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A Mild Hydroaminoalkylation of Conjugated Dienes Using a Unified Cobalt and Photoredox Catalytic System

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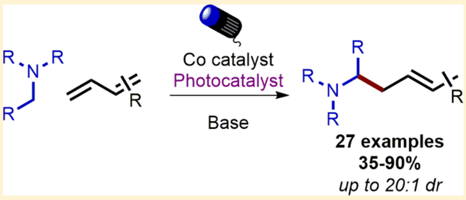
Supporting Information

ABSTRACT: Metallo-photoredox catalysis has redefined the available bond disconnections in the synthetic arsenal. By harnessing the one-electron chemistry of photoredox catalysis in tandem with low-valent cobalt catalysts, new methods by which functionalities may be stitched together become available. Herein we describe the coupling of photoredox-generated α-amino radical species with conjugated dienes using a unified cobalt and iridium catalytic system in order to access a variety of useful homoallylic amines from simple commercially available starting materials. We present a series of mechanistic experiments that support the intervention of Co−hydride intermediates that undergo diene insertion to generate Co−π-allyl species.



INTRODUCTION

Hydroaminoalkylation of double bonds is a powerful method to access linear amine functionalities from simple starting materials. This is traditionally achieved through hydroformylation/reductive amination of an alkene by a noble metal catalyst.[1] More recently, hydroaminoalkylation can be accomplished by the direct activation of an alkylamine, most often *N*-methyl, and its addition across a π unsaturation catalyzed by early transition metal complexes (Figure 1, eq 1).[2,3] Despite the power of this approach, these conditions struggle with low functional group tolerance, forcing reaction conditions, and substrate scope. The hydroaminoalkylation of dienes, in particular, is problematic using established approaches (Figure 1, eq 2).[4]

Our group has recently explored the coupling of photoredox catalysis[5,6] with cobalt catalysis in order to access low-valent cobalt(I) or cobalt(0) intermediates for the construction of arenes through [2 + 2 + 2] cycloadditions.[7] These low-valent cobalt species are traditionally accessed in situ using strong reducing conditions such as heterogeneous metals or Grignard reagents because of their synthetic challenge and poor bench stability.[8] The problem of limited functional group tolerance with an in situ Grignard/reducing metal reduction is overcome by using a tertiary amine as a reductive quench in a visible-light-driven photoredox cycle. The α-amino radicals thus generated are known to undergo addition to very electron-deficient olefins such as alkylidene malonates (Figure 1, eq 3). It is noteworthy that the use of simple acrylates under these conditions leads to lower yields.[9]

We became particularly drawn to cobalt's predilection for unactivated dienes[10] as a method to render these species reactive toward photoredox-generated α-amino alkyl radicals. The realization of this coupling could lead to an array of useful building blocks, including homoallylic amines.

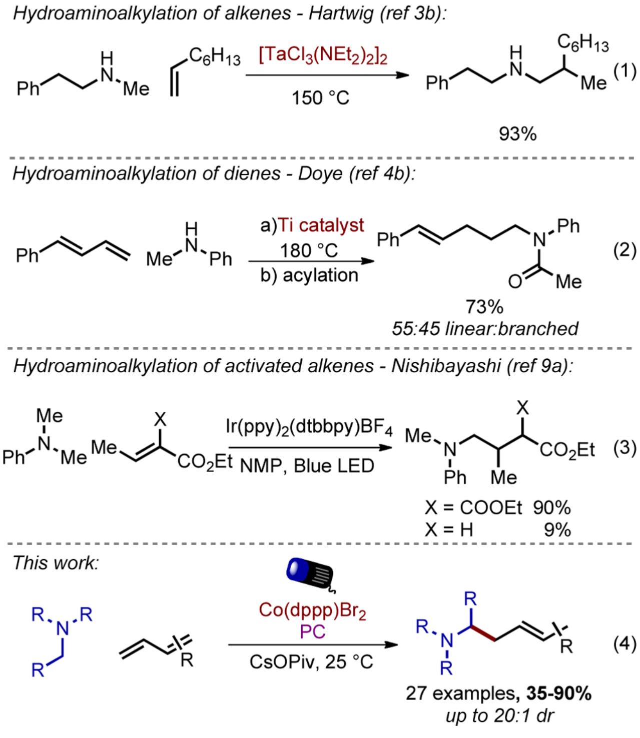


Figure 1. Catalyzed hydroaminoalkylation.

