation to give **4am** as the single regioisomeric product, albeit with a slightly lower ee value. For the internal disubstituted allene **2n**, the methyl group and the ester group were accurately recognized, and the C–N axially chiral product **4an** was formed with a high enantioselectivity of 91% ee.

Furthermore, the scope for the annulation of sulfonamides with alkynes was examined, as shown in Table 4. Generally, sulfonamide substrates bearing electron-donating (–alkyl, –Ph, –OMe, and –NHAc) or electron-withdrawing groups (–X and –CF₃)



Table 6 Reaction scope for electro-oxidative annulation^a

^a Reaction conditions: carbon cloth (15 mm × 20 mm × 0.33 mm) anode, stainless steel plate (15 mm × 20 mm × 1.0 mm) cathode, constant current = 1 mA, sulfonamides **1** (0.25 mmol) and **3** (0.5 mmol), $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (20 mol%), **L7** (20 mol%), EtOH (10.0 mL), HOAc (0.5 mL), NaOAc (2.0 equiv.), 75 °C, 10 h, air, and isolated yields. ^b Gram scale reaction using 3 mmol of **1a**.

at the *para*-, *ortho*-, and *meta*-positions of the aryl ring reacted smoothly to give the corresponding products **5aa–5oa** in moderate to good yields (43–95%) and excellent enantioselectivities (97–99% ee). The protocol also tolerated disubstituted sulfonamides, furnishing the desired products with high enantiocontrol (97% ee). Additionally, naphthyl and heterocyclic thienyl sulfonamides were compatible with this method.

Moreover, sulfonamides bearing substituents at the C5 or both the C5 and C7 positions of the quinoline ring could also furnish the products **5ua–5xfa** with a high level of enantioselectivities (97–>99% ee).

Next, the generality of alkynes **3a** with various substitutions was investigated (Table 5). A wide range of diarylacetylenes bearing electron-rich or -deficient groups underwent the



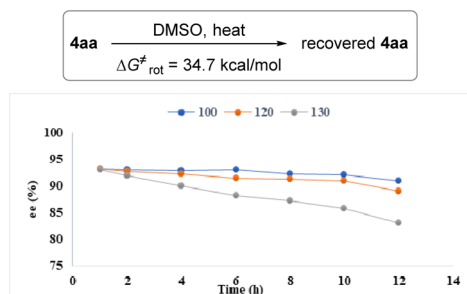
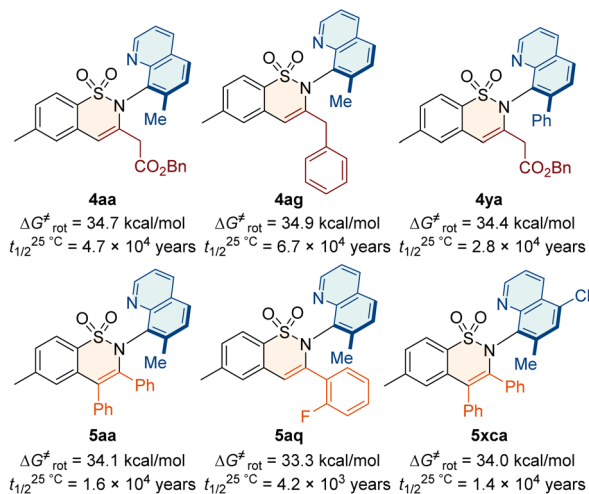
a) the ee values of compound **4aa** in DMSO at 100 °C, 120 °C and 130 °Cb) The rotation barrier and the $t_{1/2}$ of **4aa**, **4ag**, **4ya**, **5aa**, **5aq**, **5xca**

Fig. 2 Study on stereochemical stability.

reaction with high enantioselectivities (**5ab–5ai**, 95–99% ee). The aliphatic internal alkynes also reacted smoothly to deliver **5aj** in 81% yield and 98% ee. Moreover, the annulation proceeded effectively with terminal alkynes **3k–3r** containing electron-withdrawing and electron-donating substituents, affording **5ak–5ar** in good yields (75–94%) and high enantiopurities (91–99% ee). The trimethylsilylacetylene **3s** and diphenylphosphinoacetylene **3t** were also well tolerated, giving annulation products **5as** and **5at** with 99% ee values, which provides an opportunity for further asymmetric transformation and application.

