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Photochemical Nozaki−Hiyama−Kishi Coupling Enabled by Excited Hantzsch Ester

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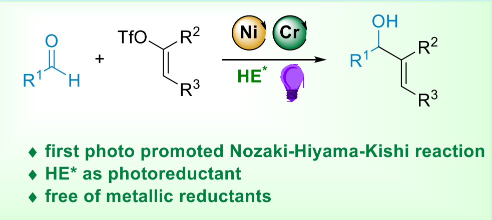
ABSTRACT: This work reports the first photochemical Nozaki−Hiyama−Kishi coupling enabled by bioinspired Hantzsch ester. The salient feature of this process is that commercially available and low-cost organic photoactive Hantzsch ester can serve as both an electron and a proton donor to reduce Cr/Ni to low-valent species and hydrolyze the Cr^{III}-alkoxy bond, thus bypassing the use of stoichiometric metallic reductants and additives such as TMSCl and Cp_2ZrCl_2. The mild conditions and operationally easy method showed broad compatibility with various alkenyl triflates and aldehydes, including electron-poor pentafluorobenzaldehyde which failed under previous conditions.



Chromium-mediated carbon−carbon forming reactions played a key role in contemporary organic synthesis.[1−5] Particularly, the addition of vinyl-organochromium reagents to carbonyls, known as Nozaki−Hiyama−Kishi (NHK) coupling, has been proven to be a powerful and efficient method to construct valuable allylic alcohols. Because of unique features, such as excellent chemoselectivity and broad compatibility with functional groups, NHK reactions have been widely used in medicinal chemistry and total synthesis of natural products.[4] Initially, NHK coupling required a Ni catalyst and a stoichiometric amount of $CrCl_2$ (Figure 1a).[6−9] Later, a catalytic protocol was developed using Mn(0) as terminal reductants, thereby achieving the asymmetric induction with a chiral ligand.[3,10−13] Alternatively, an electrochemical NHK reaction was reported bypassing the use of superstoichiometric metallic reducing agents (Figure 1b).[14−16] In terms of reaction mechanism, oxophilic additives such as TMSCl or Cp_2ZrCl_2 are indispensable for the NHK reaction, as they play the role of cleaving the Cr^{III}-alkoxy bond and releasing free Cr^{III} species in the catalytic cycle. However, these Lewis acid type additives can also activate aldehydes through coordination with the oxygen atom. Especially for electron-poor aryl-aldehydes, this activation led to single-electron reduction of aldehydes by low valence $CrCl_2$ producing undesired pinacols via ketyl radicals.[10] Additional operation of aqueous workup in the presence of n-Bu_4NF to remove the silyl group of the crude product is required. Given the prevalent utilization of NHK couplings in the synthetic and industrial community, the development of sustainable conditions to avoid the use of superstoichiometric metallic reductants and exogenous additives and further expand the substrate scope is still highly desired.

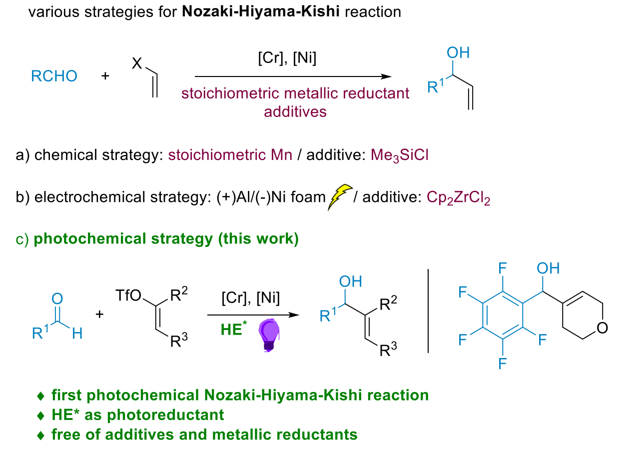


Figure 1. State of the art of NHK reaction.

