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Dual Catalysis Relay: Coupling of Aldehydes and Alkenes Enabled by Visible-Light and NHC-Catalyzed Cross-Double C−H Functionalizations

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Cite This: *ACS Catal.* 2021, 11, 9715−9721

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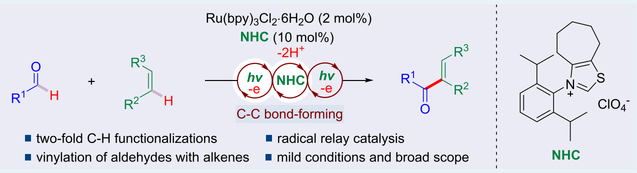
ABSTRACT: Direct functionalizations of two distinct inert C−H bonds represent the most ideal ways to construct C−C bonds. Herein, we report an intermolecular vinylation of aldehydes using alkenes as the vinylating reagents through sequential two-fold C−H functionalizations. The merging of visible light and N-heterocyclic carbene catalysis allows for the coupling of alkenes with aldehydes through a dual catalysis relay enabled cross-dehydrogenative coupling mechanism. The use of diphenoquinone is essential for the success of this reaction, which plays an intriguing two-fold role in the reaction, as an electron acceptor as well as a radical reservoir for the radical coupling enabling the C−C forming process.

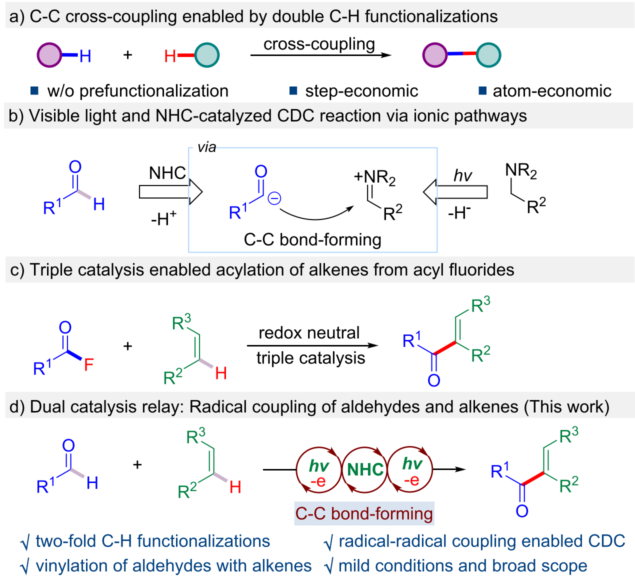


KEYWORDS: *dual catalysis relay, cross-dehydrogenative coupling, NHC catalysis, visible-light catalysis, radical−radical coupling*

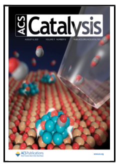
Carbon−carbon bonds represent one of the most abundant and important chemical bonds in organic compounds.[1] Thus, the development of efficient construction of C−C bonds has been a long-term interest in synthetic chemistry and related areas.[2] Conventional cross-coupling reactions between C−X/C−X and C−H/C−X, where X = (pseudo)halides or metals, to form C−C bonds rely heavily on preinstallation of activated chemical handles for starting materials.[3] Although these reactions are highly powerful and synthetically useful, the preactivation of substrates requires additional steps to prepare and generate a stoichiometric amount of metal salts as byproducts. For this reason, cross-dehydrogenative coupling (CDC) represents an ideal alternative for C−C bond formation between two distinct C−H bonds.[4] The significant features of CDC reactions include the following: (1) no prefunctionalization of substrates is required, improving step- and atom-economy with reduced waste; (2) direct C−H functionalizations are highly desirable for late-stage functionalizations (Scheme 1a).[5]

On the other hand, N-heterocyclic carbene (NHC) catalysis[6] and visible-light catalysis[7] have emerged as enabling tools for organic synthesis over the past decades.[8] Therefore, merging visible-light catalysis and NHC catalysis for CDC reactions is attractive yet challenging. Rovis' group reported the α-acylation of tertiary amines enabled by the visible-light and NHC-catayzed cross-dehydrogenative coupling of aldehydes with the α-position of amines via ionic pathways (Scheme 1b).[9] The visible-light and NHC-catayzed cross-dehydrogenative coupling via single electron pathways remains underdeveloped. Recently, NHC-involved single electron transfer reactions have emerged as novel and intriguing reaction modes for bond-forming processes.[10] Thus, combin-

