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Cobalt-catalyzed multisubstituted allylation of the chelation-assisted C–H bond of (hetero)arenes with cyclopropenes†

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Cyclopropenes are highly strained three-membered carbocycles, which offer unique reactivity in organic synthesis. Herein, Cp*Co^{III}-catalyzed ring-opening isomerization of cyclopropenes to cobalt vinylcarbene has been utilized for the synthesis of multisubstituted allylarenes *via* directing group-assisted functionalization of C–H bonds of arenes and heteroarenes. Employing this methodology, various substituents can be introduced at all three carbons of the allyl moiety with high selectivity. The important highlights are excellent functional group tolerance, multisubstituted allylation, high selectivity, gram scale synthesis, removable directing group, and synthesis of cyclopenta[*b*]indoles. In addition, a potential cobaltocycle intermediate was identified and a plausible mechanism is also proposed.

Introduction

Allylated arenes and heteroarenes are prevalent structural motifs found in various natural products and biologically important molecules.[1] Synthetically, substituted allyl groups serve as an excellent handle to increase the complexity of a molecule with simple synthetic operations. These allyl groups are traditionally introduced into arenes *via* either the Friedel–Crafts allylation of electron rich arenes[2] or reaction of pre-functionalized organometallic reagents with allyl electrophiles.[3] These methods have only limited substrate scope and require sensitive organometallic reagents. In contemporary organic synthesis, traditional methods are wisely replaced with the transition metal catalyzed direct allylation of directing group-assisted C–H bonds of (hetero)arenes.[4] In the past few decades, precious transition metals such as Pd,[5] Ru,[6] Rh,[7] Ir,[8] *etc*.[9] were efficiently utilized for the allylation of various C–H bonds. Recently, Cp*Co^{III} based catalysts have emerged as efficient alternatives to the precious metal catalysts in allylation[10] and other C–H bond functionalization reactions.[11] In addition, due to the small size and hard nature of cobalt catalysts, complementary reactivity was observed in a number of other transformations. All these allylation methods utilize either allylic alcohol derivatives or vinyl-epoxides, -cyclic carbonates and -cyclopropanes, allenes and others (Scheme 1a). Most of these transformations offer access to simple allylated and mono-substituted allylated arenes. Nevertheless, methods for introduction of allyl group containing substitution at allylic and alkene carbons are rather limited because most of these reactions involve an initial 1,2-migratory insertion of a C–metal bond into the alkene of the allylating reagent, which is highly controlled by the steric factor. Hence, it is highly desirable to develop a complementary approach for the multisubstituted allylation of C–H bonds utilizing a unique allylating reagent, which would involve an unconventional mode of allylation.

Substituted cyclopropenes constitute an important class of building blocks in organic synthesis.[12] Due to their high ring strain energy, cyclopropenes demonstrated versatile and exceptional reactivity, which are efficiently exploited in various transformations. In general, the reactivity of cyclopropenes can be classified into two types: (1) reaction of alkenes without ring-opening such as 1,2-addition and carbometallation, and (2) reaction accompanied by ring opening[13] such as cycloisomerization, metathesis and reaction of vinyl carbenes (Scheme 1b). On the other hand, application of cyclopropenes in transition metal-catalyzed C–H bond functionalization of (hetero)arenes is in its infancy.[14] The known transformations involve cyclopropanation of arenes *via* addition to alkene[15] or cycloisomerization to heterocycles employing Rh(III)-based catalysts[16] (Scheme 1c). However, transition metal-catalyzed ring-opening of cyclopropenes to vinylcarbenes[17] and its application in C–H bond functionalization is yet to be explored.