RESULTS AND DISCUSSION

We began our study by screening a variety of cobalt precatalysts in the presence of dimethylaniline and isoprene (Table 1). The

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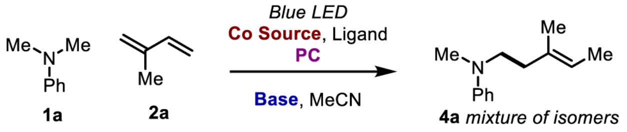
Table 1. Reaction Optimization



Entry[a]	Co Source	Base	Ligand	Yield (%)
1	$Co(OAc)_2$	KOAc	-	trace
2	$CoBr_2$	KOAc	dppp	52
3	**$CoBr_2$**	**CsOPiv**	**dppp**	**71**
4	$CoBr_2$	CsOPiv	bpy	62
5	$CoBr_2$	-	dppp	trace
6	-	CsOPiv	dppp	trace
7[b]	$CoBr_2$	CsOPiv	dppp	-

[a] Optimizations were performed on a 0.1 mmol scale using **1a** (2 equiv), **2a** (1 equiv), Co source (10 mol %), ligand (10 mol %), base (0.4 equiv), and **PC** (0.5 mol %) over a period of 12 h. [b] The reaction was run in the absence of a photocatalyst.

extensively used commercial $[Ir(dF\text{-}CF_3ppy)_2dtbbpy]PF_6$ (**PC**) was primarily used since it was deemed suitable for the reduction of cobalt in our prior studies.[7] We observed a trace mass corresponding to our intended product in the presence of $Co(OAc)_2$. In the presence of a diphosphine ligand (dppp), the yield increased to 52%. Further optimization of the reaction conditions revealed that CsOPiv is the optimal base for this reactivity. Control studies indicated that cobalt, light, and the photocatalyst are all needed for reactivity, although the reaction proceeds using several other common bidentate ligands. It should be noted that with electron-deficient dienes, such as ethyl sorbate, there is a background reaction in the absence of cobalt that proceeds in ∼10% yield. For electron-neutral and -rich dienes, there is trace or no background reaction (<1%).

The reaction shows good fidelity with respect to alternating periods of irradiation and darkness, indicating that this reaction is not subject to a radical-chain propagation mechanism.[11] Additionally, the quantum yield of the reaction was measured and found to be 4%, which also suggests that a radical-chain propagation mechanism is unlikely. The initial reaction rate is dependent on the photocatalyst employed, with a more strongly reducing catalyst such as $[Ir(ppy)_2(dtbpy)]PF_6$ showing a higher initial rate of reaction.[12] However, the fluorinated catalyst **PC** was used in the optimized conditions because of higher yields from increased longevity. The organic photocatalyst 4Cz-IPN developed by Zhang[13] also proved competent in the reaction, albeit with lower yields.

With these optimized conditions in hand, we explored the scope of this reactivity using ethyl sorbate as the diene substrate (Figure 2). The scope of tertiary amines is quite broad, tolerating a wide variety of functionalized anilines, including aryl bromides and terminal alkynes (**3d** and **3g**, respectively). Secondary positions can also be functionalized, although with limited control over the diastereoselectivity of the two newly formed stereocenters (**3f**, **3h**, and **3j**, with the exception of **3h** formed in 8:1 dr). Fully aliphatic amines also participate in the reaction, favoring primary positions for alkylation over secondary or tertiary positions.[14] This allows for the incorporation of heterocycles such as piperidine (**3l**) and morpholine (**3m**) as well as linear aliphatic amines (e.g., **3n**). In all cases, bis- and trisaddition of the diene contributes to the loss in yield. However, this is largely mitigated through use of a moderate excess of amine substrate (1.25 to 2 equiv).