In recent years, the merger of photoredox catalysis and transition metal catalysis, termed metallaphotoredox catalysis, has become a powerful and enabling tool in organic synthesis, where light-absorbing metal-polypyridyl complexes or organic dyes can modify the oxidation state of metal catalysts.[17−20] In this regard, the first report of dual chromium and photoredox catalysis for Nozaki−Hiyama allylation of aldehydes was from the Glorius group in 2018.[21,22] Later, Kanai and co-workers developed an asymmetric allylation by judicious choice of bisoxazoline ligand providing rapid access to enantiomerically pure homoallylic alcohols from simple unactivated alkenes.[23]

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However, photo-promoted Cr/Ni catalyzed NHK alkenylation of aldehydes producing allylic alcohols remains underdeveloped.

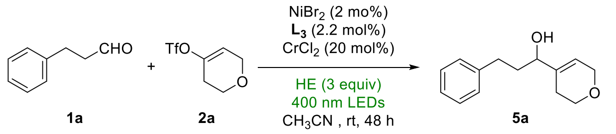
Living organisms and plants sophisticatedly use photoactive cofactors, such as NADH and flavin, to convert light energy into chemical energy to fuel metabolic activities.[24−27] The analog of NADH, 1,4-dihydropyridine (Hantzsch ester, HE), is well understood as a hydride source in the ground state and sacrificial electron donor to the photocatalyst in photochemical reactions.[28] Very recently, utilization of photoexcited HE* as a potential photoreductant (−2.28 V versus SCE) for metallaphotoredox catalysis appealed to great interests. Melchiorre and Molander respectively reported that photoexcited HE* and its analogs can reduce Ni to low valence catalytically active species for C−C bond coupling.[29,30] Inspired by these achievements, we hope to harness the reduction potential of HE* for chromium catalysis.[31] Herein, we report the first photochemical NHK coupling of alkenyl triflates and aldehydes enabled by photoexcited HE* (Figure 1c).

The multiple roles of HE are to reduce Cr and Ni to active low-valent species and serve as proton sources to break the Cr^{III}-alkoxy bond, thus bypassing the use of stoichiometric metallic reductants and additives such as TMSCl or Cp_2ZrCl_2. Another advantage of photochemical NHK is that easily single-electron reduced substrates are accommodated and produced desired allylic alcohols when classical conditions failed.

The study was started by examining phenylpropionaldehyde **1a** and vinyl-triflate **2a** derivated from 4-oxacyclohexanone as coupling partners. After variation of different reaction parameters, we found the suitable conditions in which a mixture of **1a** (0.5 equiv), **2a** (1 equiv), $CrCl_2$ (20 mol %), $NiBr_2$ (2 mol %), 4,7-Diphenyl-1,10-phenanthroline $\mathbf{L_3}$ (2.2 mol %), and HE (3.0 equiv) in acetonitrile with irradiation of a 400 nm light emitting diode (LED) lamp for 48 h afforded the desired product **5a** with a satisfactory yield of 76% (Table 1, entry 1). Ligands are found to be important for the high yield of product.[32] In the absence of any ligand, the yield of **5a** was only 43% (entry 1). When 1,10-Phenanthroline $\mathbf{L_1}$ and Neocuproine $\mathbf{L_2}$ were used the yields increased slightly (entries 3 and 4). Reactions were also sensitive to the light source. For example, irradiation with white LED, 450 nm LED, or 530 nm LED light, instead of 400 nm LED light, all resulted in very low yields of product **5a** (entries 6 and 7). This indicated that 400-nm-LED light is essential for the excitation of HE. Bench stable $CrCl_3$ was found to be suitable for the reaction affording the product **5a** in a slightly lower yield of 65% (entry 8). Several photocatalysts were tested for the reaction. However, in all cases the yields were relatively low and the conversion of **2a** was incomplete (entries 9−11). While additives such TMSCl and Cp_2ZrCl_2 were necessary for the classical catalytical approaches, it was not the case for the photoconditions and led to the decomposition of substrates (entries 12 and 13). Various solvents, including DMF, DMSO, and acetone, were evaluated, and they all resulted in less yields (entries 14−16). When reactions were performed in THF and DCM, no obvious product was formed. Moreover, the reaction did not proceed in the absence of HE, Cr, Ni, or light (entry 17).