We have been extensively involved in the *in situ* generation of metalcarbenes from various precursors[18] and its application in the construction of various complex carbo- and heterocycles through C–H bond functionalization.[19] In continuation of our work on metalcarbenes and encouraged by the unique reactivity of cyclopropenes, we envisioned the utilization of cyclopropenes as a non-diazo precursor of vinylcarbenes in

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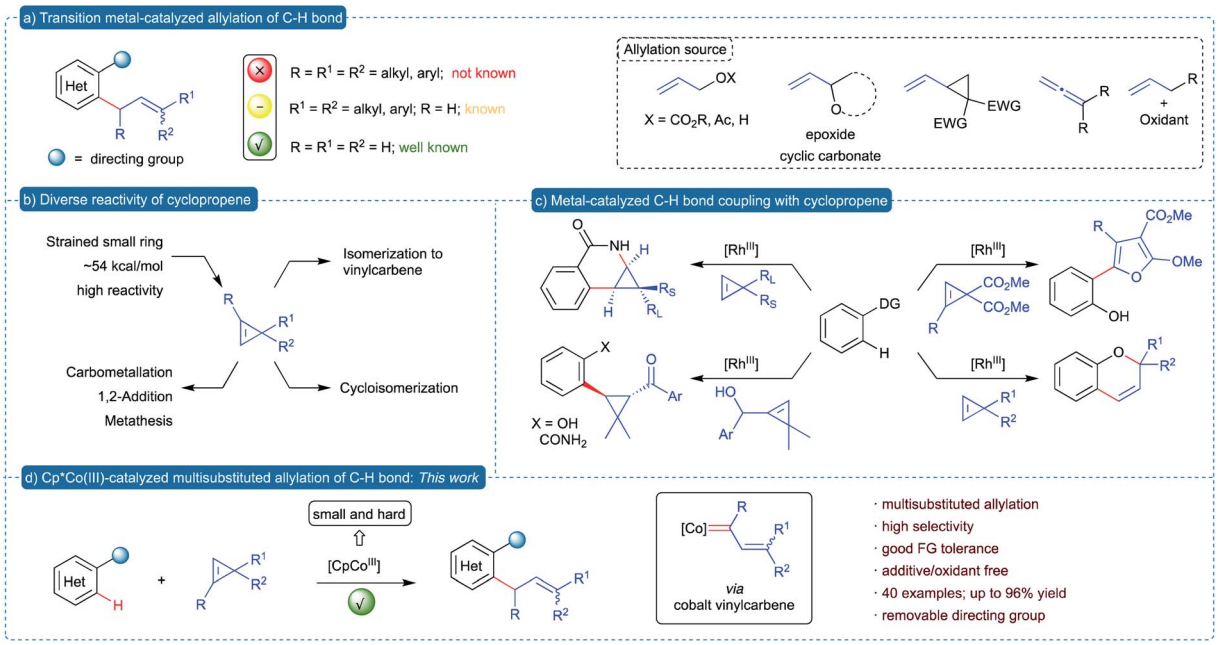


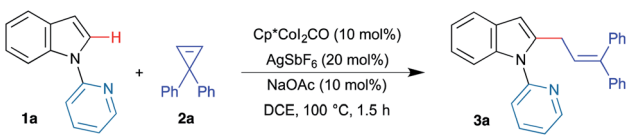
Scheme 1 Transition metal-catalyzed C–H bond allylation and reaction of cyclopropenes.

transition metal-catalyzed C–H bond functionalization for the synthesis of allylated (hetero)arenes. Due to the high reactivity of cyclopropenes, we intended to introduce substituents at all three carbons of the allyl moiety, which is otherwise difficult to achieve. We herein report the Cp*Co^{III}-catalyzed multi-substituted allylation of directing group-assisted C–H bonds of (hetero)arenes, such as indoles and pyrroles, exploiting substituted cyclopropenes as the allylating reagent.[20] This method represents the first example of multisubstituted allylation of (hetero)arenes, where substituents are introduced at all three carbons of the allyl group with high selectivity control.