The scope of the diene coupling partner was also explored (Figure 3). Simple dienes, such as butadiene and isoprene, participate in the reaction with lower fidelity for the (*E*)-olefin and lower regioselectivity (delivering products **4a** and **4b**). Ketone **4d** can be accessed directly through the use of a silyl enol ether coupling partner, which is deprotected upon workup. Electron-poor dienes participate well in the reaction, whereas many electron-rich dienes are typically low-yielding.[15] Cyclic dienes in particular are poor substrates, often giving less than

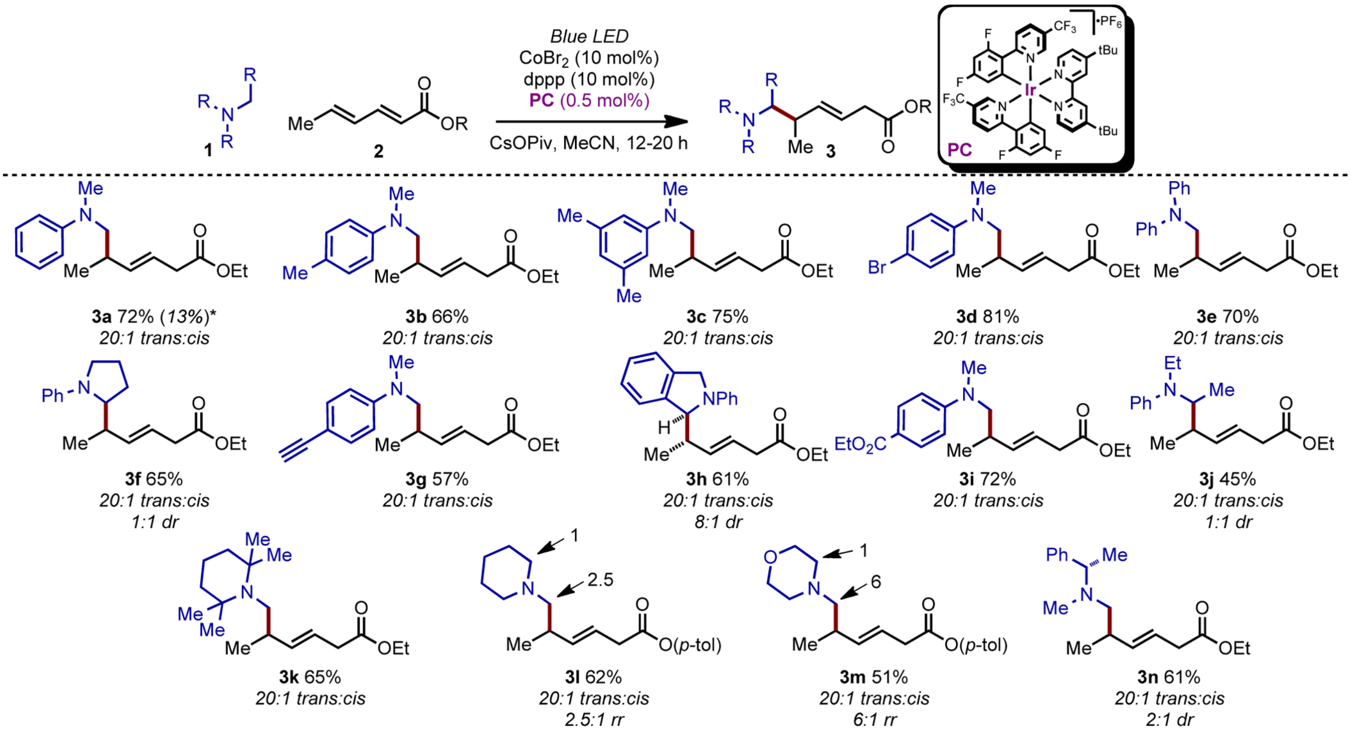


Figure 2. Amine scope. *Yield in the absence of $CoBr_2$.