With the optimal conditions in hand, we further investigated the scope of substrates. Remarkably, the reaction went well with various aliphatic/aromatic aldehydes **1** and alkenyl triflates **2**, affording the allylic alcohols in generally good yields, as depicted in Scheme 1. First, a broad range of functionalized aliphatic aldehydes were examined, including primary aldehydes **3f−3g** and secondary aldehydes **3a−3b**, yielding allyl alcohols exclusively in comparable yields. Heteroatom substituents at the terminus of alkyl chains, such as TBS protected oxygen **3d**, phthalimide **3j**, Boc-protected amine **3e**, and even chlorine atom **3c**, are accommodated perfectly. Then the scope with respect to aromatic aldehydes was investigated under the standard conditions.

Table 1. Reaction Optimization[a,b]



entry	variation from standard conditions	yield (%)
1	None	80 (76)[c]
2	No ligands	43
3	$\mathbf{L_1}$ instead of $\mathbf{L_3}$	62
4	$\mathbf{L_2}$ instead of $\mathbf{L_3}$	58
5	$\mathbf{L_4}$ instead of $\mathbf{L_3}$	70
6	white LED instead of 400 nm LED	<5%
7	450 nm, or 530 nm LED, instead of 400 nm LED	<5%
8	$CrCl_3$ instead of $CrCl_2$	65
9	4CzIPN (450 nm LED)	38
10	Ir-1 (450 nm LED)	51
11	Ir-2 (450 nm LED)	42
12	TMSCl (1 equiv) added	18
13	Cp_2ZrCl_2 (1 equiv) added	31
14	DMF instead of CH_3CN	47
15	DMSO instead of CH_3CN	38
16	Acetone instead of CH_3CN	61
17	No light/HE/$CrCl_3$/$NiBr_2$	0

[a] Reaction conditions: **1a** (0.5 mmol). **2a** (1 mmol). [b] Yields were determined by ^1H NMR spectroscopy versus an internal standard. [c] Isolated yield (details see Supporting Information (SI) S4).

It is noteworthy that, in the classical metal-reduction conditions, for the electron-poor aromatic aldehydes the yields of NHK reaction are usually extremely low, accompanied by the production of pinnacle byproducts. Although it reported that desired allylic alcohols could be obtained by lowering the temperature to 0 °C, it is limited to monosubstituted chlorine or bromine atoms. Fortunately, under the photoreductive conditions, both substrates with electron-rich groups (**4b**, **4i**) and electron-poor groups, such as F- **4k**, CF_3- **4l**, CN- **4m**, CO_2Me- **4n**, and even pentafluorobenzaldehyde **4o**, were accommodated well. For the comparison with the metal reduction conditions, these electron-poor aromatic aldehydes were resubjected to the reaction in the presence of Mn and TMSCl, but no obvious alcohol products were observed (**4k−4o** yields shown in parentheses). Various alkenyl triflates were investigated, and the results showed that regarding functionalization various structure complicated aldehydes derived from (**5f**) were well tolerated. To further illustrate the potential applicability of this protocol in the late-stage heterocycloalkenyl triflates (**5a**, **5b**), spiro cycloalkenyl triflate (**5c**), cyclic alkenyl triflate (**5d**, **5e**), and linear alkenyl triflate natural products and active drugs were examined, including probenecid, oxaprozin, indomethacin, gemfibrozil, and bezafibrate, which all proceeded well under these conditions, producing the corresponding products in comparable yields (**6a−6e**). Overall, the NHK reactions of aldehydes and alkenyl triflates were carried out quite efficiently under photo-