Scheme 1. Impetus for Dual Catalysis Relay Enabled Two-Fold C−H Functionalizations



Received: June 28, 2021
Revised: July 15, 2021
Published: July 19, 2021

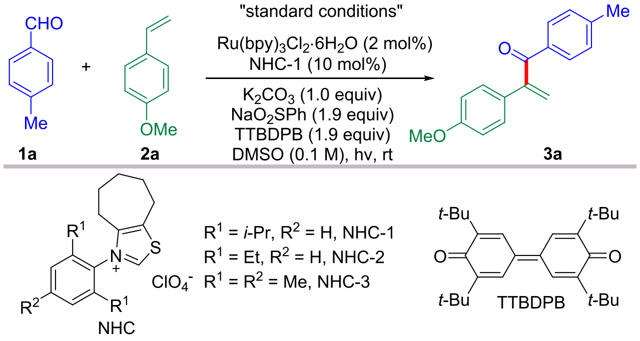


https://doi.org/10.1021/acscatal.1c02890
ACS Catal. 2021, 11, 9715−9721

ing a visible-light and NHC-catalyzed radical pathway offers new opportunities for C−C/C−X coupling reactions.[11] Recently, Ohmiya and Li et al. reported elegant examples of NHC-catalyzed coupling of aldehydes with alkyl radicals in the presence of redox-active esters or activated alkyl halides.[12] In these processes, a carbon electrophile (R−X species) couples with Breslow intermediates from aldehydes to form a C−C bond via a radical mechanism.[13] To date, no report on the formal Heck reaction of aldehydes with alkenes by dehydrogenation has been successful. During the preparation of this paper, Studer reported an elegant example of coupling of acyl fluorides with alkenes enabled by triple catalysis (Scheme 1c).[14a] More recently, Ohmiya developed the NHC-catalyzed two-component or three-component reaction using aryl iodides as the aryl radical precursors.[14b] As part of our continuous interest in visible-light catalysis and NHC catalysis,[15] we herein report the cross-dehydrogenative C−C bond-forming process from aldehydes and alkenes enabled by a dual-catalyzed radical relay (Scheme 1d). The use of a visible-light and NHC catalysis strategy allows for the direct dehydrogenative vinylation of aldehydes with alkenes.[16]

We commenced to investigate the reaction using 4-methylbenzaldehyde **1a** and 4-methoxystyrene **2a** as the prototype substrates. After extensive optimization of the reaction parameters, we define the use of $Ru(bpy)_3Cl_2·6H_2O$ (2 mol %) and NHC-1 (10 mol %) as catalysts, potassium carbonate (1.0 equiv) as base, sodium benzenesulfinate (1.9 equiv) as additive, and TTBDPB (3,3′,5,5′-tetra-*tert*-butyldiphenoquinone, 1.9 equiv) as oxidant in DMSO (0.1 M) under irradiation of 30 W blue LEDs at room temperature as the optimal conditions, affording desired vinylaryl ketone **3a** in 81% isolated yield (Table 1 and Tables S1−S8).[17] The use of another NHC catalyst could also mediate the transformation, albeit in lower conversions and yields (Table 1, entries 2 and 3, and Table S2). Other photocatalysts with reasonable oxidative potential proved efficient for this reaction (Table 1, entries 4−6, and Table S3). The use of other bases to replace potassium carbonate resulted in lower yields of **3a** (Table S4). TTBDPB is essential for the success of this two-fold C−H functionalization reaction. The use of 1,4-benzoquinone, DDQ, or potassium persulfate led to low efficiency of this reaction (Table 1, entries 7−9, and Table S6). Many other sulfinate derivatives could mediate the reaction (Table S7), among which sodium benzenesulfinate furnished the best result of **3a**. Control experiments revealed that both the NHC catalyst and photocatalyst were essential for the desired reaction (Table 1, entries 10 and 11). No desired product **3a** was formed in the absence of NHC catalyst, whereas the reaction delivered **3a** in 15% yield without photocatalyst, probably due to the formation of weak EDA complexes between sulfinate and oxidant. No light irradiation led to no formation of **3a** (Table 1, entry 12), proving that the use of visible light is critical to the success of this transformation. No **3a** was detected in the absence of sulfinate or oxidant (Table 1, entries 13 and 14).