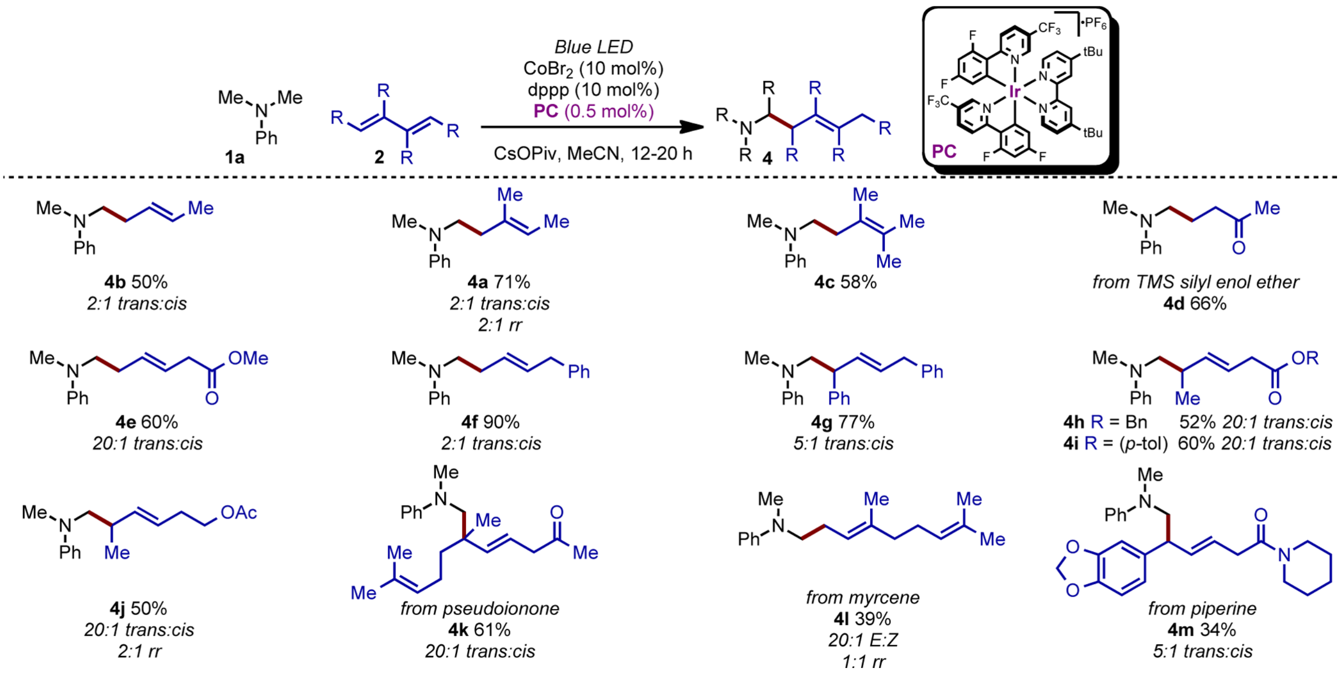


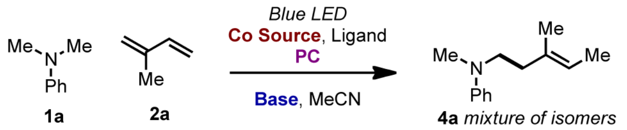
Figure 3. Diene scope.

10% yield. More complicated linear dienes such as pseudoionone, myrcene, and piperine also proved to be competent in the reaction, delivering products **4k**−**m**. Importantly, these reaction conditions are tolerant of myriad functionalities that are known to react in competing pathways, including reducible aryl halides (en route to **3d**), terminal aryl alkynes (**3g**), basic amine functionality (pentamethylpiperidine, *N*-methylpiperidine, *N*-methylmorpholine), and an enol silane and allyl acetate (starting materials en route to **4d** and **4j**, respectively). The formation of a quaternary stereocenter is also noteworthy (**4k**).

In terms of a likely mechanism, we considered that the aminoalkyl radical may simply add to an in situ-formed low-valent Co−diene complex. This chemistry seems to progress solely in the presence of carboxylate bases and shows only trace product in the presence of other common bases (entries 1 and 2 vs 3−5 in Table 2) . However, when the precatalyst salt was changed from CoBr$_2$ and dppp to Co(OPiv)$_2$·dppp, some of the reactivity with these other bases was restored (entries 8−10 in Table 2).

We further noted that a cyclic voltammetry (CV) study[16] showed an absence of a reoxidation peak of the Co catalyst in the presence of both butadiene and pivalic acid (Scheme 1a-iv). This potentially indicates that the Co(I) species generated by the electrode is fully consumed in the presence of both a carboxylic acid and a diene, presumably in an oxidative event to generate an allyl−Co(III) intermediate (Scheme 1b). Thus, the latter is incapable of undergoing a subsequent oxidation at these potentials, as evidenced by the absence of a reoxidation event in the reverse wave. Without both external components, the reoxidation to Co(II) is still observed (Scheme 1a-ii,iii). Additionally, the premade Co(dppp)(OPiv)$_2$ catalyst showed a well-behaved pseudoreversible curve within the range of the potential of **PC**.[17] This pseudoreversibility was not observed in the presence of other base/ligand types such as carbonate bases. This ligand effect of the pivalate could explain the cyclability of the catalyst solely in the presence of carboxylate bases.

