

COMMUNICATION

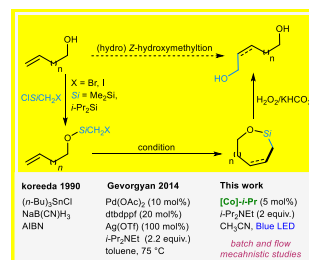
Photoexcited Cobalt Catalysed *Endo*-Selective Alkyl Heck Reaction†Chenyang Wang,^a Luis Miguel Azofra,^b Phong Dam,^a Edelman J. Espinoza-Suarez,^a Hieu Trung Do,^a Jabor Rabeah,^a Angelika Brückner,^a and Osama El-Sepelgy^{a*}Received 00th January 20xx,
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Herein we report an intramolecular *endo*-selective Heck reaction of iodomethylsilyl ethers of phenols and alkenols. The reaction leads to the formation of seven- and eight-membered siloxycycles in excellent yields which could be further converted into the corresponding allylic alcohols upon oxidation. Thus, the method could be used for the selective (*Z*)-hydroxymethylation of *o*-hydroxystyrenes and alkenols. Rapid scan EPR experiments and DFT calculations suggests a concerted β -hydrogen elimination event to take place in the triplet state.

The Mizoroki–Heck reaction¹ is a fundamental synthetic method for C–C bond formation which was awarded Nobel prize in Chemistry in 2010.² Most of the transformations involve the use of aryl halides while the application of C(sp³) halides has been less investigated due to the slow rate of oxidative addition.³ Despite these difficulties, Fu has reported the first example of an intramolecular alkyl-Heck reaction using an NHC ligand together with palladium salts.⁴ Furthermore, Alexanian has disclosed an elegant example of an alkyl-Heck reaction *via* hybrid organometallic radical mechanism using palladium catalysis under thermal conditions.⁵ Both methodologies involve conventional intramolecular 5-*exo*-trig and 6-*exo*-trig selective cyclization.^{4, 5} However, the *endo*-trig alkyl-Heck reaction is very rare and we are only aware of two examples. In 2014, Gevorgyan disclosed the *endo* selective alkyl-Heck cyclization of iodomethylsilyl to the corresponding siloxycycles,⁶ a reaction that has been previously reported by Koreeda under reductive conditions (scheme 1).⁷ The second example was reported by Liu for the synthesis of 5-phenyltetrahydropyridine derivatives from the alkyl iodide bearing a 1-aryl-substituted alkene moiety.⁸ These two examples involve the use of 10 mol% of palladium salt and operate *via* a hybrid palladium radical

mechanism under thermal conditions. The requirement of the use of 20 mol% of expensive ferrocene-based phosphine (dtbdppf) and equivalent amounts of silver salts limit the large-scale application.^{6, 8} To the best of our knowledge, there are no reports on base-metal catalysed *endo*-selective alkyl Heck reactions.



Scheme 1. Formal (hydro) (*Z*)-hydroxymethylation of alkenes

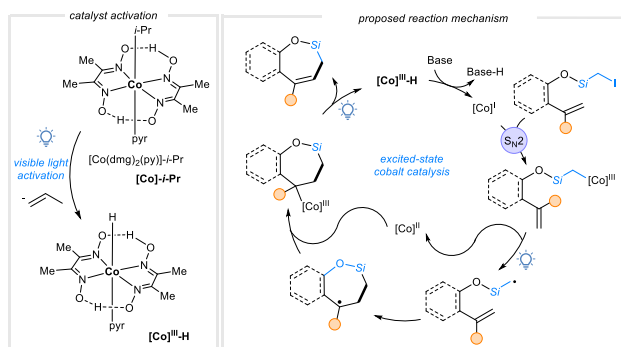
Motivated by our previous work on photoexcited cobalt catalyzed desaturation of amides,⁹ we decided to investigate whether the thermal palladium/dtbdppf/Ag(OTf) catalytic system can be replaced by a visible light photocatalytic phosphine-free alternative with base metals.¹⁰ To validate our proposal, we decided to test the cyclization reaction of iodomethylsilyl ethers of phenols and aliphatic alkenols. Herein, we report a new photoexcited cobalt catalysed *endo*-selective alkyl-Heck reaction.^{10, 11}