Table 1. Condition Evaluation for the Direct Coupling of Aldehydes with Alkenes[a]

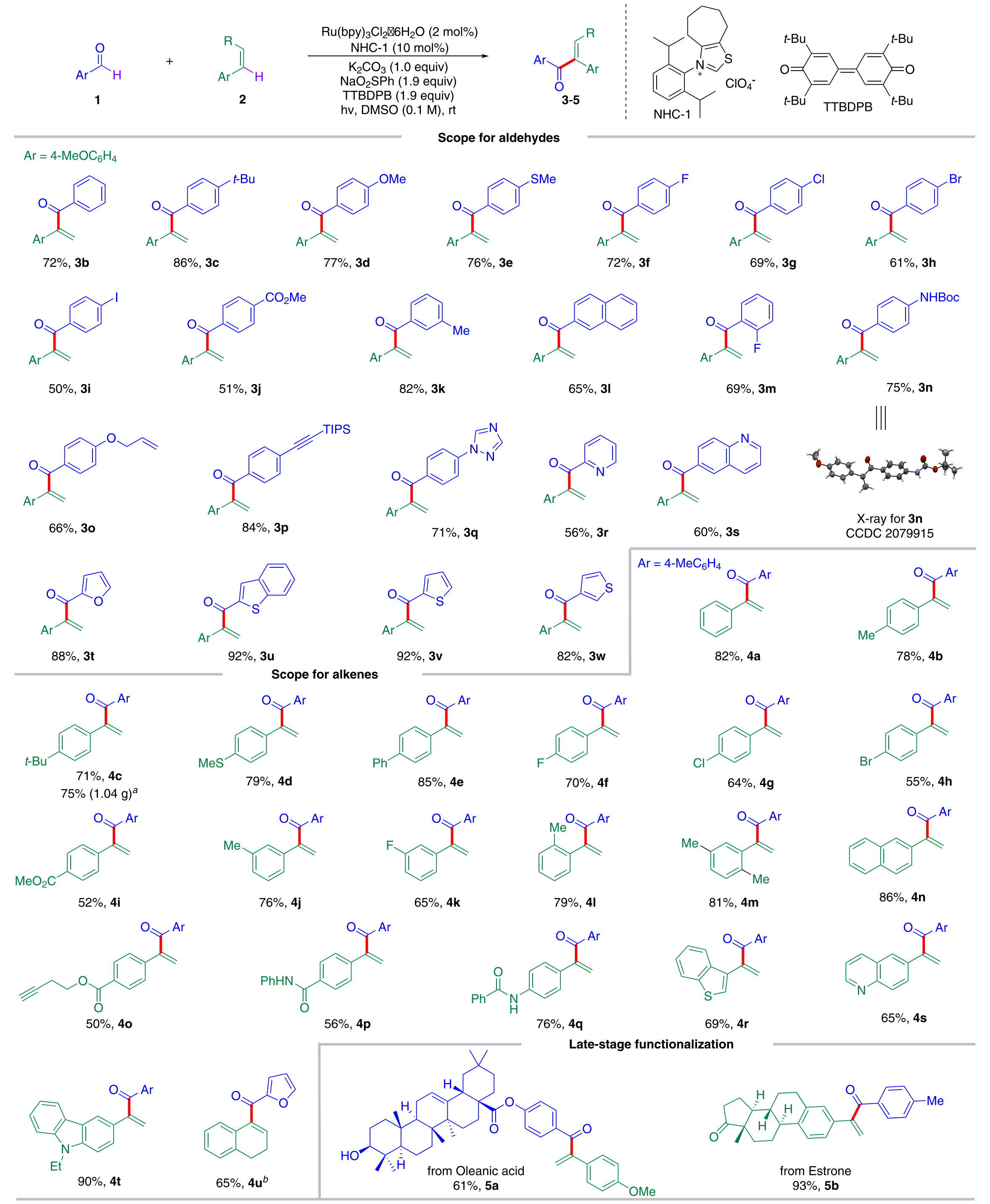


entry	variation from standard conditions	yield of **3a**[b]
1	none	83% (81%)
2	NHC-2 instead of NHC-1	64%
3	NHC-3 instead of NHC-1	72%
4	4Cz-IPN as PC	58%
5	$Ru(bpz)_3(PF_6)_2$ as PC	61%
6	$[Ir(ppy)_2(dtbbpy)]PF_6$ as PC	76%
7	1,4-benzoquinone as oxidant	7%
8	DDQ as oxidant	trace
9	$K_2S_2O_8$ as oxidant	ND
10	no NHC	ND
11	no $Ru(bpy)_3Cl_2·6H_2O$	15%
12	no light	ND
13	no $PhSO_2Na$	ND
14	no TTBDPB	trace

[a] The reaction was conducted using **1a** (0.2 mmol), **2a** (0.1 mmol), with 30 W blue LEDs under indicated conditions. [b] Yield was determined by ^1H NMR of the crude mixture of the reaction using mesitylene as internal standard. Number in the parentheses is the yield after flash chromatography. PC = photocatalyst. ND = not detected.

With the optimized conditions in hand, we evaluated the scope of this reaction. The mild conditions tolerated a wide variety of functional groups and substitution patterns in terms of aldehydes and alkenes for this dual-catalyzed vinylation reaction of aldehydes (Table 2). First, the scope of aldehydes was evaluated. Electron-withdrawing and electron-donating substituted aromatic aldehydes were well-tolerated under the reaction conditions, giving the corresponding vinylphenylketones in 50−86% yields (**3b**−**3q**). Various *para*-substituted aromatic aldehydes were all good substrates for this reaction, affording the desired C−C coupling products in 50−86% yields (**3b**−**3j**). Notably, fluoro-, chloro-, bromo-, and