Results and discussion

N-Heterocycles, particularly indoles, are of great synthetic interest due to their relevance in biological systems. Hence, we started our investigation with allylation of indole derivatives. First, we examined the reaction of *N*-pyridylindole **1a** and 3,3-diphenylcyclopropene **2a** as the model reaction in the presence of [Cp*CoI$_2$CO] catalyst. Based on the initial optimization (see the ESI† for more details), reaction of **1a** and **2a** in the presence of 10 mol% of [Cp*CoI$_2$CO], 20 mol% of AgSbF$_6$ and 10 mol% of NaOAc in DCE at 100 °C for 1.5 h afforded the expected allylated product **3a** in 91% yield (Table 1, entry 1). In the absence of

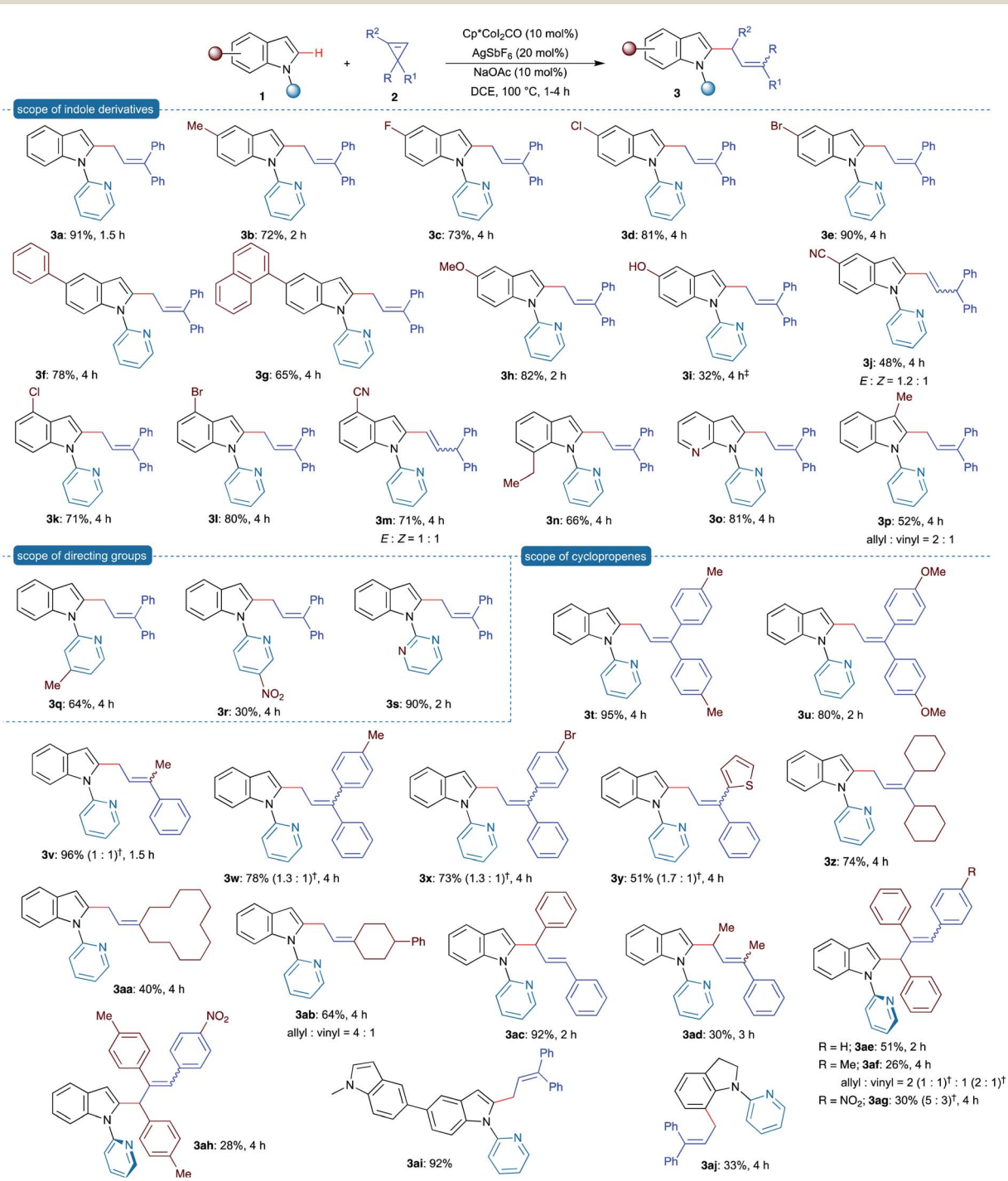
Table 1 Cp*Co^{III} catalysed allylation of the C–H bond of **1a** with cyclopropene **2a**[a]



