Dual Cobalt and Photoredox Catalysis Enabled Intermolecular Oxidative Hydrofunctionalization

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Supporting Information Placeholder

ABSTRACT: A general protocol has been developed for the Markovnikov-selective intermolecular hydrofunctionalization based on visible-light-mediated Co/Ru dual catalysis. The key feature involves the photochemical oxidation of an organocobalt(III) intermediate derived from hydrogen atom transfer, which is supported by electrochemical analysis, quenching studies and stoichiometric experiments. This unique redox process enables the efficient branch-selective alkylation of pharmaceutically important nucleophiles (phenols, sulfonamides and various N-heterocycles) using a wide range of alkenes including moderately electron-deficient ones. Moreover, light-gated polar functionalization via organocobalt species was demonstrated.

The Brønsted acid-mediated intermolecular Markovnikov addition has been known for more than a hundred years.[1] On paper, it offers a straightforward and modular approach to many pharmaceutically relevant structures such as branched-alkyl-substituted phenols and N-heterocycles, without resorting to pre-activated coupling partners or subsequent multi-step conversions (Scheme 1a).[2] Not surprisingly, such transformations in practice are often complicated by the thermodynamically disfavored protonation process and high-energy carbocations involved.[3] To this, chemists have been searching for catalytic alternatives mimicking this process in a more controlled fashion.[4] Guided by the rich literatures on the first-row transition metal,[5] in particular the cobalt-catalyzed hydroelementations via hydrogen atom transfer (HAT),[6] we recently introduced an I(III)-promoted intermolecular oxidative hydrofunctionalization reaction catalyzed by a cobalt salen complex.[7] Highly chemo- and regio-selective additions to unactivated terminal olefins and electron-rich styrenes have been realized with a number of heteroatom-based nucleophiles, which includes carboxylic acids, phenols, and sulfonamides. More recently, benzotriazoles have also been added as viable reaction partners by Yahata and Akai.[8] A key mechanistic hypothesis of this transformation involves the oxidation of an organocobalt(III) intermediate **A** into a Co(IV) species **B**, an organometallic radical cation that displays polar reactivity (Scheme 1b).[9] Our studies suggested that a Co(III)−X complex (X = counterion/anionic ligand) **C** likely functions as the oxidant for this process, whose reduction potential lies close to the oxidation potential of **A**.

