Allenes: Versatile Building Blocks in Cobalt-Catalyzed C–H Activation

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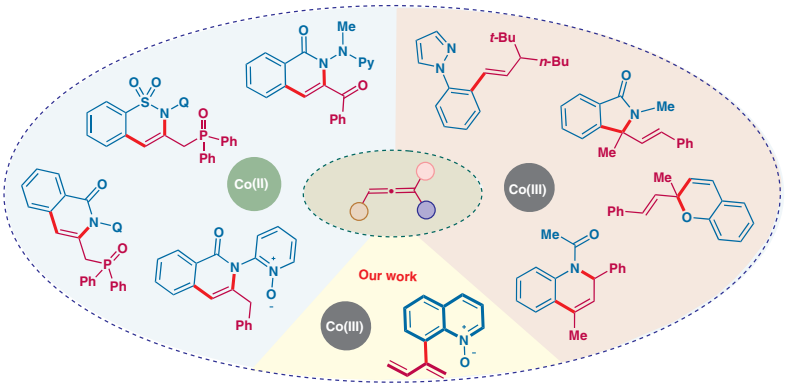

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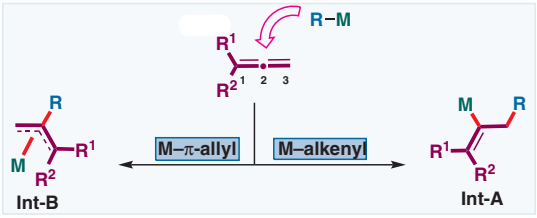
Abstract The unique reactivity of allenes has led to their emergence as valuable coupling partners in transition-metal-mediated C–H activation reactions. On the other hand, due to its high abundance and high Lewis acidity, cobalt is garnering widespread interest as a useful catalyst for C–H activation. Here, we summarize cobalt-catalyzed C–H activations involving allenes as coupling partners and then describe our studies on Co(III)-catalyzed C-8 dienylation of quinoline *N*-oxides with allenes bearing a leaving group at the α-position for realizing a dienylation protocol.

Key words cobalt catalysis, C–H activation, allenes, dienylation, quinolines

1 Introduction

1.1 Allenes in C–H Activation

The unique reactivity of allenes has led to an outburst in their popularity as valuable building blocks in various elegant synthetic transformations.[1] Their versatility allows them to participate in a variety of reactions, such as cycloadditions, cyclizations, and nucleophilic and electrophilic additions, as well as noble-metal-catalyzed carbocyclizations.[2,3] Along these lines, allenes have also been extensively studied as coupling partners in transition-metal-catalyzed C–H functionalization reactions.[4] The carbometallation of an allene with an organometallic intermediate R–M (formed after C–H activation) depends on both the stereoelectronic properties of substituents present on the allene and on the nature of the metal M. The prospect of chemo-



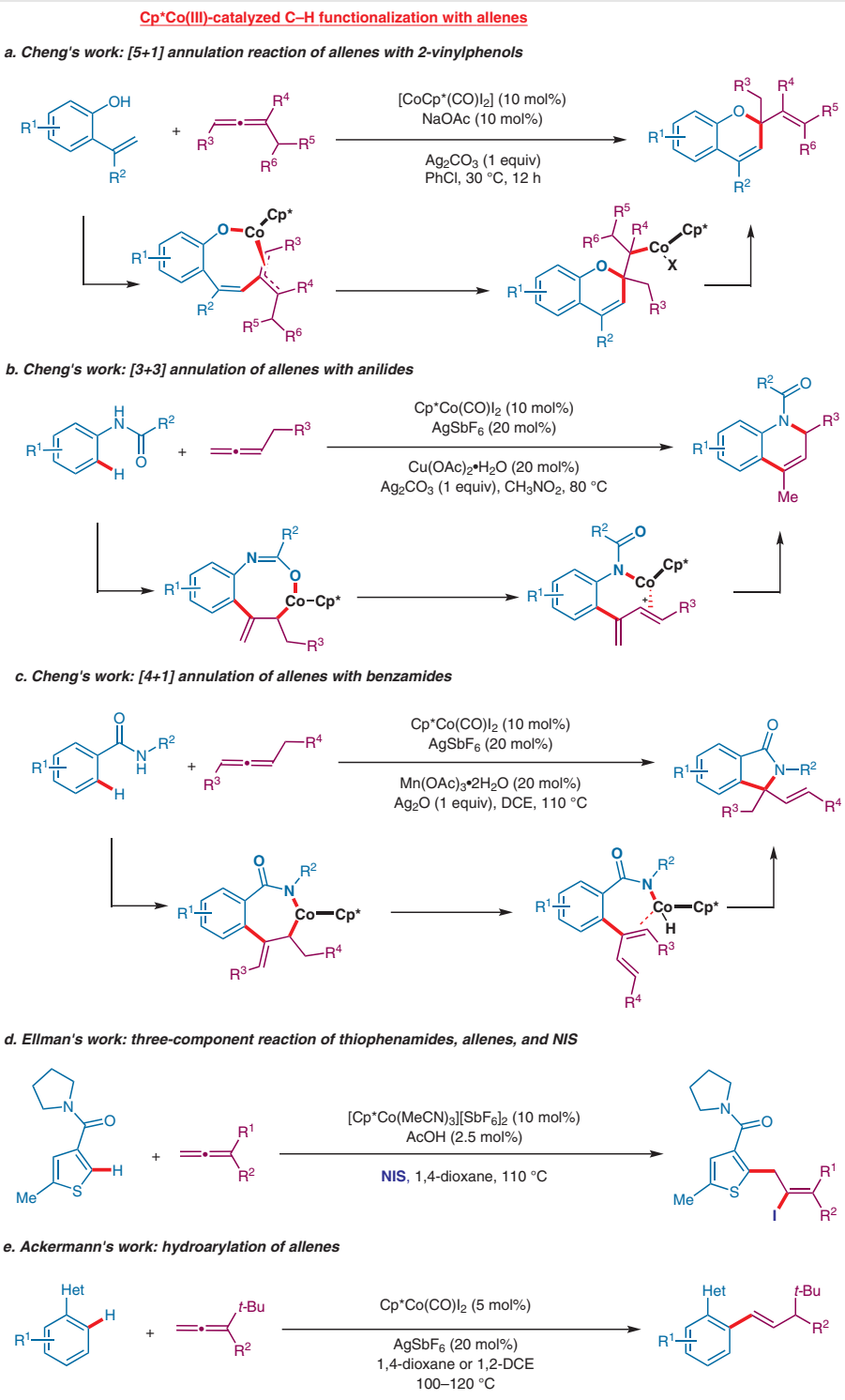
Scheme 1 Reactivity of allenes in carbometallation