Entry	Conditions	Yield[b] (%)
1	Standard conditions	91 (69)[c]
2	Absence of Cp*CoI$_2$CO or AgSbF$_6$	NR
3	Without NaOAc	5
4	KOAc instead of NaOAc	60
5	NaOPiv instead of NaOAc	56
6	AgOAc instead of NaOAc	51
7	DMF, DMSO and CH$_3$CN instead of DCE	NR
8	Toluene instead of DCE	28
9	With [Cp*Co(CH$_3$CN)$_3$](SbF$_6$)$_2$ instead of the catalyst and AgSbF$_6$	47

[a] Reaction conditions: **1a** (1.0 equiv.), **2a** (2 equiv.), [Cp*CoI$_2$CO] (10 mol%), DCE, 100 °C, 1–2 h. [b] All are isolated yields. [c] With 5 mol% of [Cp*CoI$_2$CO].

either [Cp*CoI_2CO] or $AgSbF_6$, allylation was not observed. Although **1a** was recovered from the reaction mixture, **2a** underwent intramolecular rearrangement to the indene derivative and was isolated in high yields (Table 1, entry 2). A similar result was observed when NaOAc was removed (Table 1, entry 3). These observations suggest that the reaction is catalyzed by Cp^*Co^{III}, and $AgSbF_6$ and NaOAc are essential for the observed activity of the catalyst. Replacement of NaOAc with other bases such as KOAc, NaOPiv and AgOAc gave product **3a** in lower yield, reiterating the importance of NaOAc (Table 1, entries 4–6). Screening of solvents revealed that polar solvents, such as DMF, DMSO, and CH_3CN that can chelate with metals, are not suitable for the present transformation (Table 1, entry 7). Also use of non-polar aromatic solvents such as toluene was not beneficial (Table 1, entry 8). Reducing the catalyst loading to 5 mol% or use of the Lewis acidic catalyst [Cp*$Co(CH_3CN)_3$]$(SbF_6)_2$ in the absence of $AgSbF_6$ gave the product **3a** in reduced yield (Table 1, entries 1 and 9). Thus, 10 mol% of [Cp*CoI_2CO],



Scheme 2 Cp*Co(III)-catalysed multisubstituted allylation of chelation-assisted C–H bonds with cyclopropenes. ‡From the corresponding allyl ether. †Ratio of stereoisomers.

20 mol% of $AgSbF_6$ and 10 mol% of NaOAc in DCE at 100 °C were chosen as optimal conditions for the allylation of C–H bonds of indole **1** with cyclopropenes **2**.

After successfully establishing the allylation of the C–H bond with cyclopropene, the scope and limitation of the strategy were investigated. To begin with, various substituted indole derivatives were examined under the optimized conditions with cyclopropene **2a** (Scheme 2). 5-Alkyl, aryl and halo substituted indole derivatives were readily allylated under the optimized conditions to furnish products **3a–3g** in excellent yields. Electron-donating (methoxy) group was well tolerated under the reaction conditions to afford the allylated product **3h** in 82% yield in 2 h. On the other hand, electron-withdrawing (cyano) group also showed reasonable compatibility and gave the vinylated product **3j** in relatively lower yield after 4 h as a mixture of *E* : *Z* isomers in 2 : 1 ratio. But the allyloxy group underwent deprotection under the reaction conditions and the corresponding hydroxy product **3i** was isolated.

