



Cite this: *Chem. Commun.*, 2025, 61, 8240

Received 6th March 2025,
Accepted 29th April 2025

DOI: 10.1039/d5cc01230a

rsc.li/chemcomm

Harnessing sulfilimine as an oxidizing directing group in Cp*Co(III)-catalyzed [4+2] annulation with alkynes and 1,3-diynes†

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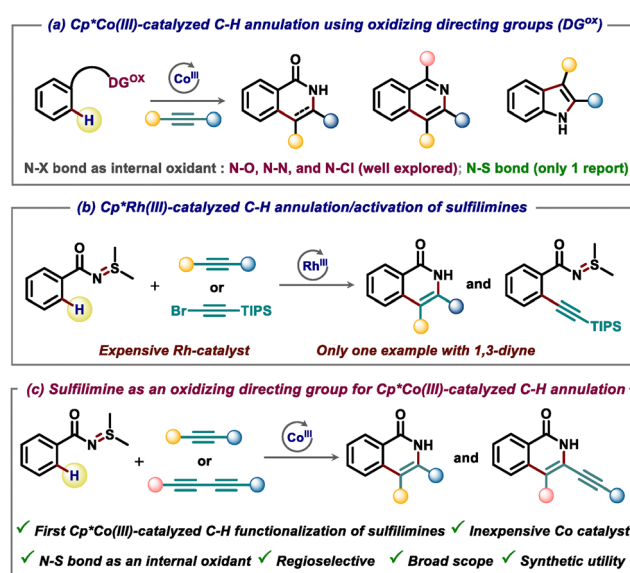
We have developed the first Cp*Co(III)-catalyzed [4+2] annulation utilizing sulfilimine as an oxidizing directing group in a redox-neutral fashion. The N–S bond of the sulfilimine serves as an internal oxidant, thereby eliminating the need for any internal oxidant. The reaction worked with various alkynes and also exhibited an excellent regioselectivity with 1,3-diynes furnishing the 3-alkynylated isoquinolones.

The use of oxidizing directing groups in transition metal-catalyzed C–H annulation has emerged as a powerful strategy for synthesizing a wide range of nitrogen heterocycles.¹ Since the pioneering contributions of Fagnou, Glorius, and others, the application of oxidizing directing groups has grown significantly.² This is due to the fact that in this particular strategy, the directing group plays the role of an external oxidant beside anchoring the metal to the specific site for performing C–H activation. Hence, the reaction can be performed under redox-neutral conditions without the requirement of any external oxidant. The oxidizing group strategy has been instrumental for C–H annulation reactions under rhodium and ruthenium catalytic systems. Apart from this, significant progress has been made in the area of Cp*Co(III)-catalysis using various oxidizing directing groups for the synthesis of important heterocycles such as isoquinolones, isoquinolines, and indoles (Scheme 1a).³ In the majority of these reports, N–O, N–N, and N–Cl bonds act as internal oxidants. To the best of our knowledge, the utilization of N–S bonds as an internal oxidant under cobalt-catalysis is scarce.⁴ Therefore, there is still significant scope for the development of novel Cp*Co(III)-catalyzed redox-neutral C–H annulation protocols utilizing novel oxidizing directing groups based on N–S, N–P and O–O bonds as an internal oxidant.

On the other hand, sulfilimines represent an important class of organic molecules widely utilized in amination

reactions either as a nitrene precursor⁵ or as an *N*-nucleophile.⁶ Very recently, Huang and co-workers have successfully demonstrated the utility of sulfilimines in C–H activation and annulation reactions. However, the reaction was performed using precious Rh catalyst (Scheme 1b).⁷ Considering the high cost of the Rh-catalyst and need for the development of more sustainable C–H functionalization approaches, it is highly desirable to develop a method for the C–H functionalization of sulfilimines using first-row transition metal catalysts like Cp*Co(III) catalysts (Scheme 1c). Moreover, to the best of our knowledge there is no report on the redox-neutral synthesis of isoquinolones using N–S bonds as an internal oxidant under high-valent cobalt-catalysis.