Chandra Volla (right) was born in Parvathipuram (Andhra Pradesh, India). He received his M.Sc. degree in 2005 from the University of Hyderabad and then joined the group of Professor Pierre Vogel at EPFL (Lausanne, Switzerland) for his doctoral studies. In 2010, he moved to RWTH Aachen to work with Professor Magnus Rueping and then, in 2013, he joined the group of Professor Jan-E. Bäckvall at Stockholm University for his postdoctoral studies. Chandra returned to India in October 2014 to join the Department of Chemistry, IIT Bombay, as an assistant professor and was promoted to associate professor in May 2018.

Rahul Shukla (left) was born in Alipur Sarawan (Uttar Pradesh, India) and completed his M.Sc at the Dr. H. S. Gour University Sagar, India. In 2015, he started his doctoral studies at the Indian Institute of Technology Bombay with Professor Chandra M. R. Volla.

Akshay Nair (center) was born in Thrissur (Kerala, India) and obtained his M. Tech. from NIPER-Mohali, India. Subsequently, he started his doctoral studies at the Indian Institute of Technology Bombay with Professor Chandra M. R. Volla in 2016

and regioselective formation of two disparate carbometalated intermediates M–alkenyl (Int-A) or M–π-allyl (Int-B) (through either 3,2-insertion or 2,1-insertion, respectively) with allenes (Scheme 1) makes their study both challenging and intriguing. These intermediates, being highly reactive, undergo various transformations such as annulation, pro-