Our hypothesis involves the use of a nucleophilic [Co]^I complex which could be photo-generated *in situ* from a simple [Co]-*i*-Pr catalyst and a suitable base under visible light irradiation. This cobalt species could react with alkyl halide to give the corresponding alkyl-[Co]^{III} intermediate which under visible light irradiation could form a [Co]^{II} species and an alkyl radical intermediate.^{11,12} Then the alkyl radical undergoes intramolecular radical addition followed by recombination with [Co]^{II}. Under visible irradiation, the formed [Co]^{III} species generates the Heck product together with [Co]^{III}-H which could be then deprotonated by a suitable base to restore the nucleophilic [Co]^I species (Scheme 2).

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† Electronic supplementary information (ESI) available: experimental details and characterization of all compounds, and copies of 1 H and 13C NMR spectra for selected compounds.

Scheme 2. Plausible mechanism of the *endo*-selective cyclizationTable 1. Control Reactions of Optimized Conditions^a

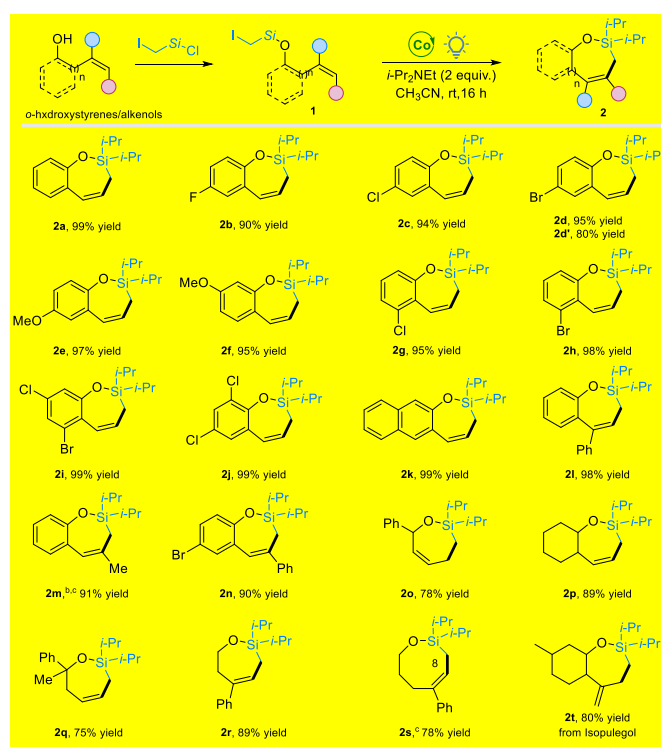
entry	deviation from the standard conditions	yield (%)
1	none	99
2	no [Co]-i-Pr or no light	n.d.
3	70 °C instead of light	trace
4	1 equiv. K ₂ CO ₃ as base	72
5	1 equiv. K ₂ CO ₃ , 20 mol% <i>i</i> -Pr ₂ NEt as base	81
6	DMAP as base	trace
7	DBU as base	trace
8	DCM as solvent	85
9	THF as solvent	71
10	TEMPO was added	n.d.

^a Standard condition: substrate **1a** (0.1 mmol), [Co]-*i*-Pr (0.005 mmol, 3.6 mg), *i*-Pr₂NEt (0.2 mmol, 35 μ L), CH₃CN (1 mL), rt, Blue LED (19 W, Ledxon), 16 h, isolated yields.