As part of the continuing effort exploring the oxidative functionalization of organocobalt complexes in catalysis by a mechanistic-driven approach, it came to our attention that such reversible electron transfer between cobalt species could be a major limiting factor. When either the oxidation of **A** or the following nucleophilic trapping of **B** is sluggish, significant increase in the concentration of **A** is anticipated, which would eventually lead to traditional radical-based reactions via Co−C bond homolysis. For instance, the resulting radical **D** once escaped from a solvent cage could dimerize, abstract a halogen atom, or
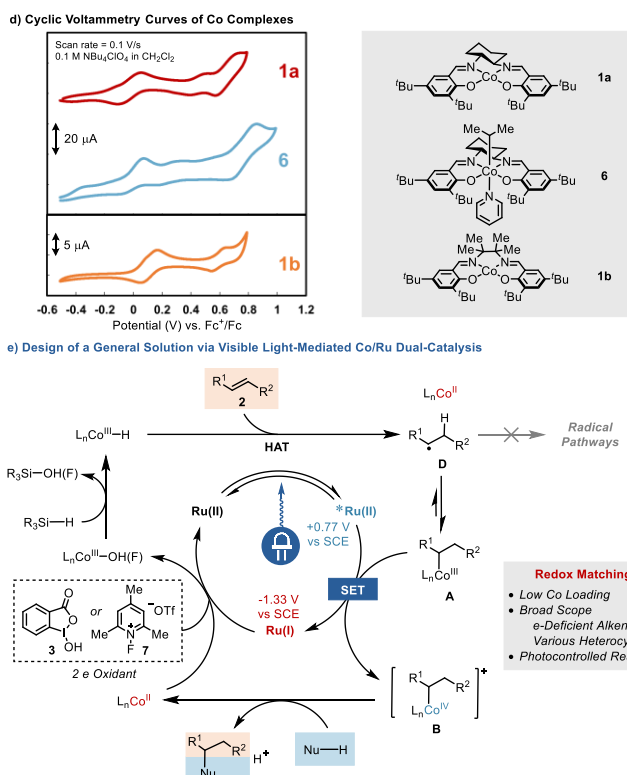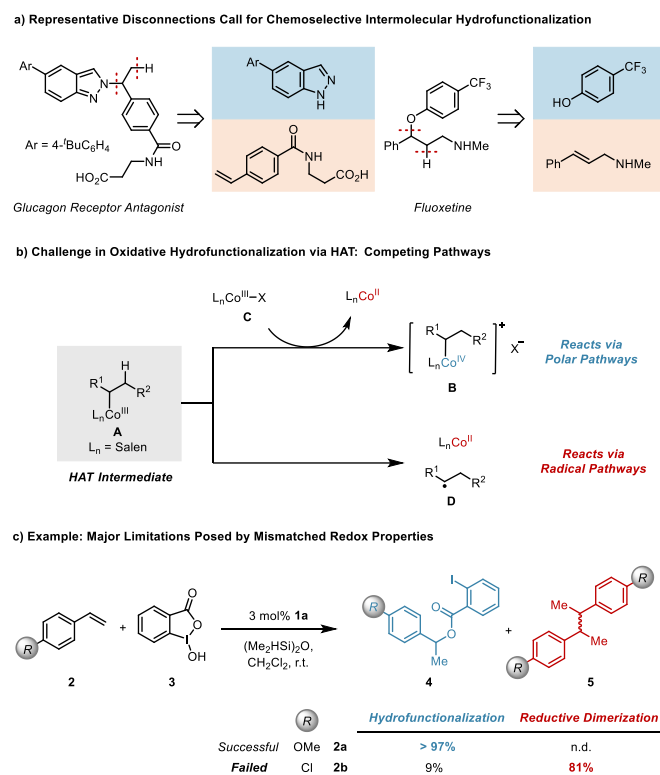
react with trace dioxygen. It is thus predicted that the reaction efficiency would be largely limited by the electronic property of the alkyl group in **A** and the nucleophilicity of the reaction partner.[10] In other words, the outcome would be highly substrate-dependent. Indeed, we observed contrasting behaviors of p-methoxystyrene (**2a**) and p-chlorostyrene (**2b**) under the standard reaction conditions (Scheme 1c). The former produced Markovnikov adduct in quantitative yield, while the latter virtually only underwent reductive dimerization.

In order to overcome this limitation by a general catalyst-controlled solution, a natural thought would be to modify the structure of the cobalt salen complex. However, such approach would likely lead to marginal effect because both **A** and **C** are subjected to change in a rather similar way. Therefore, we sought an alternative mechanism involving a stronger catalytic oxidizing species that is compatible with the HAT conditions. In this work, we report the realization of this approach via a merger of a photoredox cycle with HAT catalysis. The dual catalysis significantly expands the viable redox window, and thus leads to an efficient and general single-step entry into a range of pharmaceutically relevant structures. The regioselectivity and scope of this protocol complement established methodologies, for example the anti-Markovnikov dehydrogenative hydrofunctionalizations via cobaloxime catalysis.[11] In addition, we provide a rare example where the polar reactivity of an organocobalt intermediate was gated by external physical stimuli.

To assist the design, we began by evaluating the electrochemical properties of cobalt salen complexes **1a** and **1b**, as well as an alkylcobalt(III) complex **6** bearing an isopropyl group as a model for **A** (Scheme 1c).[12] The $E_{1/2}$ for the **1a⁺/1a** redox couple locates at −0.02 V vs Fc⁺/Fc in dichloromethane, and is slightly lower than that of the **1b⁺/1b** couple (0.11 V).[13] Complex **6** displayed an irreversible oxidation wave at $E_{p/2}$ = −0.01 V vs Fc⁺/Fc, likely corresponding to the R−Co(III)/R−Co(IV) oxidation based on literature reports.[9a, 14] The measured potentials corroborates the previous mechanistic hypothesis regarding the SET between Co complexes, which was further supported by a titration experiment.[15] It is noted that the Co complexes undergo additional redox events at both more positive and negative parts of the spectrum. Ideally, a photoredox catalyst should not trigger such undesired processes.