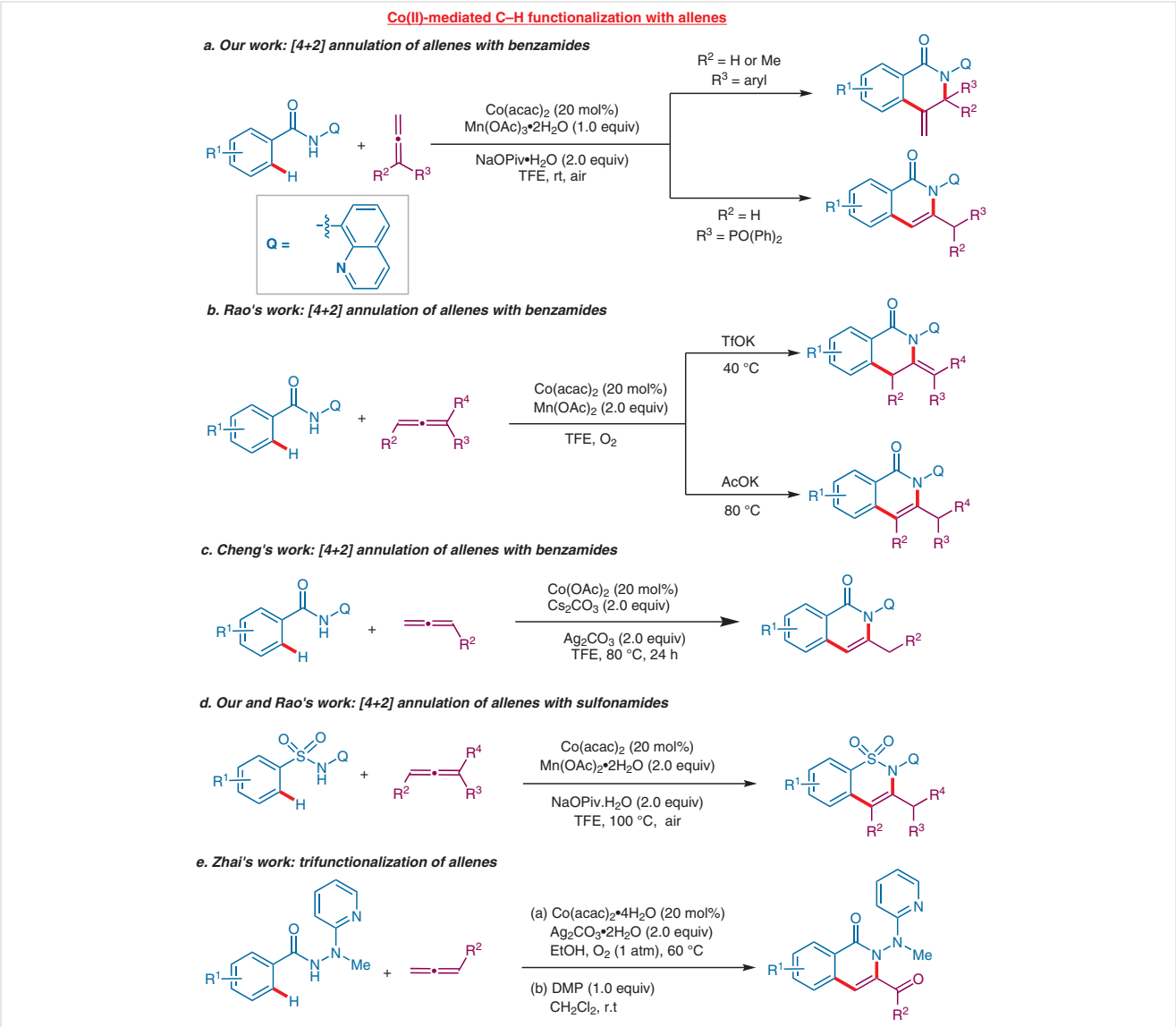


Scheme 2 Cp*Co(III)-catalyzed C–H functionalizations with allenes

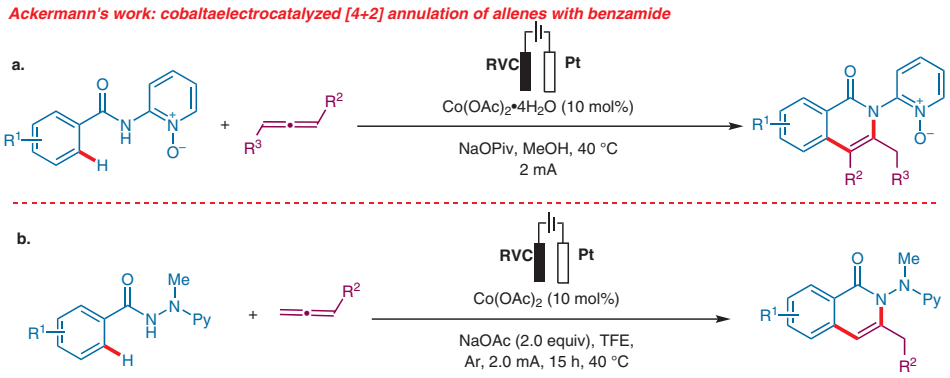
tonation, reductive elimination, or β-hydride elimination, furnishing structurally variant frameworks. In 2009, Krische and co-workers reported the first application of allenes as coupling partners in C–H activation reactions in the presence of an Ir(III) catalyst.[5] Subsequently, Cramer and co-workers developed Rh(I)-catalyzed C–H functionalization reactions with allenes.[6] Although elegant, these methods suffer from the requirement of rare and expensive noble-metal catalysts.[7] This motivated various research groups to develop C–H transformations of allenes by using inexpensive metal catalysts such as Ru,[8], Ni,[9] Mn,[10] Fe,[11] or Co.[12–21]

1.2 Cobalt(III)-Catalyzed C–H Activation with Allenes

In 2013, Kanai and Matsunaga and their co-workers made notable inroads toward replacing expensive noble-metal catalysts [Cp*Rh(III) or Cp*Ir(III)] (Cp* = pentamethylcyclopenta-1,3-diene) with inexpensive Earth-abundant first-row Co(III) salts.[22] Consequently, cobalt-catalyzed C–H activations have found a niche in synthetic chemistry, owing to the general abundance and high Lewis acidity of cobalt.[22b] The first report of the use of allenes in cobalt-catalyzed C–H activation was disclosed by Cheng and co-workers in 2016. They demonstrated a Cp*Co(III)-catalyzed vinylic C–H activation of 2-vinylphenols with allenes to-