iodo-substituted aldehydes were successfully transformed into the desired products in 50−72% yields (**3f**−**3i**), leaving a chemical handle for further elaboration. *meta*-Substituted aromatic aldehyde could be converted to the desired product **3k** in 82% yield. Naphthyl aldehyde could be coupled with **2a** to give the desired product **3l** in 65% yield. *ortho*-Substituted aldehyde could be tolerated to give the desired product **3m** in 69% yield. Moreover, the reaction was compatible with highly functionalized aldehydes. Various sensitive functional groups, such as amides with free N−H, alkenes, and alkynes, were well-tolerated in the reaction, delivering the two-fold C−H functionalization products in 66−84% yields (**3n**−**3p**). The structure of the products was unambiguously assigned by the X-ray diffraction analysis of **3n**. Furthermore, heteroaromatic aldehydes containing triazoles, pyridines, quinolines, furans, benzathiophenes, and thiophenes were all good substrates for this transformation, affording corresponding heteroarylvinyl ketones in 56−92% yields (**3q**−**3w**). Unfortunately, aliphatic aldehydes led to no formation of desired enones. Next, the scope of alkenes was tested. Aromatic alkenes with *para*-substitutents, such as thioethers, halides, and esters, could be converted to the desired vinylketones in 52−85% yields (**4a**−**4i**). The practicality of this reaction was showcased by the gram-scale synthesis of **4c** without erasing the efficiency of this

Table 2. Scope for the Double C−H Functionalization Reaction with Respect to Aldehydes and Alkenes[†]