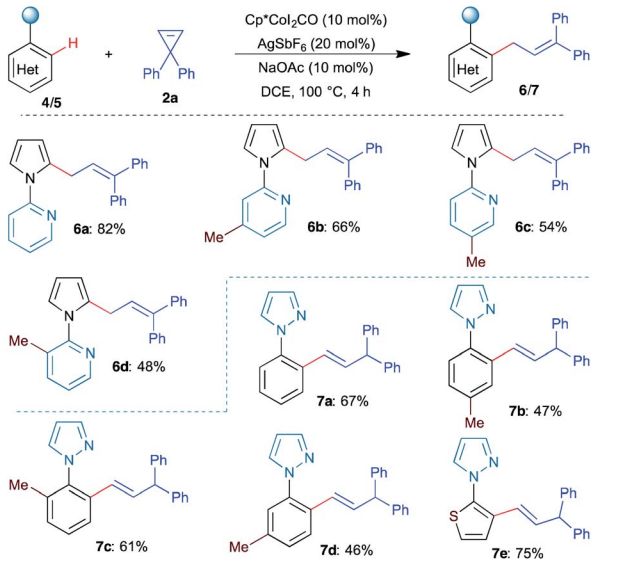
Similar results were observed with indole substituted at the 4-position, and synthesis of allyated products **3k–3m** was achieved in good yield. Importantly, sterically congested 7-ethylindole and 3-methyl indole derivatives underwent a smooth reaction to give the allylated products **3n** and **3p** in relatively low yields (66 and 52% yields, respectively), and the latter was isolated as a 2 : 1 mixture of allylated and vinylated products. Furthermore, a 7-azaindole derivative having an additional coordination site also furnished the allylated product **3o** in 81% yield. Subsequently, the effect of substituents on the pyridine directing group was examined. The 4-methylpyridine derivative effectively directed the allylation to provide the product **3q** in 64% yield. But the electron deficient 5-nitropyridine derivative showed poor directing ability and the formation of product **3r** was observed in 30% yield. Interestingly, replacement of pyridine with pyrimidine as the directing group, which can be readily removed after the reaction, furnished the product **3s** in excellent yield.

Successively, the scope and limitations of cyclopropenes were explored. Symmetrically 3,3-disubstituted cyclopropenes on reaction with **1a** under the optimized conditions afforded the products **3t** and **3u** in excellent yields. Use of unsymmetrical 3,3-diaryl, 3-aryl-3-heteroaryl and 3-alkyl-3-aryl cyclopropenes also afforded the corresponding allylated products **3v–3y** in excellent yields as a mixture of E/*Z* isomers with variable ratio. Interestingly, symmetrical cyclopropenes derived from dialkyl ketones, such as dicyclohexyl ketone, cyclododecanone and 4-phenylcyclohexanone, also showed high level of compatibility under the optimized conditions to deliver allylated products **3z**, **3aa** and **3ab** in good yields. Replacement of symmetrical disubstituted cyclopropene with unsymmetrical 1,3-diphenylcyclopropene furnished the product **3ac** in 92% yield with complete *E*-selectivity. Consequently, trisubstituted cyclopropenes were examined. Formation of allylated product **3ad** having substituents at allylic and alkene carbons in moderate yield from 1,3-dimethyl-3-phenylcyclopropenes was observed. Similar observations were noted with 1,2,3-triarylcyclopropenes containing substituents at the alkene carbon, where allylated products **3ae–3ah** were obtained in moderate yields. This observation suggests that the steric factor in cyclopropene significantly affects the outcome of the reaction.

