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C-8-Selective Allylation of Quinoline: A Case Study of β-Hydride vs β-Hydroxy Elimination

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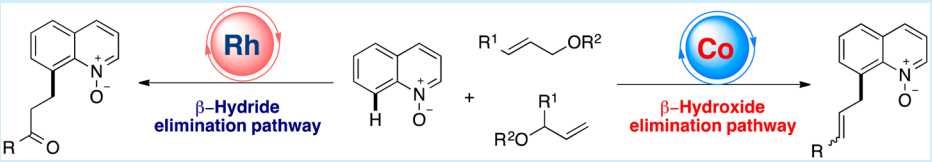
Supporting Information



ABSTRACT: An unprecedented C(8)−H bond allylation of quinoline with allyl carbonate and allyl alcohol catalyzed by Cp*Co(III) using a traceless directing group via β-oxygen and β-hydroxy elimination is described. This site-selective allylation reaction proceeds smoothly with various functional group tolerance including quinoxaline and phenanthridine. Under the nonoxidative reaction conditions, the difference in selectivity between Rh(III) and Co(III), which proceeds through β-hydride and β-hydroxy elimination using allyl alcohol, is shown for the first time.

Over the past decade, activation of C−H bonds emerged as an important tool for atom- and step-economic synthesis.[1] In particular, Cp*Rh(III) has attained its pinnacle over the past few years for a vast number of synthetic transformations through C−H bond functionalization.[2,3] Due to its meager resources and its extortionate prices, however, we need an alternative for bringing our research to a more pragmatic or industrial level. In 2013, Kanai and Matsunaga showed Cp*Co(III), which is not only an alternate catalyst for its noble counterpart [Rh(III)] but also unique in its reactivity and selectivity.[4] However, often the requirement of strong chelating groups such as pyridine and its analogues disfavors its expediency in practical applications.[5] Glorius,[6] Chang,[7] Matsunaga,[8] Ackermann,[9] Sundararaju,[10] and others[11] circumvented this problem recently in a few cases, but the potential for exploiting the unique reactivity of Cp*Co(III) is still great when weakly chelating/traceless directing groups are used.

At the outset of our continuous efforts to examine new reactivity of Cp*Co(III) which includes oxidant-free annulation,[10d] sequential C−H activation/oxygen atom transfer,[10b] C(sp^3)−H bond alkenation,[10a] and C−H bond allylation using allylic substrate including allyl alcohol are reported in this study. Direct allylation of arenes and heteroarenes are of significant value due to its efficacious modification of olefins upon allylation. Though Cp*Co(III)-catalyzed allylation of C−H bonds was demonstrated by Glorius under mild conditions, this required a strong chelating group such as pyridine or its analogues and activated allylic substrate such as carbonate or acetate.[12] Later, Kanai/Matsunaga and Glorius showed that activation of allyl alcohol with other directing groups including amide proceeds via a β-hydroxy elimination pathway using Co(III) as a catalyst.[13] It was in contrast with allylation shown by Glorius and others with Rh(III) and Ru(II) under oxidative conditions, which proceeds via β-hydride elimination pathway.[14] This distinctive behavior of Co(III) and Rh(III) raised our curiosity to explore further reactions which can answer a few more queries. (1) Is β-hydroxy elimination substrate dependent or catalyst dependent? (2) If it is catalyst (metal) dependent, why did Rh(III) gave poor yield compared to Co(III) (for example, see ref 13c)? (3) Do properties of group 9 elements (Co, Rh, Ir) such as atom size, electronic configuration, nucleophilicity, and oxophilicity have any effect in elimination pathway? (4) Can we obtain β-hydroxy and β-hydride elimination products selectively with allyl alcohol using two different metals from group 9 under the same reaction conditions (preferably nonoxidative conditions)?

To gain perspicuity and understanding to answer the above questions, we decided to scrutinize our results on allylation with simultaneous use of Co(III) and Rh(III) employing allyl alcohol as a coupling partner. Owing to the higher activity exhibited against hepatitis by 8-allylquinoline and its lack of presence in the literature for direct synthesis of this novel compound,[15a] we studied the sequential allylation/alkene metathesis catalysis and selective linkage of functionalized alkenes for further applications.[15b] These multifold advantages encouraged us to choose quinoline *N*-oxide as a traceless directing group for remote C−H bond allylation. In order to establish the reactivity of Cp*Co(III) for C−H bond allylation with quinoline *N*-oxide, we have chosen allyl carbonate as the coupling partner, Cp*Co(III) as a catalyst, and carboxylate as an additive in trifluoroethanol as solvent. To determine the best conditions for the reaction, various catalysts, additives, and temperatures were screened thoroughly, and the optimization