We commenced our investigation by using *S,S*-dimethyl-*N*-acetylsulfilimine (1a) and diphenyl acetylene (2a) as model substrates where the N–S bond is expected to play the role of an internal oxidant. After performing a series of reactions, we



Scheme 1 Oxidizing directing group strategy for C–H functionalization/annulation under Cp*Co(III) and Cp*Rh(III) catalysis.

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† Electronic supplementary information (ESI) available. CCDC 2425784 and 2425785. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d5cc01230a>

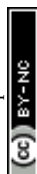


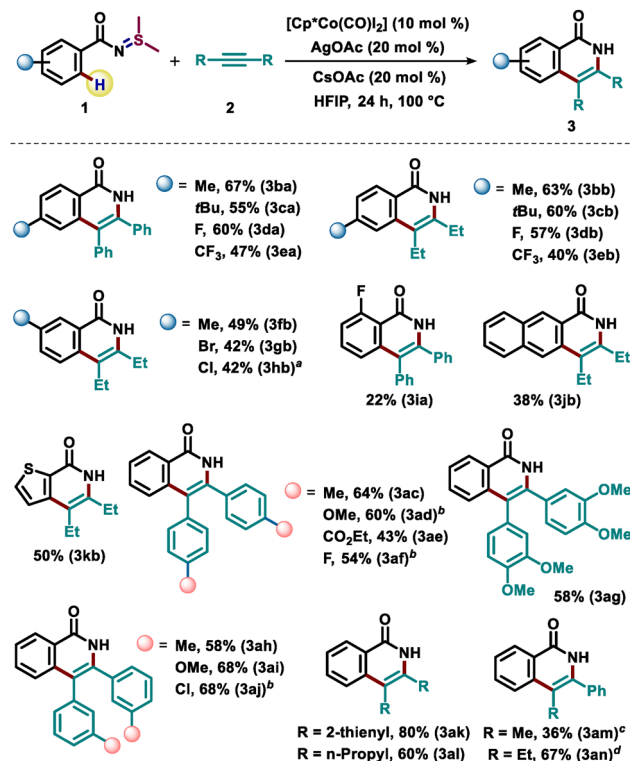
Table 1 Optimization study^a

Entry	Variation from standard conditions	Yield ^c (%)
1	None	76
2	Without AgOAc	Trace
3	KOAc/NaOAc instead of CsOAc	72/68
4	PivOH/AcOH instead of CsOAc	46/48
5	1,2-DCE as a solvent instead of HFIP	n.d.
6	TFE as a solvent instead of HFIP	65
7	AgSbF ₆ /AgNTf ₂ instead of AgOAc	40/50
8	12 h instead of 24 h	60
9	80 °C instead of 100 °C	58
10	Without CsOAc	65
11	Without [Cp*Co(CO)I ₂]	n.d.

^a Reaction conditions: **1a** (0.15 mmol, 1.5 equiv.), **2a** (0.10 mmol), [Cp*Co(CO)I₂] (10 mol%), Ag(i) salt (20 mol%), and additive (20 mol%) and solvent (0.6 mL) at the indicated temperature and time. ^b Isolated yields are given under the standard conditions. ^c Yields are based on crude ¹H NMR (internal standard: 1,1,2,2-tetrachloroethane). n.d. = not detected.

found that the optimal reaction conditions of treatment of diphenyl acetylene (**2a**, 0.1 mmol) with *S,S*-dimethyl-*N*-acylsulfilimine (**1a**, 0.15 mmol) in the presence of [Cp*Co(CO)I₂] (10 mol%), AgOAc (20 mol%), and CsOAc (20 mol%) at 100 °C for 24 h in HFIP furnished the desired isoquinolone derivative **3aa** in 76% yield (Table 1, entry 1) (isolated yield 72%). When the reaction was performed using an alkyne having alkyl substituents (3-hexyne, **2b**), it furnished the required product in 67% isolated yield. When the reaction was performed without AgOAc, it furnished only trace amount of the product (Table 1, entry 2), demonstrating that AgOAc is crucial for this transformation. Other acetate additives like KOAc, NaOAc, PivOH and AcOH were found to be less effective as compared to the CsOAc (Table 1, entries 3 and 4). Employing a solvent other than HFIP, such as 1,2-DCE, resulted in no detection of the product and a decrease in the yield for TFE (Table 1, entries 5 and 6). The reaction was conducted with other silver additives, such as AgSbF₆ and AgNTf₂, resulting in a lower yield in both instances (Table 1, entry 7). The reaction was tested by reducing the time to 12 hours and decreasing the temperature to 80 °C, but in both cases the yield dropped (Table 1, entries 8 and 9). Furthermore, when the reaction was performed in the absence of CsOAc, it resulted in a decrease in the product yield (Table 1, entry 10). The reaction yielded no product without a cobalt catalyst (Table 1, entry 11).