We were pleased to discover that the electrooxidative Co/Salox catalyzed enantioselective C–H annulation of **1a** with alkyne **3k** yielded the desired C–N axially chiral product **5ak** with 95% yield and an excellent enantioselectivity of 99% ee, when conducted in an undivided cell setup equipped with a carbon cloth (C) anode and a stainless steel (SS) plate cathode under optimized conditions (for details, see the ESI†). Control experiments confirmed that the omission of electricity or the cobalt catalyst resulted in complete inactivity of the asymmetric annulation. Subsequently, the robustness of the electrochemical C–H annulation was demonstrated by using a broad range of sulfonamides and terminal alkynes (Table 6). Both electron-donating and electron-withdrawing substituents were compatible, delivering products **6a–6l** with 65–99% yields and 95–>99% ee values. Disubstituted, naphthyl and thienyl

sulfonamides were also suitable partners to give **6m–6o** with high enantioselectivities. In addition, phenylacetylene alkynes bearing functional groups, heterocycle-substituted alkynes (such as 4-ethynylpyridine and 3-ethynylthiophene), and conjugated enyne and aliphatic alkynes all reacted smoothly to afford the desired products **6p–6w** with good yields and excellent enantiocontrol. Moreover, the annulation proceeded effectively with internal alkynes (5-decyne or phenylpropyne), affording **5aj** and **6x** in high enantiopurities (99% ee). However, the use of diphenylacetylene is ineffective in this protocol, probably due to the steric hindrance. Furthermore, sulfonamides bearing substituents at the C7 position (such as alkyl, aryl, styryl, and heteroaromatic thienyl groups) or at the C5 position were well tolerated under this electrochemical system, and the corresponding products **6y–6ze** were obtained with good efficiency. The reaction was conducted on a gram scale using 3 mmol of **1a** and the product **6a** was obtained with a 67% yield and 99% ee (see the ESI†).

Study on the product stability

To investigate the stereochemical stability of the C–N axially chiral sulfonamides, we conducted racemization experiments (Fig. 2). First, we heated the compound **4aa** in DMSO at 100 °C, 120 °C and 130 °C and recorded the ee values at different times ranging from 1–12 h. The ee value of **4aa** decreased by 11% after 12 hours at 130 °C (Fig. 2a). The rotational energy barrier of **4aa** was calculated to be 34.7 kcal mol^{−1}, and its half-life ($t_{1/2}$) was up to 4.7×10^4 years at 25 °C. The effect of the substituted groups on stereochemical stability was also investigated. Accordingly, we calculated the rotational energy barrier and the $t_{1/2}$ of **4ag**, **4ya**, **5aa**, **5aq**, and **5xca** in DMSO at 130 °C (Fig. 2b). The results showed that the C–N axially chiral sulfonamides feature high atropostabilities.

Mechanistic investigation and synthetic application

To elucidate the mechanism, we conducted a series of control experiments (Fig. 3). The atroposelective synthesis of **4aa** and **5aa** was successfully carried out on gram scales without any loss of enantioselectivities (Fig. 3a). H/D exchange experiments under standard conditions for the synthesis of **4aa** indicate that the C–H bond cleavage was irreversible (Fig. 3b, left). The competitive kinetic isotope effect (KIE) value of 1.6 and the parallel KIE value of 1.8 suggested that the C–H bond cleavage might be the rate-determining step (Fig. 3c, left).

Similarly, H/D exchange experiments under conditions for the synthesis of **5aa** were performed and a competitive KIE value of 2.0 was observed, indicating that the C–H bond cleavage might also be involved in the rate-determining step (Fig. 3b and c, right). Furthermore, a control experiment by using deuterated allenes **2a–D** was carried out, and the deuterium labeling of product **4aa** was found at the α -position of the ester group (Fig. 3d). This illustrated that the formation of **4aa** might involve a 1,3-hydrogen migration step. Additionally, we demonstrated the asymmetric application of the C–N axially chiral product **5at** containing a monophosphine skeleton as a suitable chiral ligand for the Pd-catalyzed asymmetric Tsuji–