Guided by the electrochemical data, we envisioned that the excited state of Ru(bpy)₃²⁺ (bpy = 2,2'-bipyridyl, $E_{1/2}[*Ru^{II}/Ru^{I}]$ = 0.77 V vs SCE in acetonitrile) might allow for the efficient oxidation of organocobalt(III) complex **A**.[16] A proposed catalytic cycle is depicted in Scheme 1e. It commences with the formation of **A** via HAT between a Co−H species and an alkene **2** followed by cage collapse. The key step thus involves the facile reductive quenching of visible light-generated *Ru(II) by **A**, which would efficiently produce the electrophilic Co(IV) complex **B** with minimal reverse reaction. **B** is subsequently trapped by a nucleophile to give the Markovnikov adduct. The resulting Ru(I) and Co(II) complexes then react with a stoichiometric two-electron oxidant, either the hypervalent iodine reagent **3** or an N-fluoropyridinium salt **7**, to

Scheme 1. Mechanistically-Guided Design of a Dual-Catalysis Approach to Broad-Spectrum Oxidative Hydrofunctioalization.

a) Representative Disconnections Call for Chemoselective Intermolecular Hydrofunctionalization

Ar = 4-^{t}BuC$_6$H$_4$

Glucagon Receptor Antagonist

Fluoxetine

b) Challenge in Oxidative Hydrofunctionalization via HAT: Competing Pathways

L$_n$Co^{III}–X **C** → L$_n$Co^{II}

$[\text{R}^1 \text{ R}^2 \text{ L}_n\text{Co}^{IV}]^+$ X$^-$ **B** *Reacts via Polar Pathways*

R^1 H R^2 L$_n$Co^{III} **A** L$_n$ = Salen **HAT Intermediate**

R^1 R^2 L$_n$Co^{II} **D** *Reacts via Radical Pathways*

c) Example: Major Limitations Posed by Mismatched Redox Properties

3 mol% **1a**
(Me$_2$HSi)$_2$O,
CH$_2$Cl$_2$, r.t.

2 **3** → **4** + **5**

			Hydrofunctionalization	Reductive Dimerization
Successful	OMe	**2a**	> 97%	n.d.
Failed	Cl	**2b**	9%	81%

d) Cyclic Voltammetry Curves of Co Complexes

Scan rate = 0.1 V/s
0.1 M NBu$_4$ClO$_4$ in CH$_2$Cl$_2$

20 µA **1a** **6**
5 µA **1b**

Potential (V) vs. Fc$^+$/Fc

Complexes: **1a**, **6**, **1b**

e) Design of a General Solution via Visible Light-Mediated Co/Ru Dual-Catalysis

L$_n$Co^{III}–H **HAT** R^1 H R^2 • **D** ⟶ *Radical Pathways*

R$_3$Si–OH(F) Ru(II) *Ru(II) +0.77 V vs SCE

R$_3$Si–H L$_n$Co^{III}–OH(F) **SET** R^1 R^2 L$_n$Co^{III} **A**

–1.33 V vs SCE Ru(I)

3 OH or **7** (Me, N, F, OTf) 2 e Oxidant

Redox Matching
- Low Co Loading
- Broad Scope
  e-Deficient Alkenes
  Various Heterocycles
- Photocontrolled Reactivity

$[\text{R}^1 \text{ R}^2 \text{ L}_n\text{Co}^{IV}]^+$ **B**

L$_n$Co^{II} R^1 R^2 Nu H$^+$ Nu–H

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regenerate Ru(II) and Co(III) species, respectively. The latter finally reacts with a silane and return to the inital Co−H complex.