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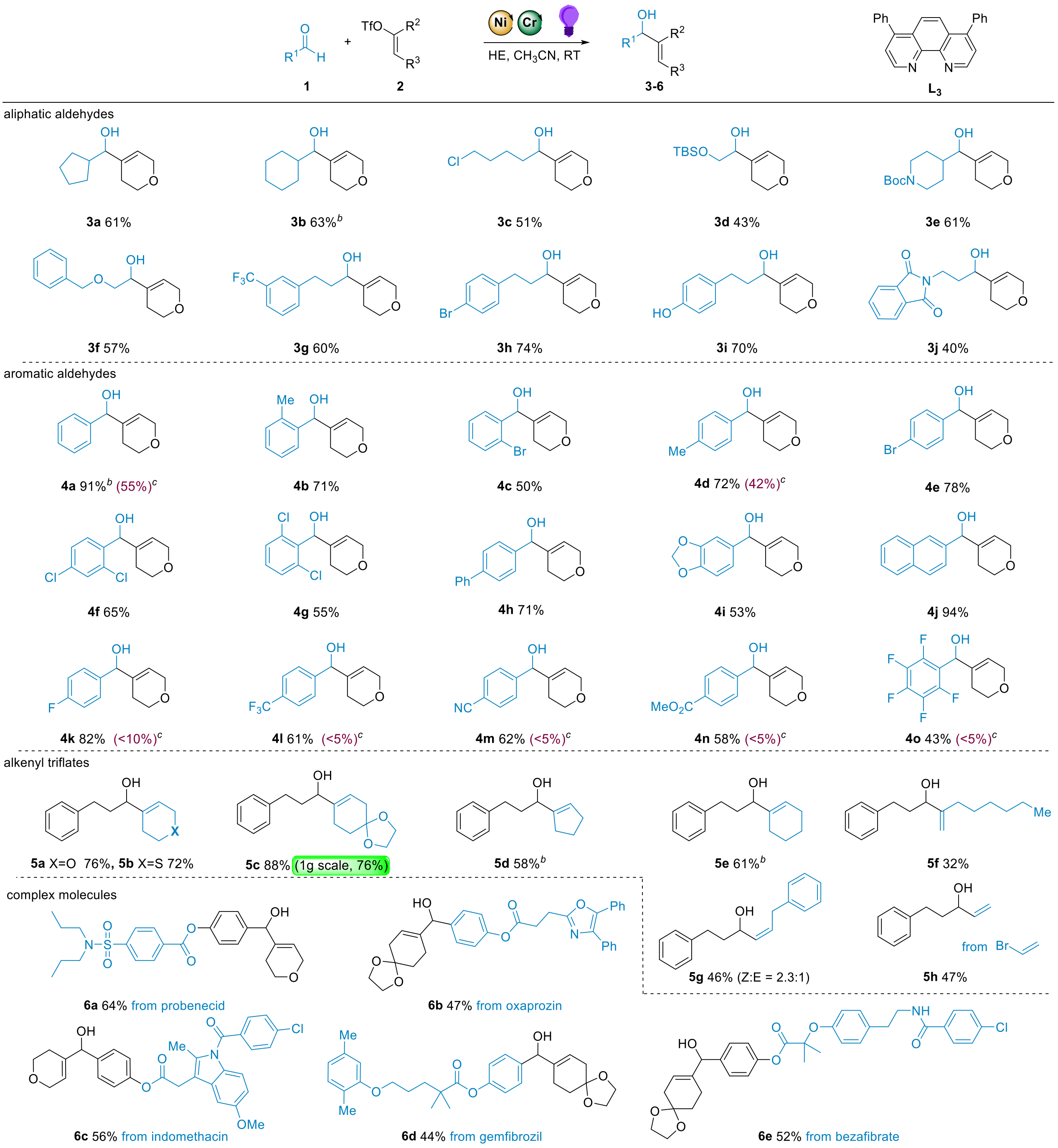
Scheme 1. Scope of Photochemical NHK Reaction[a,b,c]