Upon successfully optimizing the reaction conditions, we turned our attention to investigating the scope of various sulfilimine derivatives and alkynes (Scheme 2).⁸ The sulfilimines having electron-donating groups, such as Me and ^tBu, at the *para*-position furnished products in good yields with both diaryl and dialkyl alkynes, *i.e.*, diphenyl acetylene and 3-hexyne (**3ba–3ca**; **3bb–3cb**). The reaction was found to be compatible with sulfilimines having electron-withdrawing groups such as F



Scheme 2 Scope of sulfilimines and alkynes. Reaction conditions: **1** (1.5 equiv.), **2a** (0.30 mmol), [Cp*Co(CO)I₂] (10 mol%), AgOAc (20 mol%), and CsOAc (20 mol%) in HFIP (1.8 mL) at 100 °C for 24 h. Isolated yields are given. ^a Inseparable regioisomers in a 1.0 : 0.05 ratio. ^b 2.0 equiv. of sulfilimine **1a** was used. ^c The other regio-isomer was formed in 24% yield. ^d Inseparable regioisomers in a 1.0 : 0.6 ratio.

and CF₃ at the *para*-position, and annulated products in moderate yields (**3da–3ea**; **3db–3eb**). The reaction was found to be highly regioselective for *meta*-substituted sulfilimines having Me and Br substituents (**1f** and **1g**), furnishing a single isomer product in which the C–H activation occurs at the less hindered position in moderate yields (**3fb**, **3gb**). However, in the case of 3-Cl substituted sulfilimine, we have observed the formation of a non-separable mixture of regioisomeric products, of which the product **3hb** is the major isomer. The reaction was sluggish with an *ortho*-substituted sulfilimine derivative (**1i**) having a fluorine substituent, furnishing the required annulated product **3ia** in 22% yield. The reaction was found to be compatible with sulfilimine derivatives having a naphthalene and thiophene moiety, resulting in the formation of the required products in low to moderate yields (**3jb**, **3kb**).

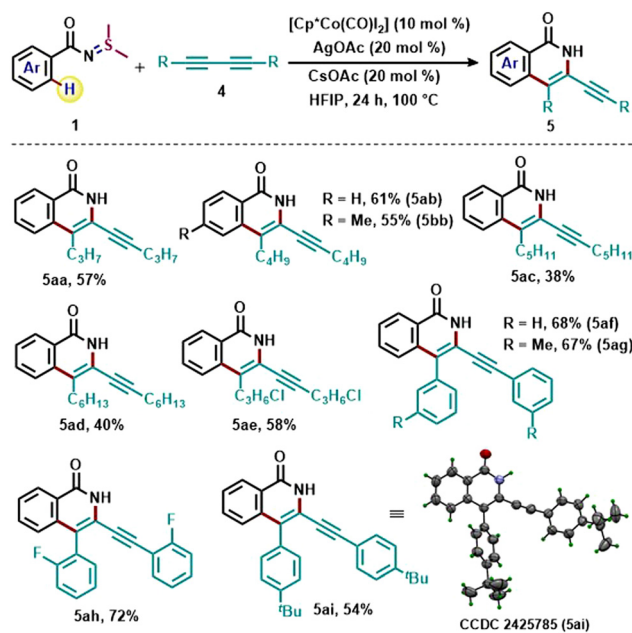
Next, the scope of the annulation reaction was further examined for various di-substituted acetylene derivatives (Scheme 2). The diaryl-acetylene derivatives having electron-donating as well as electron-withdrawing groups such as Me, OMe, CO₂Et, and F at the *para*-position delivered the corresponding isoquinolone derivatives in moderate to good yields (**3ac–3af**). The disubstituted alkyne, 1,2-bis(3,4-dimethoxyphenyl)ethyne (**2g**) afforded the corresponding isoquinolone derivative in 58% yield (**3ag**). Similarly, diaryl-alkynes having different substituents like Me, OMe, and Cl at the *meta*-position yielded the annulated products