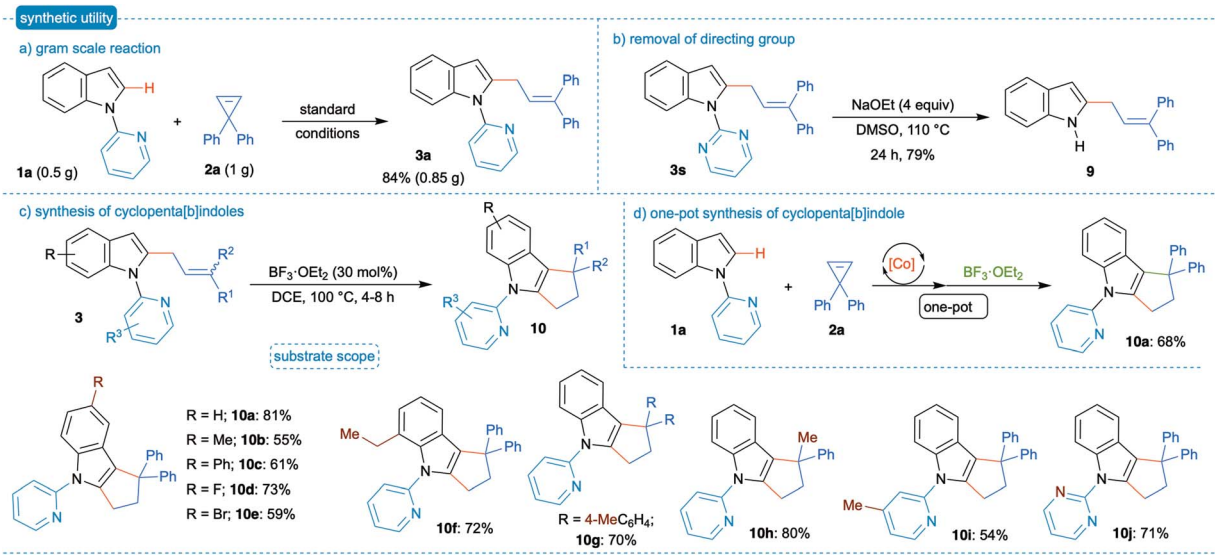
Subsequently, studies were directed to understand the importance of the directing group. Thus, bisindole having different substituents at nitrogen, methyl and pyridyl, respectively, selectively afforded the allylation at pyridyl substituted indole (**3ai**), which supported the importance of the directing group. It is important to note that formation of C7-allylated product **3aj** was observed in 33% yield when *N*-pyridylindoline was treated with **2a** under the optimized conditions. This result further expands the scope of allylation to the C7–H bond of the indole derivative.

Having successfully studied the allylation of indole derivatives, we next focused on the allylation of pyrroles and arenes using pyridine and pyrazole as the directing group, respectively. The reaction of *N*-pyridylpyrrole **4a** with **2a** in the presence of [Cp^*Co^{III}] under the optimized conditions furnished the allylated product **6a** in 82% yield (Scheme 3). Similarly, other substituted allylpyrroles **6b–6d** were obtained in moderate to good yields. Next, *N*-phenylpyrazole reacted efficiently with **3a** under the optimized conditions and afforded vinylated product **7a** in 67% yield as the sole product, instead of the corresponding allylated product. Similar results were obtained with other substituted *N*-arylpyrazole derivatives and gave vinylated products **7b–7e** in good yields.

After having shown the wide substrate scope, the synthetic application of the developed strategy was investigated. Gram scale synthesis of **2a** and **1a** furnished the allylated product **3a** in comparable yield, suggesting that the reaction can be readily scaled up and the methodology is applicable to the large-scale preparation of allylated derivatives (Scheme 4a). Reaction of **3s** with NaOEt furnished 2-allylated indole **9** in good yield, revealing that the employed directing group could be readily removed, and the method can be used for further synthetic manipulations (Scheme 4b).