Our study was initiated by the investigation of the of silyl-tethered *o*-hydroxystyrene **1a** as a model substrate for the intramolecular Heck-reaction. We found that the combination of 5 mol% of [Co(dmgl)₂(py)]-*i*-Pr and Hünig's base (DIPEA) in acetonitrile under blue LED irradiation at room temperature was optimal for affording the 7-membered siloxycycle **2a** in quantitative yield (Table 1, entry 1). It is worth noting that this catalytic system does not require the use of an additional photoredox catalyst,¹³ strong reductive conditions,¹⁴ and Grignard reagents.¹⁵ Control experiments revealed that no background reactivity in the absence of the cobalt catalyst or the blue light (Table 1, entries 2 and 3). Investigation of different organic and inorganic bases revealed that Hünig's base is the best choice (Table 1, entries 4-7). Switching of the reaction solvent from CH₃CN to DCM or THF led to lower yields (Table 1, entries 8 and 9). Finally, the addition of TEMPO leads to no product formation (Table 1, entry 10).

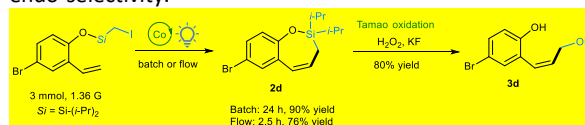
Next, the generality of our catalytic system was investigated under the optimized reaction conditions (Table 2). Arene tethered substrates bearing different substituents (Cl, Br, F, Me and OMe) in the 4 different positions of the phenyl ring afforded the corresponding *endo*-selective Heck products **2b-2j** in excellent yields (95-99%). Importantly, the use of alkyl bromide analogue of the **1d** led to the formation of the desired product

in 80% yield. Furthermore, the naphthyl derivative **1k** furnished the cyclic product in quantitative yield. Then substrates bearing substituents in the olefin was studied. The substrate with the substituent on the α -position produced the *endo*-product **2i**. In addition, **1m** bearing substituents in the β -position leads to the formation of the oxasilepine **2m**, albeit with moderate selectivity (60 % of major isomer). As for the (*E*)-2-styrylphenol **1n**, the selectivity of the formation of **2n** was extremely improved.

Table 2. Scope of *o*-hydroxystyrenes and alkenols^a

^a Reaction conditions: **1** (0.2 mmol), [Co]-*i*-Pr (0.01 mmol, 7.2 mg), *i*-Pr₂NEt (0.4 mmol, 70 μ L), CH₃CN (2 mL), rt, Blue LED (19 W, Ledxon), 16 h, isolated yields. ^bmixture of isomers (6.4:1:1.6:1.6), see SI for details. ^c NMR yield.

Encouraged by these promising results, we tested more challenging systems such as aliphatic alkenols. The cyclization of the secondary homoallylic alcohol **1o** led to the formation of the allylic siloxycycle **2o** in 78% yield. Interestingly, the substrate bearing two vicinal substitutions at the α - and β - positions of the tethered alcohol efficiently furnish the siloxysilane **2p** in very good yield. Remarkably, tethered tertiary alcohol **1r** was also found to tolerate the catalytic system and produce the desired product in 75% yield. Importantly, the tethered primary alcohols **1r** and **1s** underwent 7-*endo*-trig and 8-*endo*-trig cyclization in 89% and 78% yield respectively. In addition, the application of the methodology on the naturally occurring isopulegol led to the formation of **2t** in very good yield and excellent *endo*-selectivity.

Scheme 3. Gram scale formal (*Z*)-hydroxymethylation of styrene derivatives

To showcase the practical applicability of this photoexcited catalytic transformation, we carried out a 3 mmol scale alkyl-Heck reaction for the substrate **1d** in batch. Fortunately, the desired product **2d** was obtained in 90% yield in 24 hours. To further improve the efficiency of the developed methodology, we reperformed the reaction using a microflow reactor. Impressively, 76% of the isolated cyclic product **2d** was obtained after only 2.5 hours. Afterwards, we turned our attention to further derivatization of the cyclic products. To our delight, the oxasilepine **2d** was smoothly oxidized to the (*Z*)-allylic alcohol **3d** via Tamao oxidation (Scheme 3).