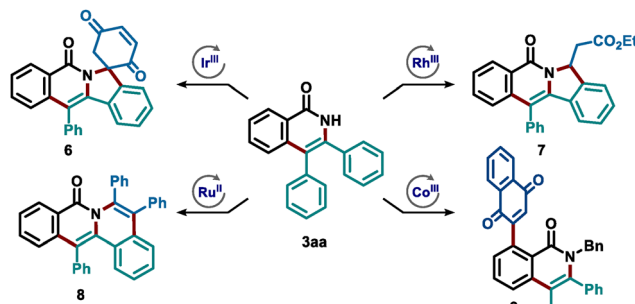
in yields of 58%, 68%, and 68%, respectively (**3ah–3aj**). The reaction was found to be compatible with the heteroaryl alkyne having thiophene rings (**2k**), furnishing the desired product **3ak** in 80% yield. The scope was further extended to dialkyl alkyne, *i.e.*, 4-octyne, which furnished the product **3al** in 60% yield. The structure of the product was confirmed by X-ray crystallographic analysis.⁹ Furthermore, reactions with unsymmetrical alkynes such as 1-phenyl-1-propyne and 1-phenyl-1-butyne resulted in the formation of a mixture of regioisomers (**3am–3am'**; **3an–3an'**). However, our attempt to utilize a terminal alkyne (phenyl acetylene) as a coupling partner was futile.

After testing the scope of various alkyne derivatives towards the Cp*Co(III)-catalyzed [4+2] annulation reaction using sulfilimine as an oxidizing directing group, we were interested in utilizing 1,3-diynes as a coupling partner (Scheme 3).⁸ In recent years, 1,3-diynes have been employed in various C–H annulation reactions for the synthesis of a diverse array of heterocyclic compounds.¹⁰ However, due to the presence of the two alkyne units, utilization of 1,3-diynes as a coupling partner in C–H annulation becomes challenging due to chemo-selectivity and regio-selectivity issues.

We were pleased to see that reaction of *S,S*-dimethyl-*N*-acetylsulfilimine (**1a**) with various dialkyl 1,3-diynes under the optimized conditions resulted in the formation of 3-alkynylated isoquinolones in moderate to good yields. The reaction also tolerated the primary chloride functionality present in the 1,3-diyne moiety. The protocol also works well with 1,3-diynes having aryl groups.¹¹ The regioselectivity of alkyne insertion leading to the formation of 3-alkynylated isoquinolones was unambiguously confirmed by the X-ray analysis of the product **5ai**.



Scheme 3 Scope of 1,3-diynes for the regioselective synthesis of 3-alkynylated isoquinolones. Reaction conditions: **1** (1.5 equiv.), **4** (0.30 mmol), [Cp*Co(CO)I₂] (10 mol %), AgOAc (20 mol %), and CsOAc (20 mol %) in HFIP (1.8 mL) at 100 °C for 24 h. Isolated yields are given.



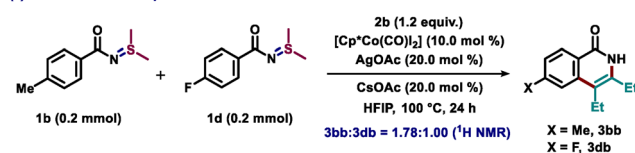
Scheme 4 Synthetic utilities.⁹

Next, we focused on the synthetic utility of the synthesized isoquinolone derivative **3aa** (Scheme 4).⁹ Various annulation reactions were performed using benzoquinone, ethyl acrylate, and diphenyl acetylene under Ir, Rh, and Ru catalytic systems to furnish **6**, **7**, and **8** in moderate to good yields.¹² Later, the *N*-benzylation of the isoquinolones followed by Cp*Co(III)-catalyzed C–H olefination with naphthoquinone¹³ resulted in the formation of **9**. Finally, we carried out preliminary mechanistic studies to gain some information about the reaction mechanism (Scheme 5). In an intermolecular competitive experiment (Scheme 5a), it was found that sulfilimine having an electron-donating Me substituent (**1b**) at the *para*-position reacts preferably over the sulfilimine having an electron-withdrawing F substituent (**1d**). This observation indicates that the C–H activation occurs through an electrophilic activation mechanism.