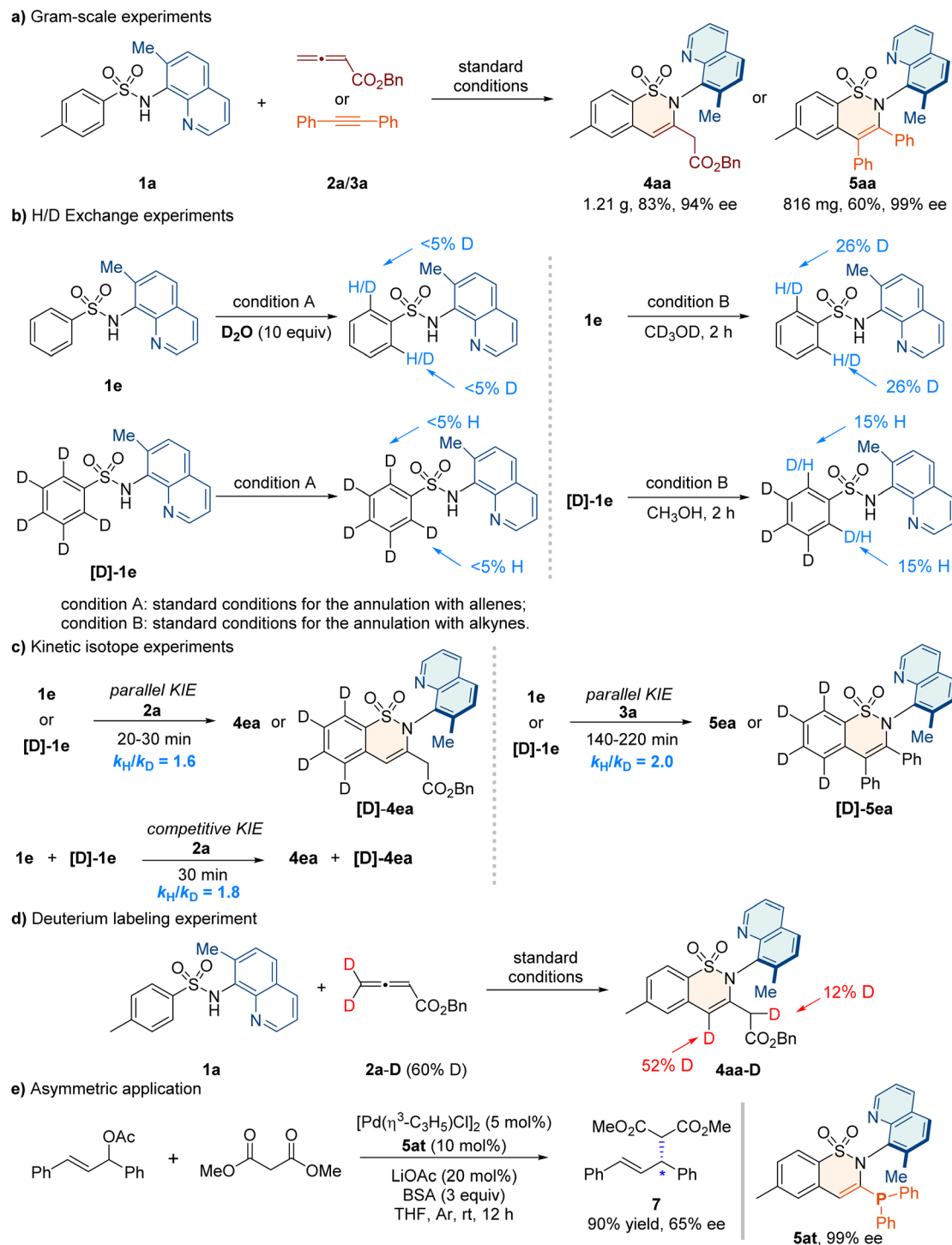


Fig. 3 Mechanistic studies and synthetic application.

Trost reaction, and the product **7** was obtained with a 90% yield and 65% ee (Fig. 3e).⁷⁸

Based on the previous cobalt-catalyzed C–H activation of aryl sulfonamides,^{64–68} the electrochemical C–H/N–H annulations⁷⁹ and the above control experiments, we propose a plausible mechanism for annulation with allenes or alkynes (Fig. 4). Initially, the oxidation of cobalt salt (ii) produces Co(III)-species,

which undergoes ligand exchange and C–H activation to form the key intermediate **A**. Subsequently, the allene **2a** or alkyne **3** coordinates with **A** and inserts into the C–Co bond to form the seven-membered intermediate **B** or **B'**. The reductive elimination of **B** leads to the cyclic compound **C**, which undergoes 1,3-hydrogen migration to deliver product **4aa**. The reductive elimination of **B'** releases product **5** or **6**. Finally, the generated