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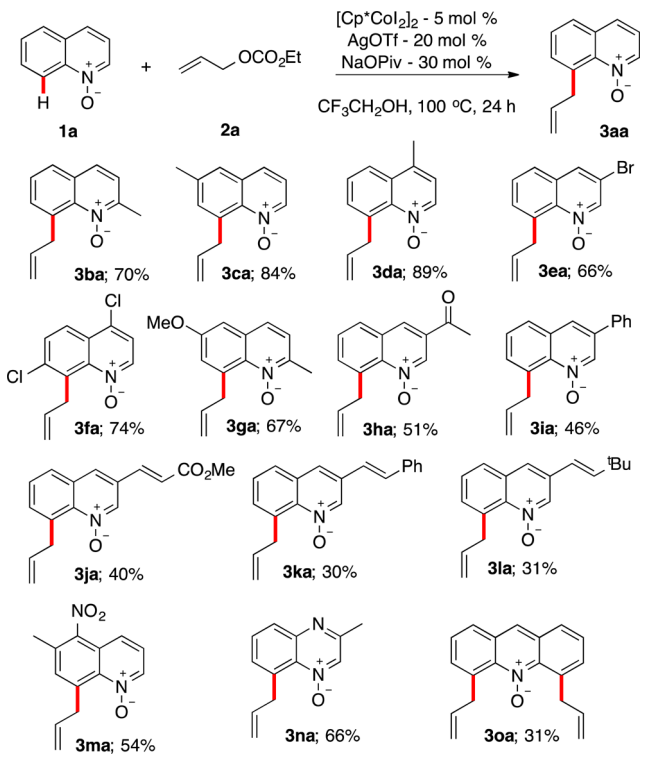
results are shown in Table S1 (see the Supporting Information).

The desired product **3aa** was obtained in 66% yield using Cp*Co(CO)I_2 (**A**) (5 mol %) along with NaOPiv (30 mol %) as an additive after a brief screening of metal carboxylates at 80 °C (Table S1, entry 1−6). Neither changing the solvent nor increasing the temperature provides augmentation in the product formation (entry 7). Next, we investigated the effect of ionization by the addition of various silver salts. Silver triflate gave allylated product **3aa** in 67% yield, whereas silver hexafluoroantimonate gave only 35% yield (entries 8 and 9). Further exploration of different cobalt catalysts including preformed cationic cobalt complex (**C**) revealed that $[Cp^*CoI_2]_2$ (**B**)[13d] provides the best yield at 100 °C for 24 h (entry 10−12). In addition, our controlled experiments showed that all three components are necessary to obtain **3aa** in high yield (entryies 13 and 14). Additional experiments were carried out with Rh(III) and Ir(III); while the former gave 73% yield of **3aa**, the latter did not give any product (entries 15 and 16).

With optimized conditions in hand, we further explored the scope of quinoline *N*-oxide (Scheme 1). Modest yields were

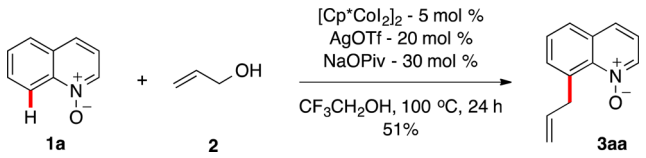
Scheme 1. Scope of Quinoline *N*-Oxide



obtained when substrates changed from electron-rich to electron-poor quinoline *N*-oxide (**3ba−ha**). Various substituents at the C-3 position of **1a** such as Ph, electron-poor, and electron-rich olefins resulted in moderate yield (**3ia−la**). A wide range of substrates having functional groups that are known to be sensitive such as nitro and ketone groups were tolerable under our reaction conditions (**3ma**,**ha**). Analogues of quinoline *N*-oxides such as quinoxaline gave the allylation product in good yield, whereas acridine gave exclusively the bis-allylation product albeit in low yield.

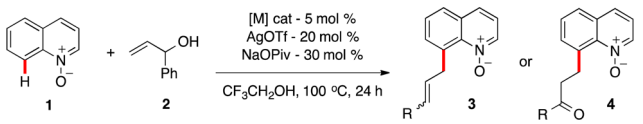
Next, we investigated allyl alcohol as a substrate with **1a** under standard conditions. To our delight, we obtained **3aa** in 51% yield (Scheme 2). This initial result probed us to investigate the allylation with allylic alcohol using Co(III).