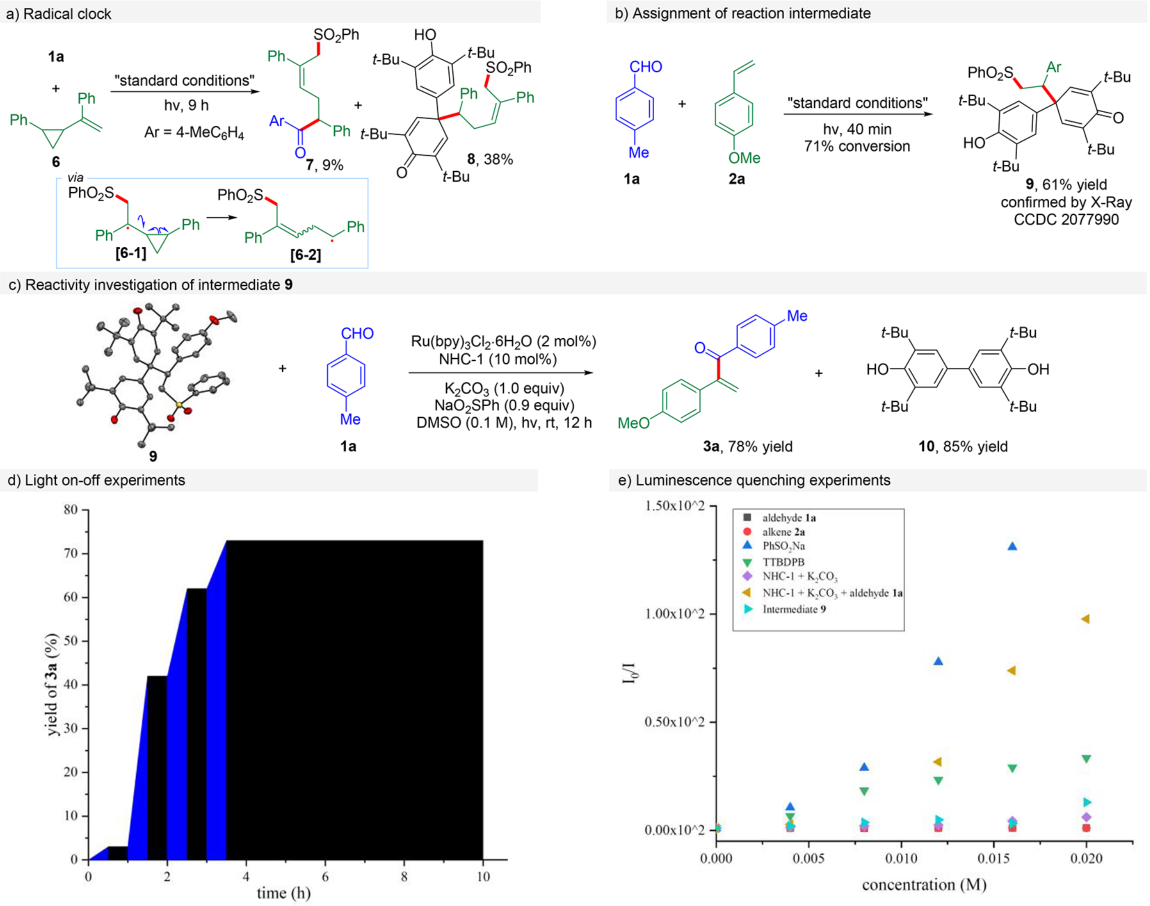


[†]Standard conditions; see Table 1 for details. [a]The reaction was conducted on 5.0 mmol scale. [b]Cs_2CO_3 was used as base, and sodium 4-chlorophenylsulfinate was used as sulfinate. See Supporting Information for details.

reaction. Under the standard conditions, 5.0 mmol of 4-*tert*-butylstyrene was successfully coupled with **1a** to afford 1.04 g of vinylarylketone **4c** in 75% yield. Alkenes with *meta*- and *ortho*-substituents could be converted to the desired vinylketones in 65−79% yields (**4j**−**4l**). Multisubstituted aromatic alkene was successfully involved in the reaction, giving the desired acylated product **4m** in 81% yield. Fused aromatic alkene was converted to **4n** in 86% yield. Moreover, alkenes bearing alkynes and amides were good substrates for the reaction, furnishing acylated alkenes in 50−76% yields (**4o**−**4q**).