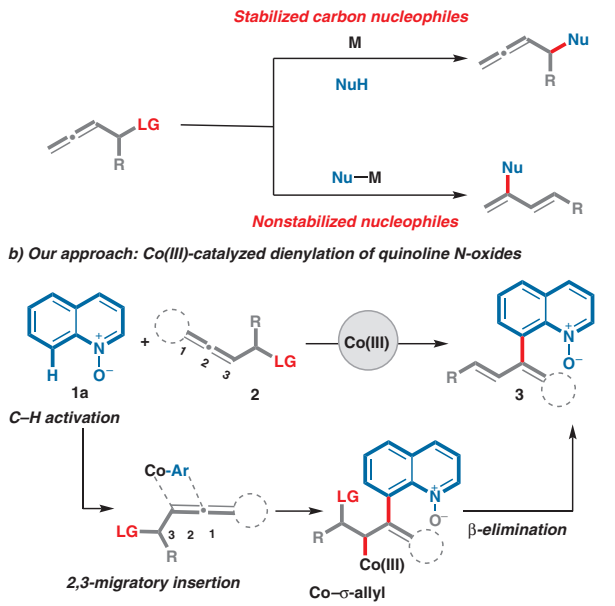
Scheme 3 Cobalt(II)-mediated C–H functionalizations with allenes



Scheme 4 Cobaltaelectrocatalyzed [4+2]-annulations of allenes with benzamides. RVC = reticulated vitreous carbon.

ward the synthesis of 2*H*-chromenes through an oxidative [5+1]-cyclization in which the allene acted as a one-carbon coupling partner (Scheme 2a).[12] Later, in 2018, the same group reported Cp*Co(III)-catalyzed [3+3]-[13] and [4+1]-annulation[14] reactions in which the allene acted as a three- or one-carbon annulation partner, respectively (Schemes 2b and 2c). All these reactions proceed through a Co–π-allyl intermediate (**Int-B**; M = Co) formed by 2,1-migratory insertion of the allene with the organocobalt species.

In 2017, Boerth and Ellman revealed a controlled cobalt-catalyzed three-component reaction of allenes with *N*-iodosuccinimide (NIS).[15] The iodination product was obtained by countering electropositive iodine with a Co–alkenyl intermediate (**Int-A**, M = Co) formed by 3,2-migratory insertion of the allene. Later, Ackermann and co-workers demonstrated an elegant Cp*Co(III)-catalyzed hydroarylation of allenes through protonation of a Co–alkenyl intermediate (**Int-A**, M = Co).[16]



Scheme 5 Chemistry of the allene leaving group

1.3 Cobalt(II)-Mediated C–H Activation with Allenes

In 2005, Daugulis and co-workers demonstrated the application of bidentate auxiliaries [8-aminoquinoline, picolinamide, or (pyridin-2-ylmethyl)amine] in Pd-catalyzed C–H activation reactions.[23] The formation of tridentate dianionic pincer-type complex with the metal center translates into versatility of these directing groups. Subsequently, in 2014, the same group demonstrated the use of bidentate auxiliaries (8-aminoquinoline or picolinic acid) in Co(II)-mediated C–H functionalization reactions.[24] The formation of catalytically viable Co(III) with the bidentate directing group from cheap and readily available Co(II) was the main highlight of this work. Shortly thereafter, our group developed an efficient Co(II)-mediated C–H activation and annulation reaction of allenes facilitated by 8-aminoquinoline as an auxiliary at room temperature (Scheme 3a).[17] Independently, Rao and Cheng also described Co(II)-catalyzed allene annulation reactions with 8-aminoquinoline benzamides (Schemes 3b and 3c).[18a,b] Because of the importance of Co(II) as a catalyst and the unique reactivity of strained π-systems, our group subsequently demonstrated a Co(II)-catalyzed aryl C–H activation/intermolecular annulation of sulfonamides (Scheme 3d), phosphoramides, and benzamides by employing various π-systems such as allenes, methylenecyclopropanes, or diynes.[25] More recently, Zhai et al. reported an elegant Co(II)-catalyzed allene trifunctionalization with molecular oxygen employing 2-(1-methylhydrazinyl)pyridine as an auxiliary (Scheme 3e).[19]

Recent years have seen the emergence of electrochemistry as an effective alternative in synthetic chemistry, bypassing the need for stoichiometric oxidants. On this basis, the Ackermann group recently developed an electrocatalytic cobalt-catalyzed pyridyl *N*-oxide-directed annulation reaction with allenes (Scheme 4a).[20] Subsequently, they also

disclosed an electrocatalytic cobalt-catalyzed annulation reaction with allenes by using 2-(1-methylhydrazinyl)pyridine as a directing group (Scheme 4b).[21]