Table 2. Carboxylate Base Effect



Entry[a]	Co Source	Ligand	Base	Yield (%)
1	CoBr$_2$	dppp	CsOPiv	71
2	CoBr$_2$	dppp	KOAc	52
3	CoBr$_2$	dppp	imidazole	trace
4	CoBr$_2$	dppp	Cs$_2$CO$_3$	trace
5	CoBr$_2$	dppp	K$_3$PO$_4$	trace
6	Co(dppp)(OPiv)$_2$	-	CsOPiv	70
7	Co(dppp)(OPiv)$_2$	-	KOAc	45
8	Co(dppp)(OPiv)$_2$	-	imidazole	20
9	Co(dppp)(OPiv)$_2$	-	Cs$_2$CO$_3$	46
10	Co(dppp)(OPiv)$_2$	-	K$_3$PO$_4$	30

[a] See footnote *a* of Table 1.

The CV experiments described above implicate an in situ-generated Co−H that acts on the diene to form a Co−π-allyl intermediate. We considered that it should prove informative to conduct a control experiment in which the low-valent Co was exposed to carboxylic acid in the absence of amine. In the event, we subjected ethyl sorbate to the reaction conditions in the presence of acetic acid but in absence of an amine (Scheme 1c).[18] The results implicate the formation of allyl species, as dimerization of the diene occurs only in a tail-to-tail fashion (product **B**) under these conditions. We often observe this dimerization under the standard reaction conditions, especially with more sluggish amines. While the majority of these dimerization events appear to be photoredox-catalyzed,[19] these experiments were conducted with limiting acid, and the observed product distribution is indicative of complete incorporation of the available protons (Scheme 1c). Under deuteration conditions, the isotope is found at both carbons α to the carbonyls, which we take as strong evidence for the

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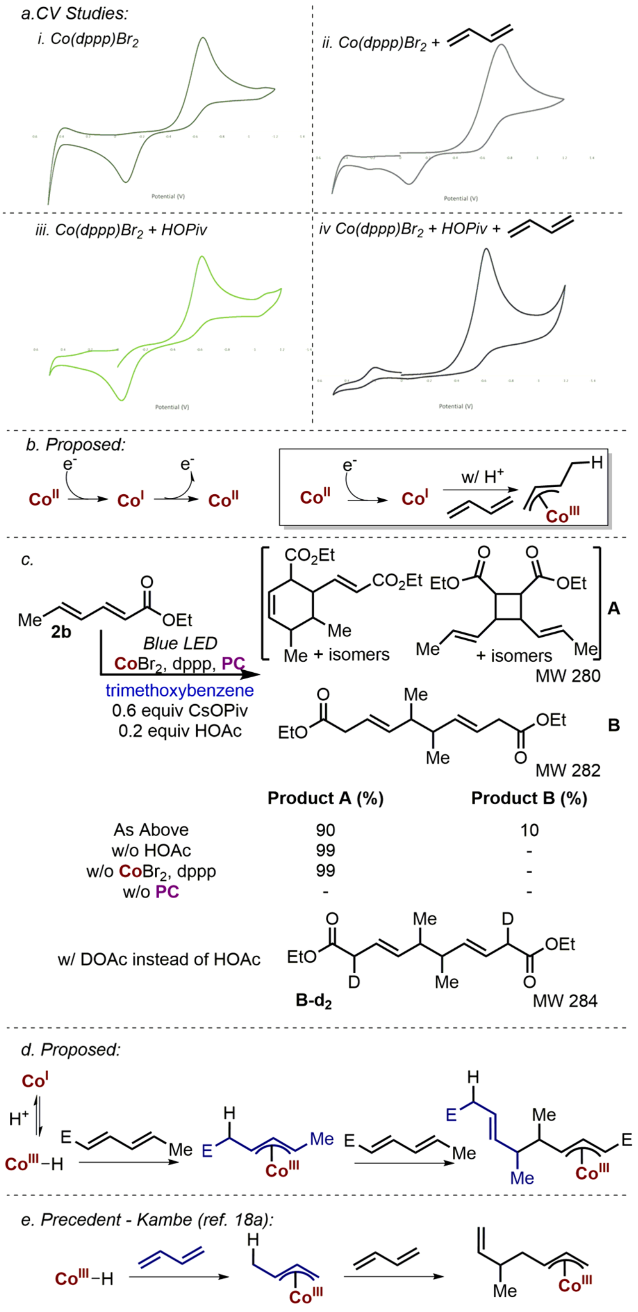
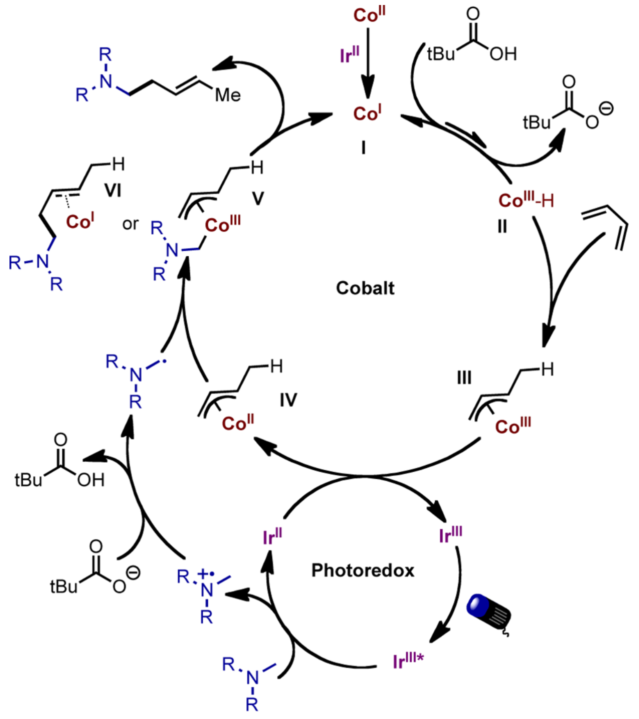
Scheme 1. Control Experiments