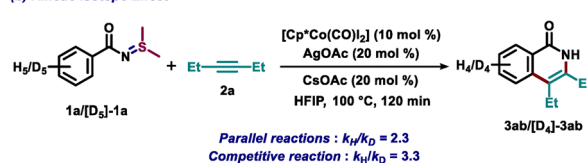
Later, the kinetic isotope effect (KIE) was determined by performing parallel reactions in separate vessels as well as a competitive reaction in the same vessel using **1a** and [D₅]-**1a** (Scheme 5b). The KIE values from these experiments were found to be 2.2 and 3.3, respectively, indicating that the C–H activation step is likely to be the rate-determining step of the reaction.

A plausible mechanism for the cobalt-catalyzed annulation of sulfilimine is illustrated in Scheme 6. Initially, the catalytically active species **A** is generated by treating [Cp*Co(CO)I₂] with AgOAc and CsOAc. This species then undergoes a rate-limiting cyclometallation with sulfilimine **1**, leading to the formation of cobaltacycle **B**. Subsequently, the insertion of an

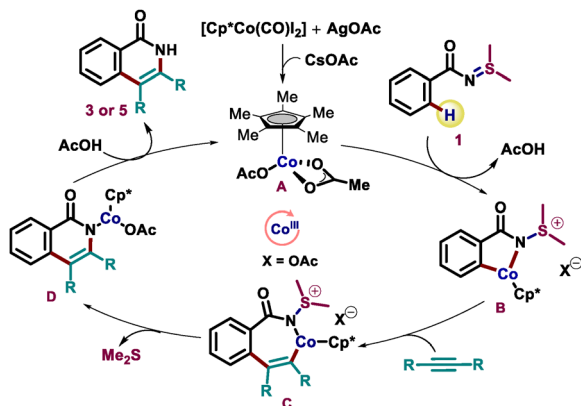
(a) Intermolecular competitive reaction between sulfilmines



(b) Kinetic Isotope Effect



Scheme 5 Preliminary mechanistic studies.



Scheme 6 Plausible mechanism.

alkyne or 1,3-diyne into the carbon–cobalt bond results in the formation of a seven-membered metallacycle **C**. The intermediate **C** undergoes reductive elimination with subsequent loss of Me₂S, and ligand exchange yielding species **D**. Finally, protodemetalation of **D** regenerates the catalytically active Cp*Co(III) species **A**, while affording the desired annulated product (**3** or **5**).

In conclusion, we have developed an efficient Cp*Co(III)-catalyzed [4+2] C–H annulation strategy for synthesizing isoquinolone derivatives, utilizing sulfilimine as an oxidizing directing group. Notably, this work represents the first example of Cp*Co(III)-catalyzed C–H functionalization of sulfilimines. The reaction works under redox-neutral conditions and employs the N–S bond of sulfilimines as an internal oxidant. The reaction exhibits high regioselectivity with 1,3-diynes and proceeds smoothly with a broad range of substitutions on both the sulfilimines and alkynes. Additionally, post-synthetic modifications of the synthesized isoquinolones were carried out successfully.

A. G. thanks the Ministry of Human Resources Development (MHRD), India, for the research fellowship. A. B. P. thanks the Science and Engineering Research Board (SERB), New Delhi, India for financial support in the form of a Core Research Grant (CRG/2023/002075).

Data availability

The data supporting this article have been included as part of the ESI†. Crystallographic data for **3aI** and **5aI** have been deposited at the CCDC under 2425784 and 2425785.

Conflicts of interest

There are no conflicts to declare.

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