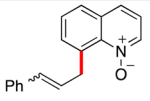
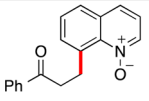
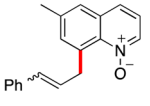
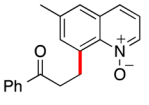
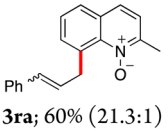
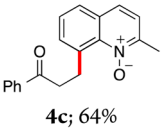
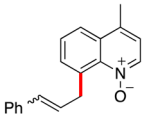
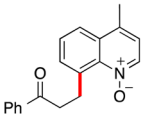
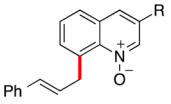
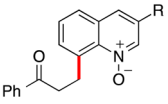
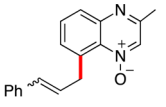
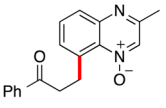
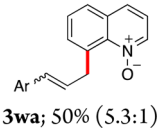
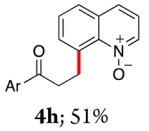
Scheme 2. C(8)−H Bond Allylation of 1a with Allyl Alcohol



The scope of allylation with cobalt(III) was carried out using α-vinylbenzyl alcohol as the allylic substrate and quinoline *N*-oxide as a traceless directing group (Table 1). Methyl

Table 1. Allylation vs β-Aryl Ketone Catalyzed by Co(III) and Rh(III)[a]



entry	2	Co(III)	Rh(III)
1		 **3pa**; 70% (8.3:1)	 **4a**; 64%
2		 **3qa**; 74% (8.4:1)	 **4b**; 52%
3		 **3ra**; 60% (21.3:1)	 **4c**; 64%
4		 **3sa**; 65% (13.3:1)	 **4d**; 40%
5		 R = Br (**3ta**); 35% R =-CH=CH-CO_2Me (**3ua**); 50%	 R = Br (**4e**); 23% R =-CH=CH-CO_2Me (**4f**); 46%
6		 **3va**; 37% (9.2:1)	 **4g**; 44%
7	 Ar = 2-napthyl	 **3wa**; 50% (5.3:1)	 **4h**; 51%

[a]Numbers in parentheses are the ratio of *E* and *Z* isomers; Co(III) = $[Cp^*CoI_2]_2$; Rh(III) = $[Cp^*RhCl_2]_2$.

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substituents at various positions of quinoline (C-2, C-4, and C-6) gave optimum yields with linear selectivity (**3pa**−**sa**). The reaction proceeded smoothly even in the presence of sensitive but useful groups such as Br- and CO_2Me-, which furnished moderate reaction results (**3ta**−**ua**). Other heterocycles such as quinoxaline also accomplished the reaction (**3va**) with 37% yield. We exposed other aryl-substituted α-vinyl allyl alcohols under the same reaction conditions with Co(III), which progressed placidly (**3wa**). While the manuscript was in preparation, Matsunaga reported C−H bond allylation of amide starting from allylic alcohols using Co(III).[13a]

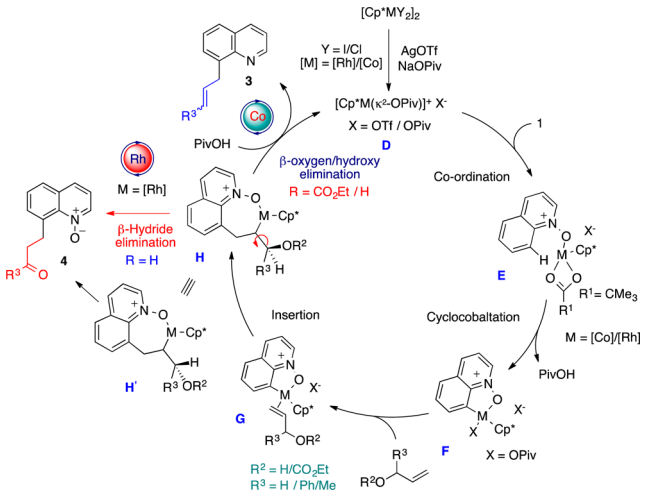
Subsequently, we carried out the allylation with Rh(III) to compare the reactivity and selectivity we obtained with Co(III) (Table 1). As per our expectations, allylation with α-vinylbenzyl alcohol using Rh(III) under our optimized conditions gave β-aryl ketone rather than **3aa**, which is confirmed through NMR and MS analysis. To prove the generality of the reaction, it was performed with various substrates, where we obtained the product with excellent selectivity under the same reaction conditions (Table 1, **4a**−**h**). It is important to note that similar compounds were obtained by Glorius and others using allyl alcohol under oxidative conditions.[14a] Kim showed recently that reaction could be performed with a substoichiometric amount of Cu(II), but the reaction proceeded only with α-alkyl-substituted allyl alcohol,[14c] which compliments to our presented results. To prove the concept, we chose *N*-pyrimidinylindole as the directing group and performed the reaction under our optimized conditions with Rh(III) and Co(III), and to our delight, we observed similar results. With Rh(III), we obtained 48% isolated yield of allylated product and β-aryl ketone product 35% yield, respectively.[16]