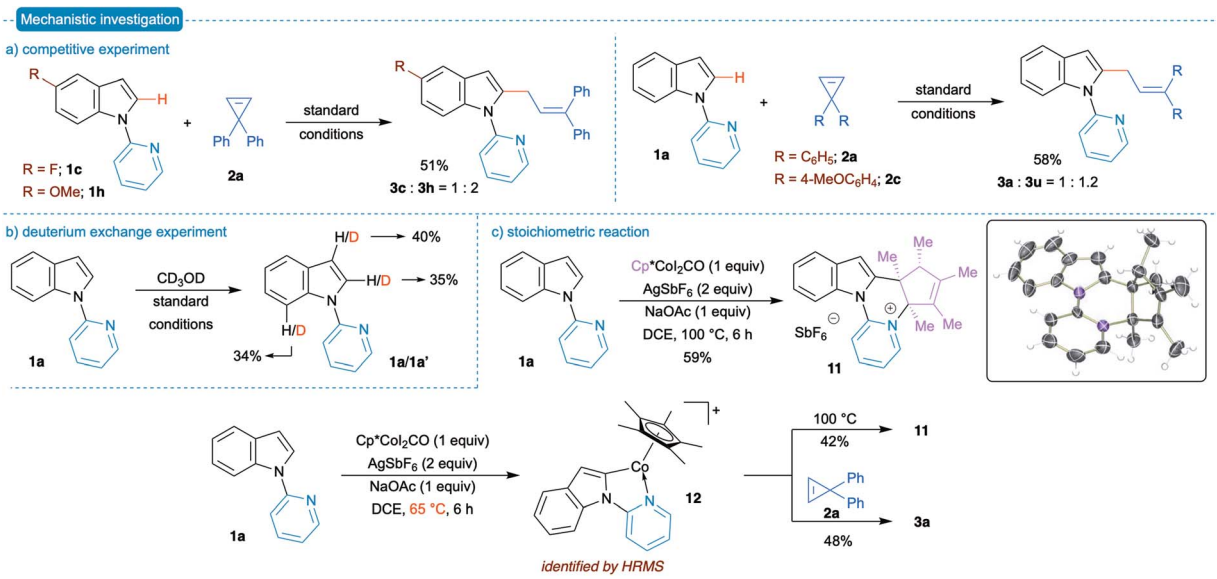
Scheme 3 Reaction of **2a** with *N*-pyridylpyrrole **4** and *N*-arylpyrazole **5**.



Scheme 4 Synthetic utility. (a) Gram scale reaction. (b) Removal of directing group. (c) Synthesis of cyclopenta[*b*]indoles. (d) One-pot synthesis of cyclopenta[*b*]indole.

Cyclopenta[*b*]indoles are important structural motifs widely found in bioactive natural products and pharmaceutically interesting compounds.[21] We next envisioned the conversion of allylated products **3** to the corresponding cyclopenta[*b*]indoles **10**. Thus, reaction of **3a** with 30 mol% of $BF_3{\cdot}OEt_2$ in DCE afforded the product **10a** in 81% yield (Scheme 4c). Subsequently, various substituted cyclopenta[*b*]indoles **10b–j** were achieved in moderate to good yields in the presence of $BF_3{\cdot}OEt_2$. Importantly, Cp*Co^{III}-catalyzed allylation and Lewis acid mediated cyclization were successfully integrated to afford cyclopenta[*b*]indole **3a** in 68% yield in one-pot (Scheme 4d).

We also performed preliminary investigation to understand the possible mechanism of the developed transformation. The initial competitive experiment with electronically different indoles revealed preference to electron-rich indole derivatives (Scheme 5a). This suggests the possible electrophilic metalation pathway for C–H bond functionalization with Cp*Co^{III}. On the other hand, electronically different cyclopropenes showed only very slight preference to electron-rich cyclopropenes, which might be due to the high reactivity of cyclopropenes. Next, a deuterium exchange experiment was performed to support the formation of the Co–C bond through C–H bond functionalization. Treatment of **1a** with CD_3OD under the optimized conditions, in the absence of cyclopropene, led to the recovery of **1a** with a significant amount of deuteration at C2- and C7-position



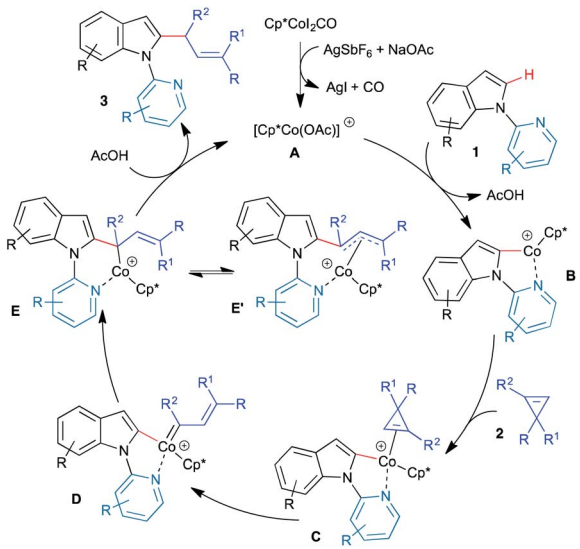
Scheme 5 Preliminary mechanistic investigation. (a) Competitive experiment. (b) Deuterium exchange experiment. (c) Stoichiometric reaction.

suggesting the potential reversible formation of the Co–C bond (Scheme 5b).