Notably, heteroaryl alkenes, such as benzothiophene-, quinoline-, and carbazole-containing alkenes, proceeded smoothly to give corresponding heteroaryl vinyl ketones in 65−90% yields (**4r**−**4t**). Internal alkenes could undergo regioselective acylation with aldehydes to give corresponding arylvinyl ketone **4u** in 65% yield. Unfortunately, aliphatic alkenes did not deliver desired enone products. To further

Scheme 2. Mechanistic Investigations of the Reaction



demonstrate the synthetic potential of this mild protocol, the reaction was applied to late-stage functionalization of natural products. Oleanic acid-derived aldehyde and estrone-derived alkene were both successfully involved in this two-fold C−H functionalization process to deliver corresponding vinylarylketones (**5a** and **5b**) in 61% and 93% yields, respectively.

To gain insight into the mechanism of this reaction, we set up experiments to shed light on the reaction mechanism (Scheme 2). First, the reaction of aldehyde **1a** with cyclopropyl styrene **6** was carried out under standard conditions. Ring opening of cyclopropane was observed, with the formation of **7** in 9% yield and **8** in 38% yield (Scheme 2a). This result suggested the reaction proceeded via the radical intermediate [**6−1**], followed by radical ring opening of cyclopropane to give radical intermediate [**6−2**]. Second, the reaction of aldehyde **1a** with alkene **2a** under standard conditions was conducted for 40 min. Intriguingly, the adduct **9** was formed in 61% yield from the addition of phenylsulfonate with quinone and alkene **2a** (Scheme 2b). The structure of **9** was further confirmed by the X-ray diffraction analysis. Compound **9** was further submitted to the reaction with **1a** in the presence of sodium benzenesulfinate (0.9 equiv) under otherwise identical standard conditions, delivering the vinylation product of aldehyde **3a** in 78% yield along with the formation of biphenol **10** in 85% yield (Scheme 2c). These results indicated the adduct **9** could be the intermediate of this dual C−H bond functionalization process of aldehydes and alkenes. Next, a light on−off experiment was carried out with aldehyde **1a** and alkene **2a** (Scheme 2d). The light on−off results indicated the reaction underwent a catalytic radical reaction instead of a radical chain pathway.[15] Then luminescence quenching experiments were examined with different components (Scheme 2e).[7a] None of aldehyde **1a**, alkene **2a**, the mixture of NHC-1 catalyst with potassium carbonate, or intermediate **9** showed a significant luminescence quenching effect to the excited state of the photocatalyst (Ru(II)*). In contrast, sodium benzenesulfinate as well as the combination of aldehyde **1a** with NHC-1 in the presence of potassium carbonate showed a very strong quenching effect on the excited photocatalyst. These observations provided evidence that either sodium benzenesulfinate or the combination of aldehyde **1a** with NHC-1 in the presence of potassium carbonate could quench Ru(II)* to give Ru(I) via single electron transfer.

Moreover, monitoring the profile for the reaction of aldehyde **1a** and alkene **2a** under standard conditions was conducted and shown in Figure 1. The results showed that alkene **2a** was quickly consumed in the first 40 min of the reaction with little formation of coupling product **3a**. Instead, the yield of **9** increased dramatically. After 40 min, the yield of **3a** increased with the consumption of **9**. **3a** was formed in 78% yield with full conversion of **9** in 4 h. These results further confirmed that this double C−H cross-functionalization of aldehydes with alkenes proceeded stepwisely via a photocatalytic radical relay process and further proved that **9** was the intermediate of this reaction.

Based on the above-mentioned mechanistic results and literature, a plausible mechanism for this transformation is