Based on the previous results of Glorius and Kanai/Matsunaga,[13] it was believed that β-hydroxy or β-oxygen elimination were facile with Co(III) compared with Rh(III), and the density functional theory results obtained by Kanai/Matsunaga et al. suggest that the energy required for β-hydroxy elimination is comparatively lower with Co(III) than it requires for Rh(III). We looked at the transition states leading to β-hydroxide elimination and β-hydride elimination products for [Cp^*Rh^{III}] catalyst as shown in Figure S1.[16] The transition state $\mathbf{5TS}_{\beta\text{-H}}$ is 5.0 kcal/mol lower in energy compared to $\mathbf{2TS}_{\beta\text{-OH}}$. The DFT results clarify the experimental observations as [Cp^*Rh^{III}] favors the β-hydride elimination pathway.[16,17]

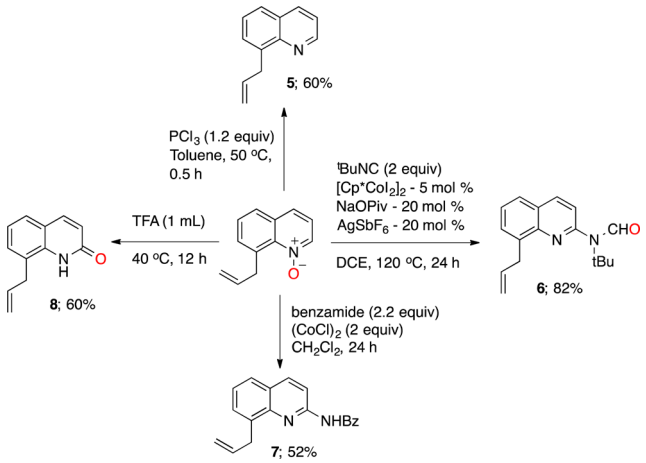
Based on previous reports on allylation with Rh(III) and Co(III),[13,14] we propose the possible mechanism in Scheme 3. Initial ionization in the presence of metal carboxylate led to intermediate **D**. Cationic complex **D** will then be coordinated to the substrate **1a** through oxygen, and subsequent deprotonation led to the cyclometalated complex **F**. This will further coordinate with allylic substrate via olefin coordination followed by 1,2-insertion, leading to intermediate **H**. Intermediate **H** will undergo β-hydride or β-hydroxy elimination depends on the metal we employ. For example, Co(III) undergoes β-hydroxy/oxygen elimination to lead to allylated product, whereas Rh(III) undergoes β-hydride elimination over β-hydroxy elimination to lead to β-aryl ketone, which was further supported by density functional theory calculations (Figure S1).[16]

Quinoline *N*-oxide is a versatile substrate, and it acts as a traceless directing group that allows further diversification at late stages by keeping the allyl fragment intact as depicted in Scheme 4. Selective removal of oxygen mediated by PCl_3 was achieved in 60% yield. *N*-*tert*-Butylformyl groups were

Scheme 3. Proposed Mechanism



Scheme 4. Diversification of 3aa



incorporated at the C-2 position of quinoline using cobalt-catalyzed sequential addition/oxygen transfer with ^{t}BuNC. A similar transformation was observed with Ag(I) salt as catalyst, but it does not give satisfactory results with **3aa**. However, we were pleased to find better product formation of **6** with cobalt(III) as mentioned in Scheme 4.[18] C-2-selective amidation and quinolone were also obtained in good yield.

In conclusion, we have demonstrated unprecedented Cp*Co(III)-catalyzed remote C(8)−H bond allylation of quinoline using *N*-oxide as a traceless directing group and allyl carbonate as a coupling partner. An oxidant-free, good functional group tolerance allylation of C−H bonds was achieved under mild conditions. Diverse selectivity was obtained with Rh(III) and Co(III) via β-hydride and β-hydroxy elimination. This difference in selectivity was shown for the first time under nonoxidative conditions and further supported by DFT calculations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01845.

Experimental methods, optimization of reaction conditions, and other supplementary data (PDF)

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Notes

The authors declare no competing financial interest.

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