Next, we focused our attention on isolating the possible transition state of C–H metalated species. Thus, equimolar ratios of **1a** and Cp*CoI_2CO were treated in the presence of 2 equiv. of $AgSbF_6$ and 1 equiv. of NaOAc in DCE at 100 °C for 6 h. We noticed a clear change in the color of the reaction mixture and the formation of a solid. Isolation and characterization of the formed solid through ^{1}H NMR showed that all five methyl groups of Cp* are not equal and one of them appeared as a doublet. Consequently, single crystal X-ray analysis of the isolated solid confirmed the formation of pyridinium salt **11** in 59% yield as a single diastereomer (Scheme 5c).[22] The formation of **11** can be explained through the initial insertion, reductive elimination followed by protonation of the resultant allyl Co-species.

To isolate the potential intermediate, the stoichiometric reaction was performed at a reduced temperature (65 °C). Various attempts to isolate the complex formed was unsuccessful. Hence, the formed intermediate was analyzed by ESI-HRMS, which showed the presence of only complex **12**. The mass spectrum was in complete agreement with the simulated spectra of complex **12** (see the ESI† for more details). Successively, treatment of the reaction mixture with cyclopropene **2a** furnished the allylated product **3a** in good yield. Interestingly, heating of complex **12** to 100 °C afforded the pyridinium salt **11** in 42% yield. These observations suggest complex **12** as a potential intermediate of the present allylation and formation of pyridinium salt **11**.

Based on the preliminary mechanistic investigation, the plausible mechanism for the multisubstituted allylation is proposed (Scheme 6). The catalytic reaction starts with the formation of **A** from the pre-catalyst Cp*CoI_2CO and $AgSbF_6$/NaOAc through exchange of ligands. Reaction of active species **A** with indole derivative **1** would furnish the cyclometallated species **B** *via* base-assisted electrophilic C–H bond functionalization. Formation of vinylcarbene **D** could be explained through the initial coordination of cyclopropene **2** to **B** followed by rearrangement. Subsequently, 1,1-migratory insertion would give intermediate **E**, which on proto-demetallation would give the product **3** and regenerate the active catalyst **A**. On the other hand, based on the substrate, intermediate **E** could exist as allyl-Co species **E′**, which on protonation would give the vinylated product. As seen in the substrate scope, a C3-allylated product could be formed *via* the intermolecular reaction of vinylcarbene with cyclometallated species **B**, which makes the C3-position more nucleophilic.



Scheme 6 Plausible mechanism.

Conclusions

In conclusion, we have developed an efficient and general multisubstituted allylation of chelation-assisted C–H bond of (hetero)arenes in the presence of Cp*Co^{III} catalyst and substituted cyclopropenes as an efficient allylating reagent. The allylation occurs through ring-opening isomerization of cyclopropenes to vinylcarbenes followed by migratory insertion, which allows introduction of substituents in all three carbons of the allyl moiety. Various functional groups were well tolerated to afford diversely substituted allyated indoles, pyrroles and arenes in good yields and selectivity. Importantly, gram scale synthesis, removal of the directing group and synthetic manifestation to cyclopenta[*b*]indoles demonstrated the synthetic applicability of the present methodology. Furthermore, a potential metalated intermediate was identified through a stoichiometric reaction, which paved way to the plausible mechanism.

Data availability

All the data have been included in the ESI.†

Author contributions

K. R. performed all experiments. Both authors contributed to the conception of the experiments, discussion of the results and preparation of manuscript.

Conflicts of interest

There are no conflicts to declare.

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