[a] Reactions were performed on a scale of **1** (0.50 mmol, 1.0 equiv), **2** (1.00 mmol, 2.0 equiv), $NiBr_2$ (2 mol %), $\mathbf{L_3}$ (2.2 mol %), $CrCl_2$ (20 mol %), HE (3.0 equiv), 400 nm LEDs, CH_3CN (0.1 M), isolated yield. [b] When the products and Hantzsch pyridine cannot be completely separated, yields were determined by ^1H NMR spectroscopy versus an internal standard. [c] Yields in parentheses based on catalytic metal-reduction conditions: **1** (0.50 mmol, 1.0 equiv), **2** (1.00 mmol, 2.0 equiv), $NiCl_2$ (3 mol %), $CrCl_2$ (15 mol %), Mn (1.68 equiv), TMSCl (2.4 equiv), DME: DMF = 20:3 (0.1 M), 50 °C, 24 h [ref 10].

conditions without the use of exogenous additives and metallic reductants.

The redox potential of HE* was estimated to be −2.28 V versus SCE,[33] and thus the single electron reduction of Cr^{III} ($E_pCr^{III/II}$ = −0.51 V vs SCE in DMF)[34] and Ni^{II} ($E_{p/2}Ni^{II/0}$ = −1.2 V vs SCE in DMF)[35] by HE* should be thermodynamically feasible. However, the excited-state lifetime of HE* is short (τ_0 = 320 ps),[33] and it is not clear whether metals can be efficiently reduced by HE* through the SET process. Therefore, a series of experiments and Stern−Volmer analysis were performed. The mixture of $CrCl_3$ (purplish-red solid) and HE in DMF was irradiated with a 400 nm LED at room temperature. The color of DMF changing to green indicated that $CrCl_2$ species was formed. The results of analysis by ultraviolet−visible (UV−vis) spectroscopy further revealed that the typical peak of $CrCl_2$ at 670, 652, and 476 nm gradually appeared within 15 min, suggesting that the photoreduction process is fast (Figure 2a). On the contrary,

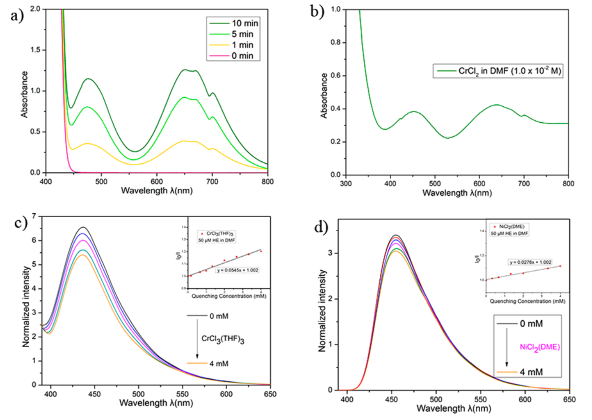


Figure 2. (a) UV−vis spectra showing the reduction of Cr^{III} to Cr^{II} by excited HE* upon photoirradiation with a 400 nm LED. (b) UV−vis spectra of Cr^{II}. (c) HE emission quenching by $CrCl_3(THF)_3$. (d) HE emission quenching by $NiCl_2(DME)$ (for details, see SI S6).

when the same reaction mixture was exposed to irradiation with a 450 nm LED, the reduction is extremely slow (over 12 h). This finding indicated that using 400 nm light is crucial for the excitation of HE. Importantly, no change of color was observed in the dark even at elevated temperatures, indicating that ground-state SET was not occurring. Then fluorescence quenching experiments were performed to investigate the electron transfer in the SET process (Figure 2c, 2d). The luminescence of HE at its λ_{max} (438 nm) in degassed THF was quenched rapidly by both $CrCl_3(THF)_3$ and Ni^{II} (SI S6), supporting the notion that HE could act as an efficient photoreductant. The UV−visible absorption spectrum of two mixtures of HE with Cr and with Ni were identical with their individual spectra, indicating the lack of charge-transfer interactions in the ground state (SI S5). Therefore, fluorescence quenching was purely diffusional.