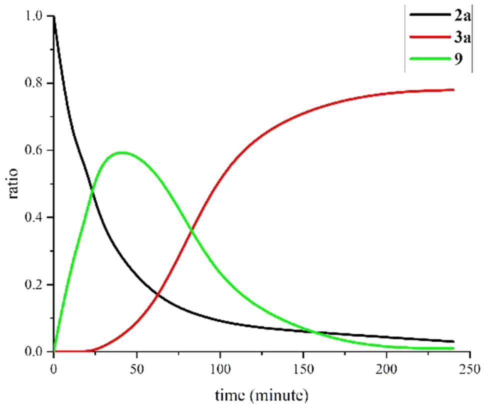
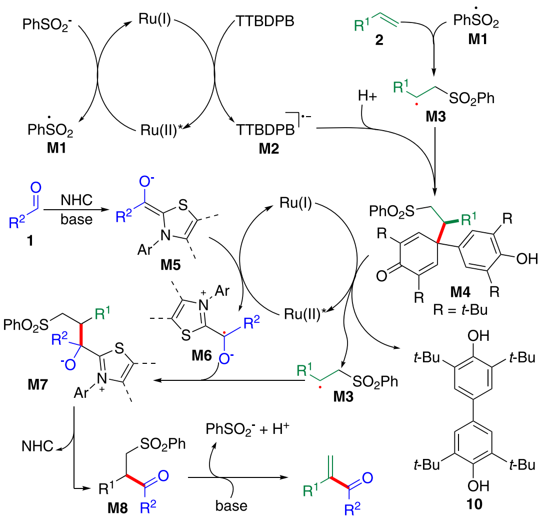


Figure 1. Reaction profile of the reaction of **1a** with **2a**.

depicted in Scheme 3. First, Ru(II)* was formed via photoexcitation of the Ru(II)-based photocatalyst, which was quenched by phenylsulfinate to give the Ru(I) species as well as phenyl sulfonyl radical **M1**. Ru(II) could be regenerated by single electron oxidation of oxidant (TTBDBB) with the formation of radical anion intermediate **M2**. In the presence of alkene, **M1** would undergo radical addition to alkene to give carbon-centered radical **M3**, which rebounded with **M2** via radical−radical coupling followed by protonation to give **M4**.

Scheme 3. Proposed Mechanism for the Reaction



Meanwhile, the radical addition of **M3** to TTBDPB, followed by single electron reduction by Ru(I) to give Ru(II) and **M4**, is also possible. Aldehyde **1** condensed with nitrogen heterocyclic carbene (NHC) catalyst to generate corresponding Breslow intermediate **M5** with the assistance of a base,[18] which could quench the excited photocatalyst (Ru(II)*) by single electron transfer to form radical cationic intermediate **M6** and Ru(I) species.[19] The reduced photocatalyst Ru(I) could reduce **M4** to regenerate radical intermediate **M3** and Ru(II) by single electron transfer. Intermediates **M3** and **M6** could undergo radical−radical coupling to deliver **M7** via C−C bond formation. **M7** was transformed to **M8** upon releasing the NHC catalyst. Final product was formed by elimination of phenylsulfinate in the presence of a base.[11b,20]

In summary, a visible-light and NHC-catalyzed vinylation of aldehydes from alkenes and aldehydes at room temperature has been demonstrated for the first time. The reaction was enabled by site- and regioselective two-fold sequential C−H cross-functionalization. Mechanistic investigations reveal the reaction features a dual catalysis relay with two independent radical−radical coupling processes. Diphenoquinone has a two-fold role in the reaction, acting as an oxidant and a reservoir for radical intermediates. The reaction tolerates a wide range of aldehydes and alkenes with good functional group compatibility. We anticipate the dual catalysis relay strategy will open an avenue for visible-light and NHC-catalyzed carbon−carbon and carbon−heteroatom bond-forming processes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02890.

> Experimental procedures, characterization of all new compounds and X-ray data for compounds **3n** (CCDC 2079915) and **9** (CCDC 2077990) (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to the 10th anniversary of the Chemistry Department at SUSTech. We sincerely thank NSFC (21971101 and 21801126), Guangdong Basic and Applied Basic Research Foundation (2019A1515011976), The Pearl River Talent Recruitment Program (2019QN01Y261), Thousand Talents Program for Young Scholars, The Stable Support Plan Program of Shenzhen Natural Science Fund (No. 20200925152608001), and Guangdong Provincial Key Laboratory of Catalysis (No. 2020B121201002) for financial support. We acknowledge the assistance of SUSTech Core

Research Facilities. We thank Dr. Xiaoyong Chang (SUSTech) for X-ray crystallographic analysis of **3n** (CCDC 2079915) and **10** (CCDC 2077990), and Dr. Yi-Dan Du (SUSTech) and Si-Fan Li (SUSTech) for reproducing the results of **3h**, **4a**, **5h**, and **6b**.

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