To test this hypothesis, we first evaluated the oxidative HAT hydrofunctionalization reaction of **2b** with **3** and a silane at room temperature (Table 1). Compared to the original reaction catalyzed solely by 3 mol% Co complex **1a** (entry 1), the addition of 1 mol% Ru(bpy)$_3$Cl$_2$•6H$_2$O accompanied by blue LED irradiation effectively suppressed the reductive dimerization and inverted the selectivity completely, affording **4b** in over 80% yield (entry 2). The dark reaction using **1b** gaves 30% yield of **4b**, presumably due to the slightly higher E$_{1/2}$ of **1b$^+$/1b** (entry 3). The combination of **1b** and the photoredox conditions further pushed the reaction to quantitative conversion without observing any dimer formation (entry 4). Control experiments under light irradiation leaving out the Co or Ru catalyst confirmed the essential roles of both (entries 5-7).

We next examined a few alternative metal-based photoredox catalysts at wavelengths close to their individual absorption maximums, respectively. For example, Ru(bpz)$_3^{2+}$ (bpz = 2,2'-bipyrazine), which possesses a highly oxidizing excited state (E$_{1/2}$[*Ru^{II}/Ru^I] = 1.45 V vs SCE), was found incompatible (entry 8). On the other end of the redox spectrum, *fac*-Ir(ppy)$_3$ (ppy = 2-phenylpyridine) did not promote the desired transformation either (entry 9). This could be attributable to either the strongly reducing nature (E$_{1/2}$[Ir^{IV}/*Ir^{III}] = −1.73 V vs SCE) or the high triplet state energy (57.8 kcal/mol) that interferes with the HAT cycle, which also indicates that energy transfer catalysis is unlikely involved in the productive mechanism.[17] Therefore, Ru(bpy)$_3^{2+}$ seems to hit a sweet spot with regard to redox matching, which is consistent with the observation made with a different Ru catalyst of similar redox properties (entry 10). Finally, the loading of **1b** in the dual catalyst system could be reduced to 1 mol% without compromising the yield (entry 11).

Table 1. Evaluation of the effect of photoredox catalysts.[a]

3 mol% **[Co]**, 1 mol% **PC**, *Light*
2.0 equiv. **3**
2.0 equiv. (Me$_2$HSi)$_2$O
CH$_2$Cl$_2$, r.t.

2b → **4b** + **5b**

Entry	[Co]	PC	Light	4b (%)	5b (%)
1	**1a**	-	-	9	81
2	**1a**	Ru(bpy)$_3^{2+}$	460 nm	83	9
3	**1b**	-	-	30	59
4	**1b**	Ru(bpy)$_3^{2+}$	460 nm	97	n.d.
5	-	Ru(bpy)$_3^{2+}$	460 nm	n.d.	n.d.
6	**1b**	Ru(bpy)$_3^{2+}$	-	15	59
7	**1b**	-	460 nm	31	57
8	**1b**	Ru(bpz)$_3^{2+}$	460 nm	9	10
9	**1b**	*fac*-Ir(ppy)$_3$	380 nm	< 5	n.d.
10	**1b**	Ru(phen)$_3^{2+}$	410 nm	89	n.d.
11[b]	**1b**	Ru(bpy)$_3^{2+}$	460 nm	98[c]	n.d.

[a]Standard conditions: **2b** (0.10 mmol), **1b** (3 mol%), photocatalyst (1 mol%), (Me$_2$SiH)$_2$O (0.20 mmol), **3** (0.20 mmol) in 1.0 mL CH$_2$Cl$_2$ at r.t. for 18 h. The yields were determined by ^{1}H NMR analysis of the crude reaction mixture. The yields of **5b** refer to the corresponding **2b** converted. See Table S2 for details. [b] **2a** (0.30 mmol), **1b** (1 mol%), photocatalyst (1 mol%), (Me$_2$SiH)$_2$O (0.60 mmol), **3** (0.60 mmol) in 1.0 mL CH$_2$Cl$_2$ at 25 °C for 36 h. [c]Isolated yield.