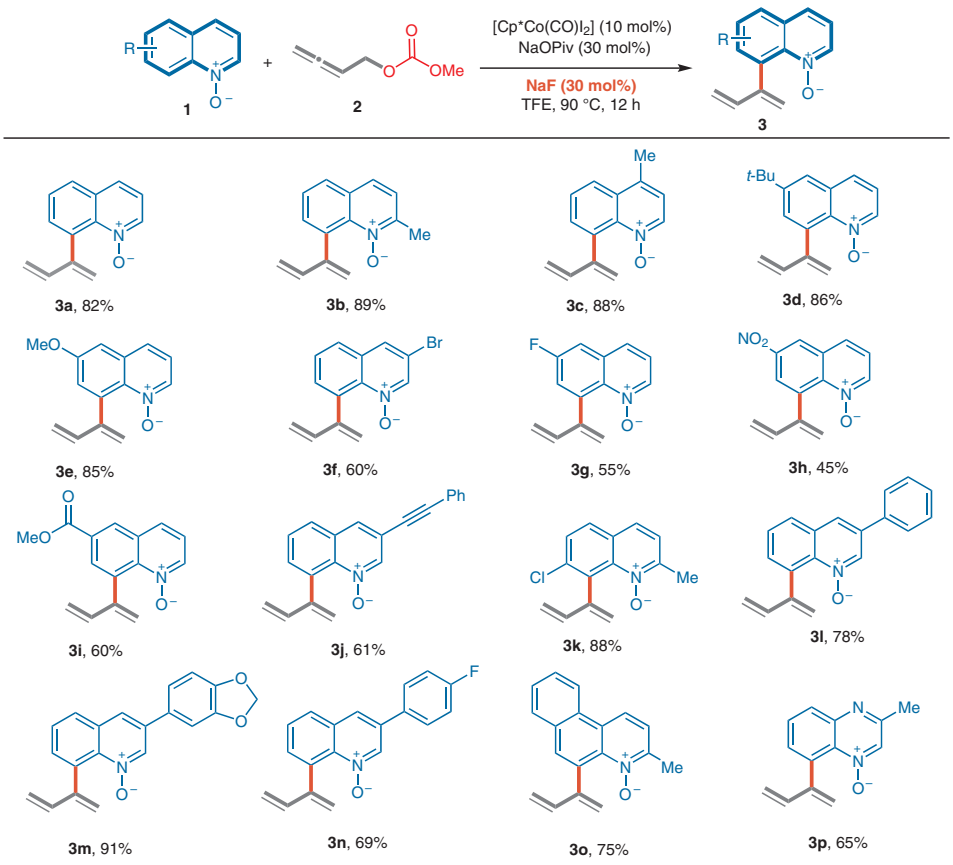
2 Cobalt(III)-Catalyzed C-8 Dienylation of Quinoline *N*-Oxides with Allenes

2.1 Background

As mentioned above, allenes were previously tested in a variety of Co-catalyzed C–H activation reactions. However, the use of allenes bearing leaving groups at the α-position as convenient coupling partners in C–H activation was much less explored. In nucleophilic substitution reactions, these allenes typically show two distinct reactivities based on the nature of the nucleophile. Stabilized carbon nucleophiles in the presence of metal catalysts furnish substituted allenes through outer-sphere nucleophilic attack (Scheme 5a).[26] However, complementary reactivity has been documented in reactions with nonstabilized nucleophiles, leading to substituted dienes and proceeding through an inner-sphere mechanism.[27] The importance of dienes as key building blocks in organic synthesis encouraged us to study the reactivity of organocobalt species generated by C–H activation with allenes bearing leaving groups to realize an efficient dienylation.[28] After C–H activation, selective 2,3-migratory insertion of allenes with a hetero-aryl–cobalt(III) intermediate leads to a key Co–σ-allyl intermediate that, after β-elimination, affords the corresponding dienylated quinolines. With this synthetic design in mind, we developed a protocol wherein allenyl carbonates efficiently reacted with quinoline *N*-oxides to furnish C-8 dienylated quinolines under cobalt(III) catalysis (Scheme 5b).

2.2 Optimization and Scope

Quinoline *N*-oxide (**1a**) and allenes having various leaving groups in the α-position were chosen as model substrates to test the facile Co-catalyzed C-8 dienylation. As expected, the choice of the leaving group was found to be crucial, and carbonates were most favorable. After extensive optimization studies, the best results were obtained by employing 10 mol% of Cp*Co(CO)I_2 and 30 mol% of NaOPiv in 2,2,2-trifluoroethanol (TFE) at 90 °C. The addition of 30 mol% of NaF was found to be crucial for achieving the de-