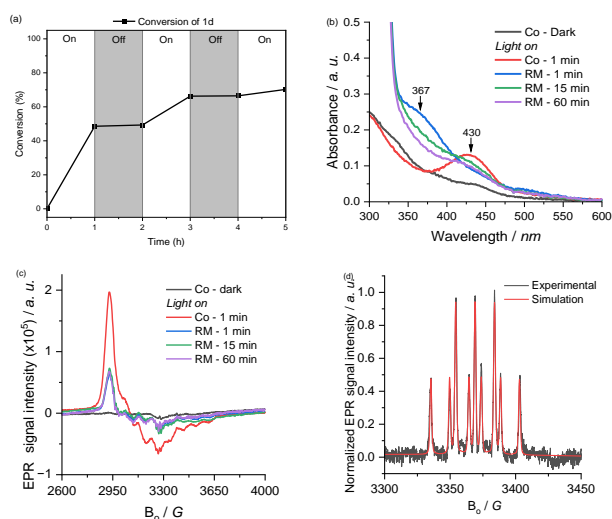


Figure 1. (a) Light on-off experiment; (b) UV-vis spectra of (0.005 mmol [Co]-*i*-Pr in 6 ml MeCN, black line) and reaction mixture ([Co]-*i*-Pr, 0.1 mmol **1d**, 0.2 mmol *i*-Pr₂NEt) before and after irradiation with time; (c) EPR spectra measured at -173 °C of (0.005 mmol [Co]-*i*-Pr, 1 ml MeCN) and reaction mixture (0.005 mmol [Co]-*i*-Pr, 0.1 mmol **1d**, 0.2 mmol *i*-Pr₂NEt, 1 ml MeCN) before and after irradiation with time. (d) Experimental and simulated EPR spectra for [Co]-*i*-Pr with DMPO using rapid scan EPR spectroscopy.

To gain more insights into the reaction mechanism, we performed preliminary experimental mechanistic studies. First, the reaction profile was studied (see the Supporting Information for details) which showed that more than 75% conversion was obtained after 4h. Furthermore, to exclude the possibility of a radical chain process, light on-off experiments were carried out. In the absence of light, no reaction was observed (Figure 1a). Under light irradiation, we obtained the quantum yield of $\Phi = 0.045$ for the photoexcited cobalt catalyzed Heck reaction (see the Supporting Information for details). Additional controlled UV-vis, EPR and NMR experiments were performed. The UV-vis spectrum of the initial [Co]^{III}-*i*-Pr complex showed three poorly resolved Ligand-to-Metal Charge Transfer (LMCT) absorption bands (LMCT) at 330, 390 and 450 nm (Figure 1b-black line).¹⁶ These bands decreased quickly during the first minute of irradiation and a new LMCT band appeared at $\lambda_{\text{max}} = 430$ nm due to the formation of [Co]^{II} species. This was also evident from the EPR spectrum of the irradiated [Co]^{III}-*i*-Pr complex, which showed an axial signal at $g_{\perp} = 2.282$ and $g_{\parallel} = 2.029$ with resolved ⁵⁹Co hyperfine structure ($I=7/2$) of the parallel component (Figure 1c). On the other hand, the ¹H NMR spectrum of irradiated [Co]^{III}-*i*-Pr in DCM-d₂ points to formation of [Co]^{III}-H and propene (see supporting information for

details). The formation of [Co]^{II} observed in the EPR spectrum might be due to a homolytic cleavage of the [Co]^{III}-H bond upon irradiation.¹⁴ In order to distinguish between the stepwise and the concerted pathways of the formation of the alkene, we performed a spin trap experiment using 5,5-Dimethyl-1-pyrrolin-N-oxide (DMPO) by rapid scan EPR spectroscopy. Interestingly, an unstable DMPO-H species ($a_{\text{N}} = 14.8$ G, $a_{\text{H}} = 19.3$ G) was formed instead of the stable DMPO-*i*-Pr spin adduct, suggesting a concerted mechanism (Figure 1d). During the catalytic reaction in the presence of *i*-Pr₂NEt and the substrate **1d**, the amount of EPR-active [Co]^{II} species was by about 70% lower than in the [Co]^{III} pre-catalyst after irradiating for 1 min and stayed nearly constant during prolonged irradiation. This indicates that the catalyst quickly reached a steady state in which an effective [Co]^I/[Co]^{III}/[Co]^{II} cycle is established that keeps the Co^{II} constant in time average. UV-Vis results also confirmed this hypothesis by showing a decrease of the [Co]^{II} LMCT band at 430 nm of Co^{II} complex along with a new band at 367 nm that might arise from the coordination of the substrate to Co sites during the catalytic reaction.