The divergent reactivities observed in the presence/absence of light prompted us to compare their kinetic profiles (Figure 1a). The light-mediated reaction displayed substantially greater rate throughout the course of the reaction (plot 1). In contrast, induction periods of different lengths were observed for both the formation of **4b** (plot 3) and **5b** (plot 4) in the absence of light. Interestingly, the reductive dimerization started to take off at t = 4 h, then rapidly overwhelmed the desired transformation, which seems to reflect a dynamic equilibrium involving cobalt species. The light-controlled switch was clearly illustrated by a reaction

carried out with intermittent irradiation (plot 2, light exposure between t = 4-6, 7.5-9 h). It is well-known that the homolysis of an organocobalt(III) can be photochemically controlled, a feature that is particularly useful for radical polymerizations.[18] However, light-regulation of polar reactivity has been essentially unexplored.[19] To this, our dual catalyst system seems to provide an interesting demonstration.

To further probe whether such dramatic improvement stems from the photochemical oxidation of the organocobalt(III) intermediate **A** as proposed, Stern-Volmer quenching studies were carried out (Figure 1b). The excited state *Ru(II) was found to be readily quenched by the model compound **6**, but not the stoichiometric oxidant **3**. This is consistent with the hypothesized reductive quenching process. In addition, mixing **6** and **3** either in the presence or absence of the Ru catalyst in dark resulted in no oxidative functionalization product **8** as expected from measured electrochemical data (Figure 1c). However, when the photocatalyst-containing mixture was exposed to blue light, **8** was formed in 15% yield. Collectively, these results strongly support that an analogous oxidation of **A** by *Ru(II) might take place in the catalytic reaction.
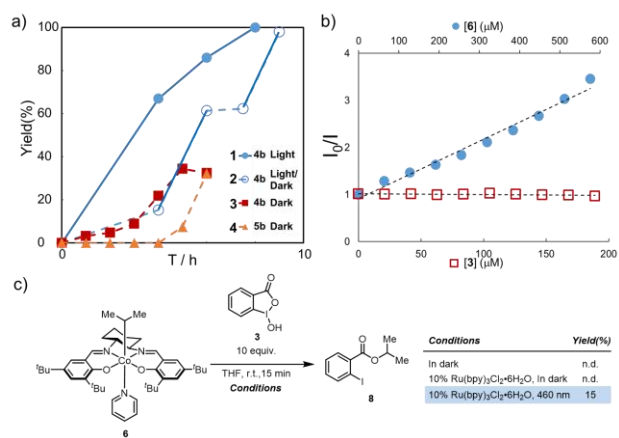

Figure 1. Mechanistic Studies. a) Reaction profiles. Conditions: **2b** (1.0 equiv.), **3** (2.0 equiv.), (Me₂SiH)₂O (2.0 equiv.) at r.t. in CH₂Cl₂. ●/○: 3% **1b**, 1% [Ru]; ■/▲: 3% **1b** only. Solid lines: exposed to 460 nm light; dash lines: in the absence of light. b) Stern-Volmer quenching studies of Ru(bpy)₃²⁺ in the presence of **3** or **6**. c) Stoichiometric experiments showing that photochemical oxidation of **6** led to oxidative functionalization product. The yields were determined by ¹H NMR analysis of the crude reaction mixtures.