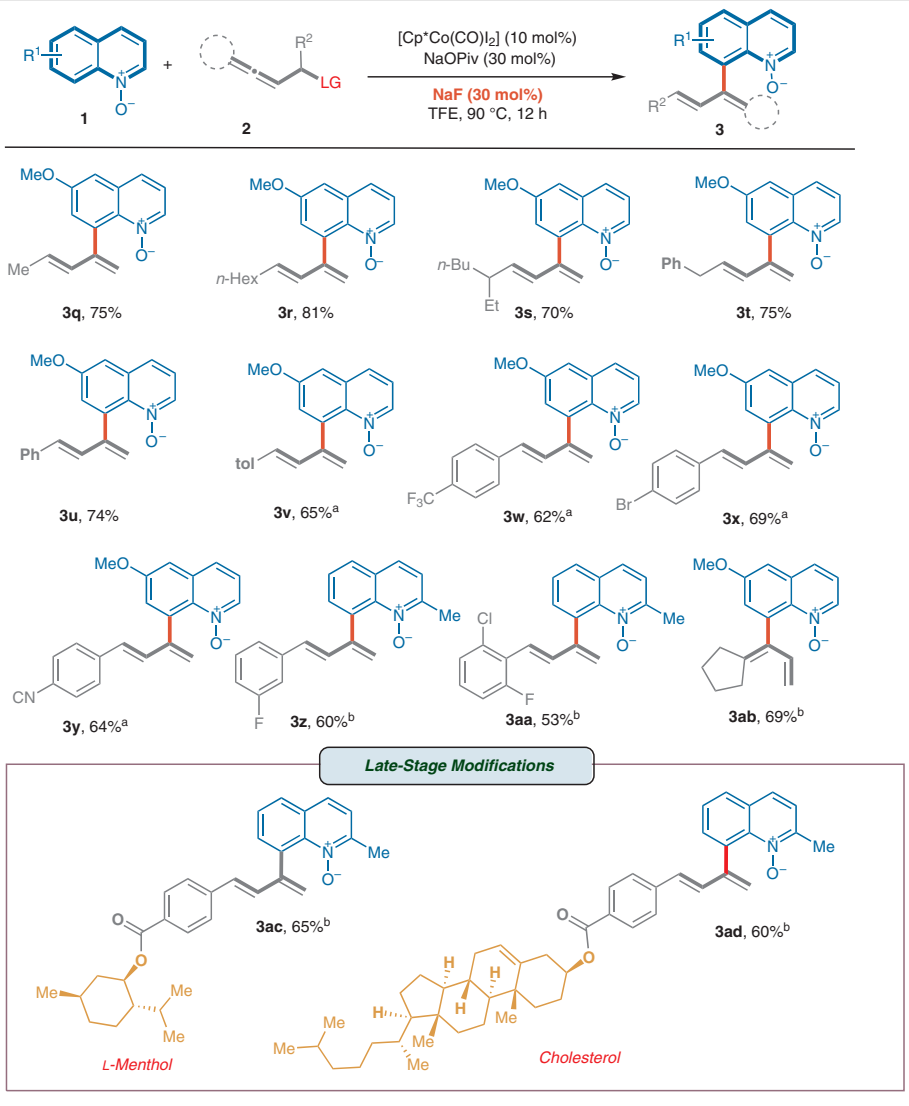
Scheme 6 Dienylation of various quinoline *N*-oxides

sired transformation (Scheme 6).[28] It is also worth mentioning that the efficacy of the transformation was considerably inferior when Rh(III) or Ru(II)-salts were tested in place of Co(III), indicating the unique reactivity of Cp*Co(III) salts in the transformation.

A variety of C-8 dienylated quinoline *N*-oxides were synthesized under the standard reaction conditions. As shown in Scheme 6, the reactivity of diversely substituted quinoline *N*-oxides was studied. To our delight, the reaction accommodated a variety of substituents, including electron-withdrawing or electron-donating groups in the 2-, 3-, 4-, 6-, or 7-positions of the quinoline moiety, and it delivered the corresponding products **3a–n** in moderate to good yields (45–91%). We were pleased to observe that the protocol could be extended to benzo[*f*]quinoline *N*-oxide and quinoxaline *N*-oxide, giving the corresponding dienylated products **3o** and **3p** in yields of 75 and 65%, respectively.

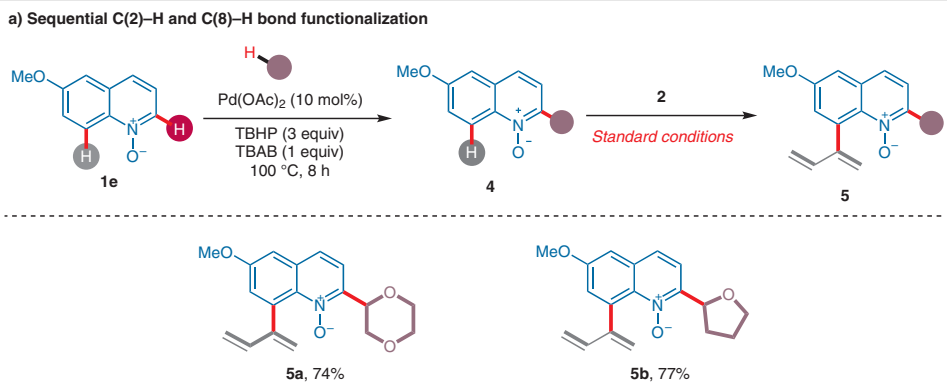
Subsequently, the scope of the allenyl carbonates **2** was also studied (Scheme 7). A variety of allenes bearing aliphatic or aromatic substituents afforded the corresponding dienes effortlessly in moderate to good yields. The protocol also permitted late-stage modification of complex bioactive molecules such as L-menthol and cholesterol by employing the corresponding allenyl carbonates.