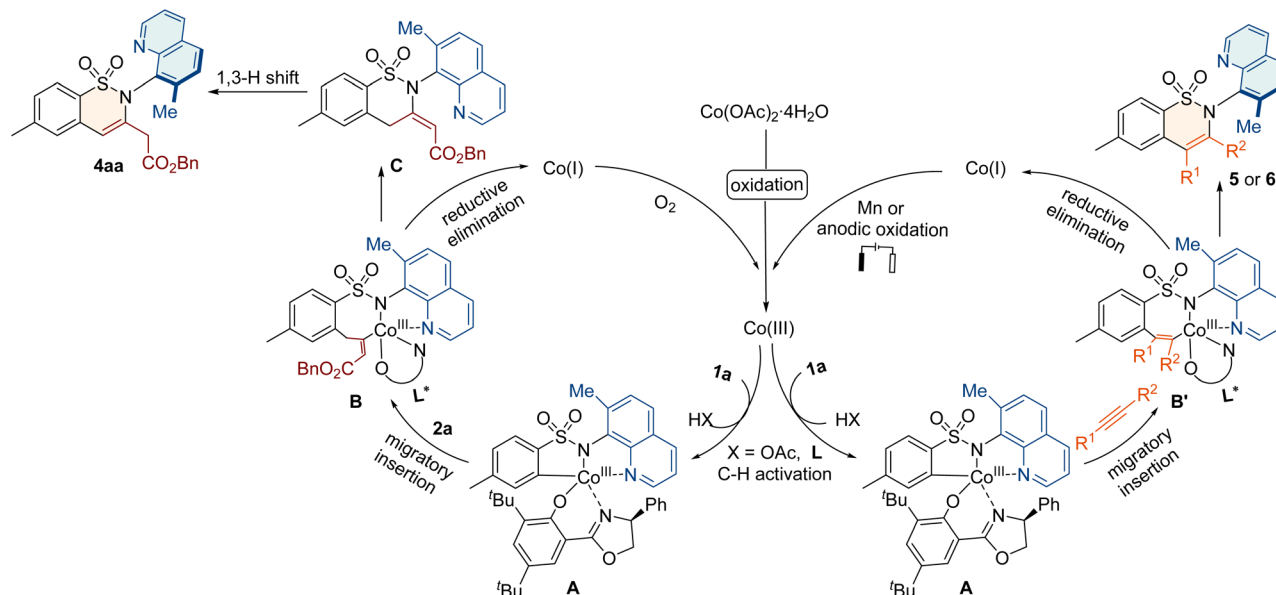


Fig. 4 Proposed mechanism.

Co(I) species is further oxidized to Co(III) for the new catalytic cycle.

Conclusions

To conclude, we have developed a highly efficient Co/Salox-catalyzed enantioselective C–H activation/annulation of sulfonamides with allenes or alkynes for the synthesis of C–N axially chiral sultams. In terms of the annulation with allenes, the reaction proceeds with O₂ as the oxidant and a low catalyst loading of 5 mol% and tolerates broad allene substrates with high regio- and enantio-selectivities. For the annulation with alkynes, the protocol exhibited good functional group tolerance and excellent enantiocontrol. Typically, by utilizing anodic oxidation in an undivided cell to recycle the cobalt catalyst, the asymmetric C–H/N–H annulation of sulfonamides with alkynes was efficiently achieved for the construction of C–N axially chiral skeletons. These results demonstrate the versatility and robustness of cobalt/Salox asymmetric catalysis, and we are actively exploring its further applications in our laboratory.

Data availability

The data supporting the findings of this work are available within the main article and the ESI.†

Author contributions

X.-J. S., X. Z., and J. W. contributed equally to this work. J.-L. N. and D. Y. conceived the concept and prepared the manuscript. X.-J. S., X. Z., J. W., X. W., and Y. Z. conducted the experiments and analyzed the data. M.-P. S. provided revisions. J.-L. N. and D. Y. directed the project.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We acknowledge the support of the National Natural Science Foundation of China (22271260 to J.-L. N.), and Natural Science Foundation of Henan Province (222300420291 to D. Y.).

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