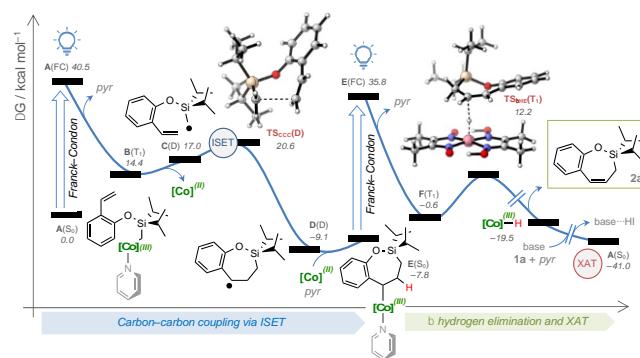


Figure 2. Detailed description of the potential energy surface (PES). Free energy results are shown in kcal mol⁻¹ at the PBE96/TZVP//BP86/6-31G-SVP(Sn,I) level of theory in acetonitrile as solvent.

Next, the reaction mechanism for the light-driven Heck reaction has been studied by means of DFT techniques (Figure 2) using **1a** as model substrate. The mechanism involves the carbon-carbon coupling *via* internal single electron transfer (ISET) and the β hydrogen elimination and S_N2 steps. Thus, complex **A** is excited from the singlet (S₀) to the triplet (T₁) state through a vertical (Franck-Condon, FC) excitation that brings the complex to a high-energy state, 40.5 kcal mol⁻¹. After relaxation, pyridine (pyr) is released to form complex **B**(T₁), followed by the breakage of the [Co]^{III}-C bond into the [Co]^{II} and the radical species **C**, both in the doublet state (D) and therefore being EPR active species. The species **C** contains an unpaired electron in the terminal carbon directly bounded to the tether, making it quite reactive. Through an internal single electron transfer (ISET) process, the radical carbon reacts with the C(sp²) of the vinyl group. This entails a carbon-carbon coupling whose transition state (TS_{CC}) lies just 3.6 kcal mol⁻¹ above in relative free energy with respect to **B** to finally produce the seven-membered ring at **D** in a very spontaneous process (-9.1 kcal mol⁻¹ relative to **A**). It should be noted that the formation of the high energetic (excited) **C** species, promoted by light irradiation, is decisive to boost the carbon-carbon coupling step that could not otherwise occur through classical thermal catalysis. The radical species **D** is recombined with

[Co]^{II} and pyridine forming complex E(S₀). This can also be excited by visible light, undergoing a second vertical (FC) transition, lying at 35.8 kcal mol⁻¹. In a similar mechanistic fashion, pyridine is again released from the complex leading to F(T₁), -0.6 kcal mol⁻¹. In accordance with the rapid scan EPR experiment, the desaturation process takes place *via* a concerted β-hydrogen elimination event in the triplet state, with a transition state (TS_{βHE}) just lying 12.8 kcal mol⁻¹ above in free energy with respect to F. As result of this, the hydride [Co]^{III}-H complex and product **2a** are formed, and complex A(S₀) is regenerated by action of the organic base and substrate **1a** *via* S_N2 pathway to be newly integrated in the photoexcited cobalt cycle. In summary, we have developed a highly selective cobalt catalyzed cyclization of iodomethylsilyl ethers of phenol and of aliphatics. Upon further oxidation of the formed siloxycycles, the corresponding allylic alcohols are produced. This method could be used for the formal hydroxymethylation of allylic alcohols and *o*-hydroxystyrenes.¹⁸ The reaction mechanism has been studied using different experimental and theoretical tools. It is anticipated that this operationally simple and scalable photoexcited base metal methodology would serve as a basis for development of greener alternative to the Pd-catalyzed alkyl-Heck reaction.¹⁹

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Conflict of Interest

There are no conflicts of interest to declare

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