Sequential Pd-catalyzed C2 C–H functionalization followed by Co-catalyzed C8 C–H functionalization permitted expedite syntheses of diversely substituted quinoline-*N*-oxides from simple quinoline *N*-oxides. A palladium-catalyzed radical C-2 alkylation was carried out in the first step and

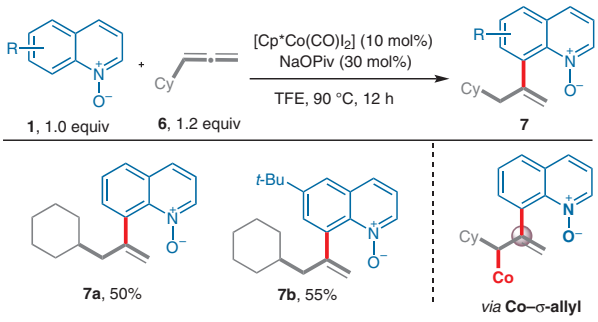


[a] LG = Boc, [b] LG = Ac

Scheme 7 Allene scope for dienylation. LG = leaving group.



Scheme 8 Sequential C-2 and C-8 functionalization



Scheme 9 Co(III)-catalyzed C-8 alkenylation

the resulting products **4** were used in subsequent C-8 dienylations under standard reaction conditions with **2a** to afford the difunctionalized quinoline *N*-oxides **5** in good yields (Scheme 8).

Consequently, selective C-8 alkenylation of quinoline *N*-oxides was demonstrated in moderate yields under the standard conditions by using allenes devoid of leaving groups (Scheme 9). The formation of the branched alkenes **7** with allenes devoid of leaving group indicates that the organocobalt intermediate undergoes a 2,1-migratory insertion leading to a Co–σ-allyl intermediate.

The dienylated quinoline *N*-oxides **3** were then shown to undergo a variety of synthetic transformations (Scheme 10). The *N*-oxide bond was selectively cleaved by using PCl_3. A clean switch of the *N*-oxide oxy functionality to the α-carbon was observed when quinoline *N*-oxide **3b** was treated with acetic anhydride to furnish α-acetoxy-substituted quinaldine **9**. To our delight, 2-triazolyl quinolines **11** were obtained in excellent yields by reaction with *N*-sulfonyl triazoles **10** under metal-free conditions.[29] Furthermore, dienylated quinolines **8** and **11**, obtained by reduction or triazolylation, respectively, were tested in a Diels–Alder reaction and in catalytic hydrogenation (Scheme 10b).

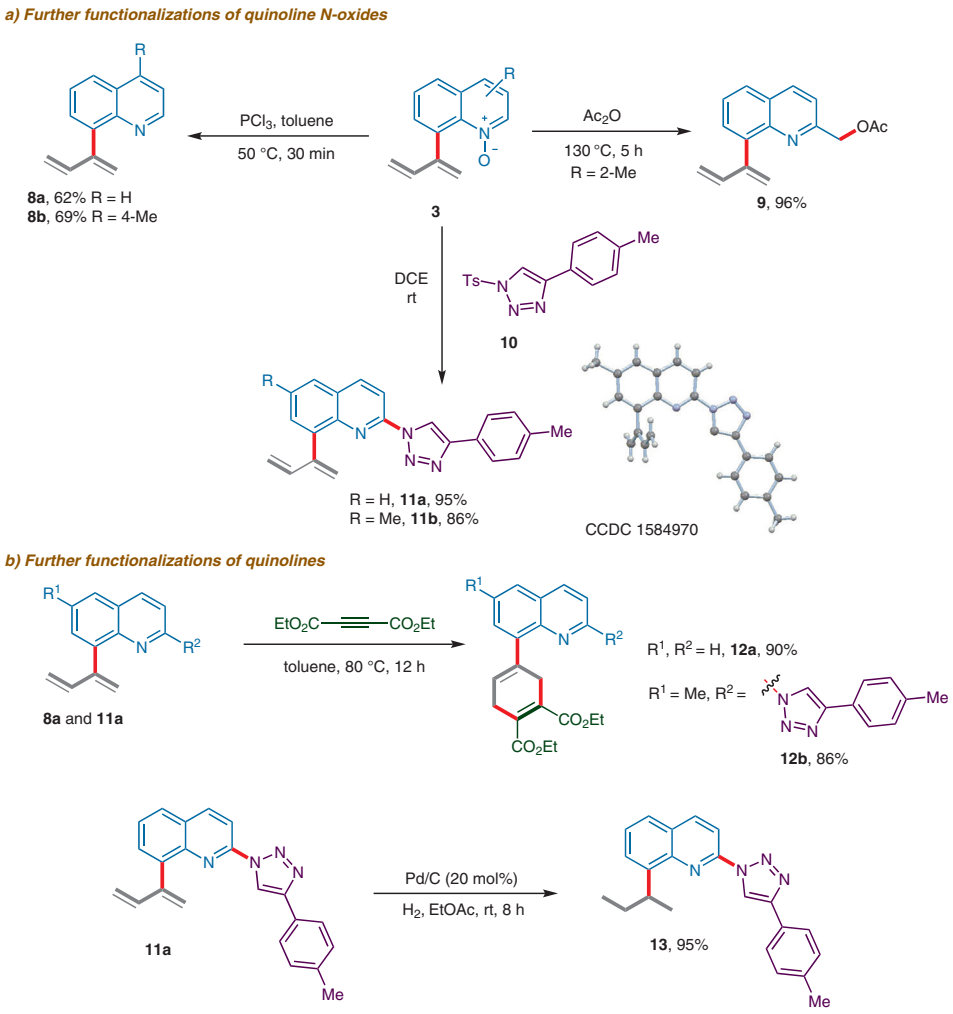
2.3 Mechanistic Studies

To shed light on the reaction mechanism, a series of preliminary mechanistic experiments were performed. Deuterium-labeling experiments were carried out under the optimized reaction conditions to examine the incorporation of deuterium at the C(8)–H position of quinoline *N*-oxide (Scheme 11). No deuterium/hydrogen scrambling occurred at the C(8) position in the presence or absence of an allene. This experiment suggests that the C–H bond-cleavage step might be irreversible.