Control experiments were carried out to explore the roles of Ni and Cr in the catalytic cycle. First, a reaction was performed only in the presence of alkenyl triflate **2s**, $NiBr_2$, ligand L_3, and HE (Figure 3a). After irradiation with 400 nm LED light for 16 h, dimer **8** was obtained in 12% yield. this result confirmed that

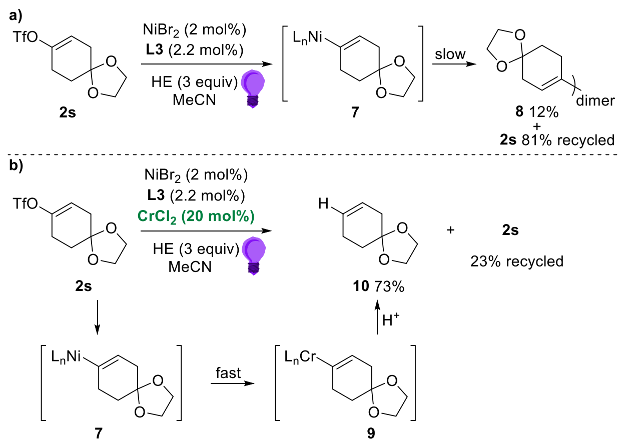


Figure 3. Control experiments to explore the roles of Ni and Cr (for details, see SI S6).

Ni^{2+} could be reduced by HE* and the low-valent Ni species could undergo oxidation addition with **2s**. The resulting **7** should be the key intermediate for the formation of dimer **8** in the catalytic cycle. Furthermore, intermediate **7** should be stable to proton/acid and can last for a long time in the reaction system, because most of **2s** was recovered (81%). The second control experiment was the same as the first one but in the presence of $CrCl_2$ (Figure 3b). In this case, reduced product **10** was obtained in 73% yield. This result indicated that the transmetalation step that converted **7** to **9** should be fast. Intermediate **9** is highly sensitive to the proton and hydrolyzes rapidly to produce **10**.

Based on these results, we tentatively propose the following catalytic cycle (Figure 4). First, Cr^{3+} is reduced to Cr^{2+} by

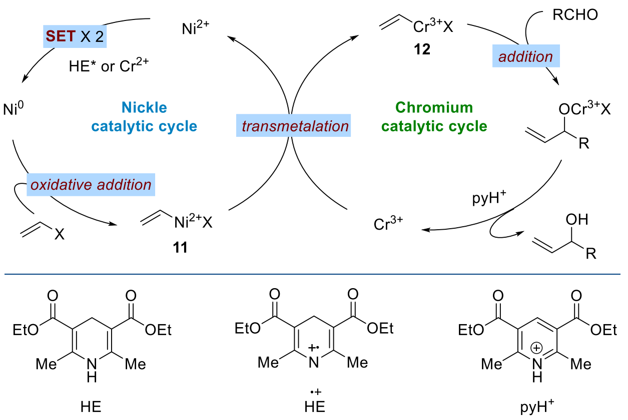


Figure 4. Proposed catalytic mechanism.

excited HE *via* a SET process. Ni^{2+} could be reduced to Ni^0 either by Cr^{2+} or by HE*. The resulting $HE^{\bullet+}$ may further participate in electron transfer events by Cr^{3+} and eventually produce pyH^+. Oxidative addition of alkenyl triflate to low-valent Ni produces intermediate vinyl-Ni **11** which is stable to proton hydrolysis. Transmetalation of **11** with Cr produces nucleophilic vinyl-Cr **12** that is subsequently coupled with carbonyls. After hydrolysis by pyH^+, the allylic alcohols are obtained and free Cr^{3+} is released.

In summary, the first photochemical NHK coupling has been developed. The additive-free conditions took advantage of the photoreduction ability of HE, bypassing the need for exogeneous photosensitizers or metal reductants. The synthetic application was demonstrated through the late-stage derivatization of drug molecules and bioactive skeletons. The unique feature of photochemical NHK is that easily SET-reduced electron-poor substrates, such as pentafluorobenzaldehyde, are accommodated well and produce desired allylic alcohols when classical conditions failed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00877.

Experimental details, characterization data of compounds, NMR spectra. (PDF)

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Notes

The authors declare no competing financial interest.

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