Scheme 2. Scope of the Dual-Catalyzed Oxidative Hydrofunctionalization via HAT.[a]
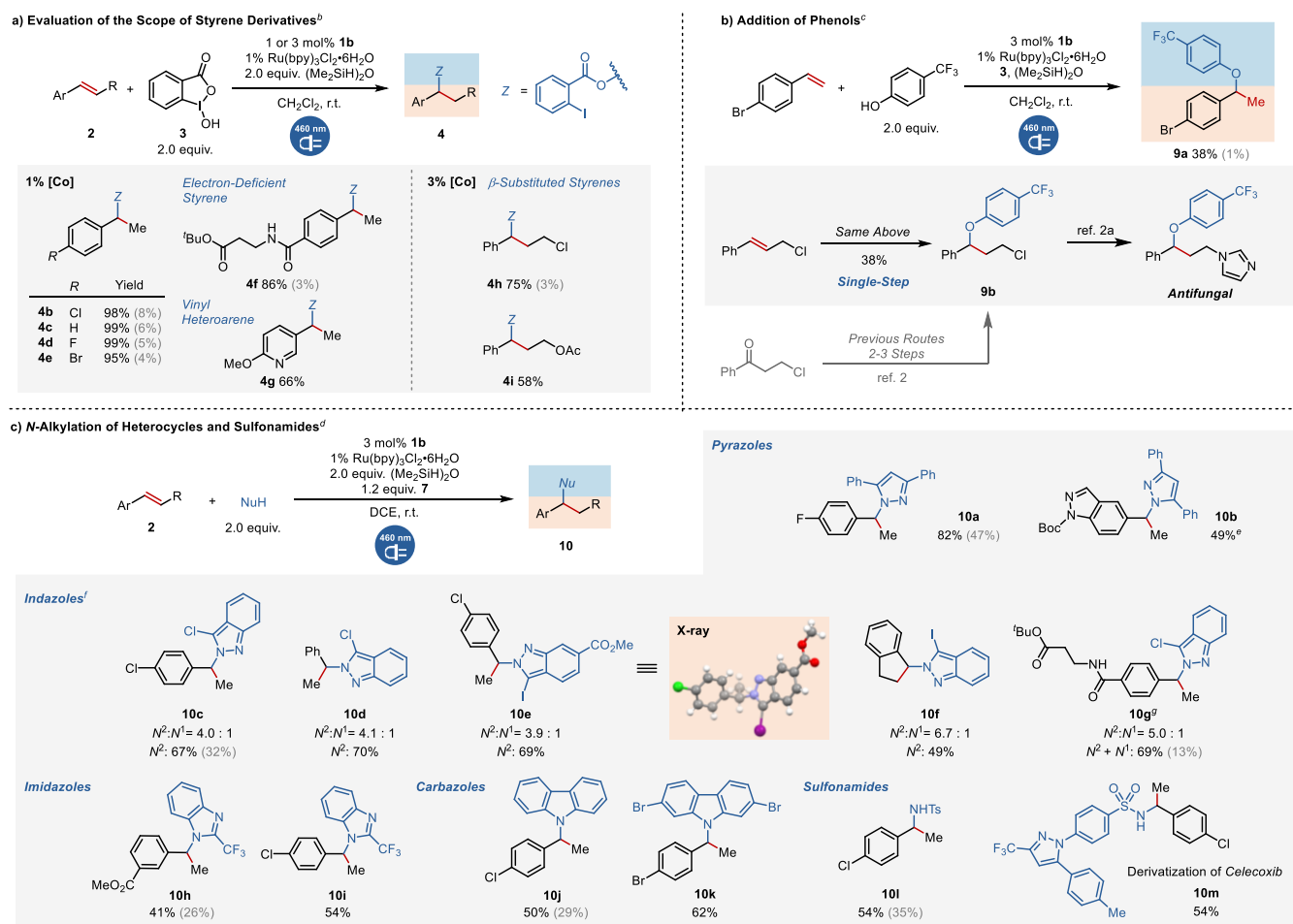
[a] Unless otherwise noted, yields correspond to isolated, analytically pure materials. Yields of control reactions performed in the absence of light and photocatalyst (shown in parentheses) were estimated by ¹H NMR analysis of crude reaction mixtures. [b] Conditions: **2** (0.30 mmol), **1b** (1 or 3 mol%), photocatalyst (1 mol%), (Me₂SiH)₂O (0.60 mmol), **3** (0.60 mmol) in 1.0 or 3.0 mL CH₂Cl₂ with blue LED irradiation at r.t. [c] Conditions: **2** (0.30 mmol), **1b** (3 mol%), photocatalyst (1 mol%), (Me₂SiH)₂O (0.60 mmol), **3** (0.60 mmol), 4-trifluoromethylphenol (0.60 mmol) in 3.0 mL CH₂Cl₂ with blue LED irradiation at r.t. [d] Conditions: **2** (0.30 mmol), **1b** (3 mol%), photocatalyst (1 mol%), (Me₂SiH)₂O (0.60 mmol), **7** (0.36 mmol), NuH (0.60 mmol) in 3.0 mL 1,2-dichloroethane with blue LED irradiation at r.t. [e] Determined by ¹H NMR analysis of the crude reaction mixture. [f] The regiomeric ratios were determined by ¹H NMR analysis of the crude mixtures. The major isomers were shown. The yields correspond to isolated N²-adduct except **10g**. [g] 10 mol% **1b** was used.