Subsequently, kinetic studies were undertaken in which a competitive isotope effect (k_H/k_D) of 1.34 was observed when a 1:1 mixture of **1a** and its 8-deuterated analogue **[D]-1a** was treated with the allene **2a** under the standard conditions (Scheme 12a), whereas two parallel reactions with **1a** and **[D]-1a** in the presence of the allene **2a**, showed a kinetic isotopic value (k_H/k_D) of 1.29 (Scheme 12b). These results implied that C–H bond cleavage is not involved in the rate-limiting step.

3 Conclusion

In conclusion, we have summarized the application of allenes as useful reaction partners in both Co(III)-catalyzed and Co(II)-mediated C–H activation reactions for realizing divergent transformations leading to structurally variant frameworks. By judicious choice of the C–H activation substrate and the leaving group on the allene, a practical and efficient C8-dienylation of quinoline *N*-oxide was demonstrated by using 10 mol% of Cp*Co(III) as a catalyst. The operationally simple conditions tolerate a wide array of functional groups on both reaction partners. Preliminary deuteration and kinetic studies have given key information on the mechanism. We expect that the versatile reactivity of allenes will find more applications in metal-catalyzed C–H activation reactions.



Scheme 10 Gram-scale further functionalization. The X-ray structure is that of **11b**.

Conflict of Interest

The authors declare no conflict of interest.

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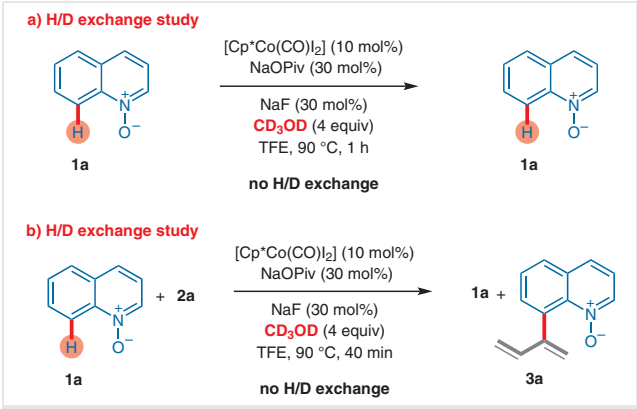
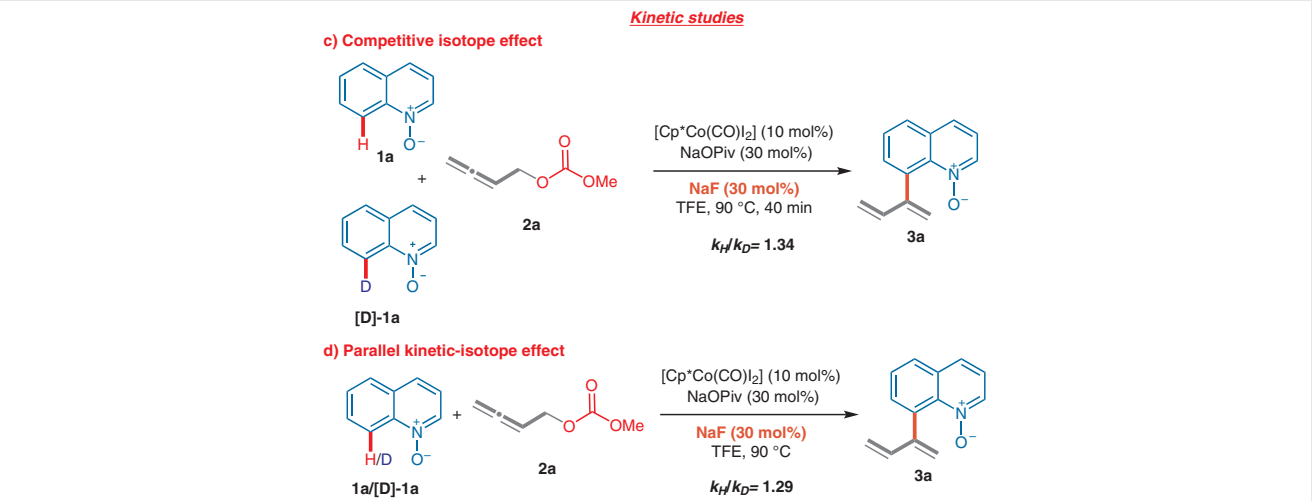


Scheme 11 Deuterium-labelling experiments with quinoline *N*-oxide



Scheme 12 Kinetic studies

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