	Product A (%)	Product B (%)
As Above	90	10
w/o HOAc	99	-
w/o CoBr$_2$, dppp	99	-
w/o PC	-	-

Scheme 2. Proposed Mechanism



intervention of Co−allyl species. A mechanistic scenario consistent with these observations is illustrated in Scheme 1d. With respect to tail-to-tail dimerization of diene coupling under these conditions, Kambe has observed that butadiene dimerization under Co catalysis occurs by insertion of the diene at the more substituted end of the Co−π-allyl (Scheme 1e).[18a]

A potential mechanism for this transformation that accounts for all of these observations could be described by the cycle presented in Scheme 2. A Co(II) salt is reduced to a Co(I) species in situ by the photocatalyst. CV studies indicate that this reduction should be easily accessible by **PC**[17] given the reduction potential of the precatalyst and the presumably formed Co(dppp)(OPiv)$_2$ (−0.66 V and −1.25 V for [Co^{II}/Co^{I}] vs Ag/AgCl, respectively).[20] This Co(I) species potentially reacts with an equivalent of carboxylic acid (generated through deprotonation of the amine radical cation) to generate a transient Co(III) hydride species, **II**.[20] An equivalent of diene can then undergo migratory insertion into the Co−H bond to form a Co(III)−allyl species. This is supported in part by previous low-valent Co studies in the presence of dienes, indicating that Co(III)−allyls can be generated with dienes and Co(III)−H.[21] This Co(III)−allyl, **III**, can then be reduced by the photocatalyst to generate a Co(II)−allyl, **IV**. Meanwhile, an α-amino alkyl radical is generated through deprotonation of the oxidized tertiary amine. This α-amino alkyl radical may then attack the Co center, **V**, which undergoes reductive elimination to afford the product and Co(I) back into the catalytic cycle. Alternatively, this radical may attack the allyl ligand directly, **VI**, affording the product and a Co(I) species.

■ CONCLUSIONS

We have explored the hydroaminoalkylation of conjugated dienes using a photoredox and Co catalytic system. This reactivity opens new potential pathways for the coupling of π-rich functionalities with photoredox-generated radical intermediates. Ongoing studies are focused on exploring the mechanism in more detail to shed light on other possible transformations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b09252.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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(15) For an extended scope, see the Supporting Information.

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(17) **PC** $[\mathrm{Ir^{III}/Ir^{II}}] = -1.37$ V vs SCE.

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