With these results in hand, we set out to apply the new dual catalysis protocol to a series of vinylarene substrates (Scheme 2a). They typically failed or led to very low turnover number under previous oxidative hydrofunctionalization conditions as indicated by the results of control experiments shown in parentheses. Quantitative to good yields were obtained for styrenes, β-substituted styrenes and a vinylpyridine derivative (**4b-i**). In all cases, no reductive dimerization was detected. It is worth noting that a moderately electron-withdrawing amide group at the *para*-position is well tolerated, showcasing the significantly expanded redox window brought by the photoredox cycle (**4f**).[20] The fact that such alkenes can be functionalized directly represents an additional notable advantage over traditional acid-mediated processes besides chemoselectivity.

This protocol proved readily amenable for phenol addition (Scheme 2b). The yields were moderate because of the competing addition of 2-iodobenzoic acid. Nonetheless, it allows for single-step modular assembly of useful structures that would otherwise require multi-step synthesis. For instance, starting from simple cinnamyl chloride, one could rapidly access **9b**, which is a common intermediate en route to a series of biologically active molecules.[2a, b] While the highly reactive allylic C−Cl bond in cinnamyl chloride is typically susceptible to nucleophiles including low-valent transition metal complexes, it did not interfere with the nucleophile addition under the oxidative hydrofunctionalization conditions.

To further demonstrate the synthetic utility and generality of this method, we next show that a reasonably broad scope of nitrogen-based heterocycles can be efficiently alkylated using 3 mol% catalyst **1b** (Scheme 2b). This includes pyrazoles (**10a-b**), indazoles (**10c-g**), imidazoles (**10h-i**) and carbazoles (**10j-k**). To avoid a competing nucleophile, we replaced **3** by *N*-fluorotrimethylpyridinium triflate (**7**) as the stoichiometric oxidant,[21] which does not change the rest of the catalytic cycles and indeed led to similar trends. These heterocycles were challenging nucleophiles under previous conditions even in the cases involving electron-rich/neutral styrenes (yields in parentheses). Dual catalysis offered doubled yields on average. It is noted that the thermodynamically less favored N^2-alkylation was the major pathway for indazoles.[22] It complements existing S_N2 chemistry and other transition metal-catalyzed methods in regioselectivity, which could potentially find use in facilitating drug-discovery processes.[23] Improved turnovers were also observed for sulfonamide *N*-alkylations, which enabled the late-stage modification of a drug molecule (**10l-m**). Finally, the excellent chemoselectivity of the process is demonstrated by a range of functional groups present besides the heterocycles themselves, such as activated aryl iodides (**10e**) and acid-sensitive protecting groups (**10b, g**).

In summary, we have developed an efficient and general protocol for the Markovnikov-selective intermolecular hydrofunctionalization of styrenes and vinylheteroarenes including moderately electron-deficient ones. The key design is the visible light-mediated Co/Ru dual catalysis that stems from electrochemical analysis. It enables the previously difficult addition of important nucleophiles, such as phenols and various *N*-heterocycles. Assisted by the photoredox cycle, 1 or 3 mol% Co catalyst was sufficient to attain a good yield in most cases. Mechanistically, quenching studies and stoichiometric reactions provided evidence for the involvement of photochemical oxidation of organocobalt(III) species. Based on these results along with the observed light-gated conversion, we anticipate possible spatial-temporal control on this bifurcated radical/polar reactivity, which may find applications in a broader context.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

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Radical Pathways

Polar Pathways

460 nm

Light-Gated Reactivity

3% [Co], 1% [Ru], 69% Yield
Broad Scope
Intermolecular Oxidative
Hydrofunctionalization