Intramolecular Hydrogen Atom Transfer Hydroarylation of Alkenes toward δ-Lactams Using Cobalt-Photoredox Dual Catalysis

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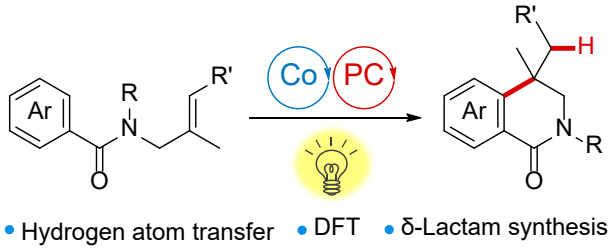
Supporting Information Placeholder

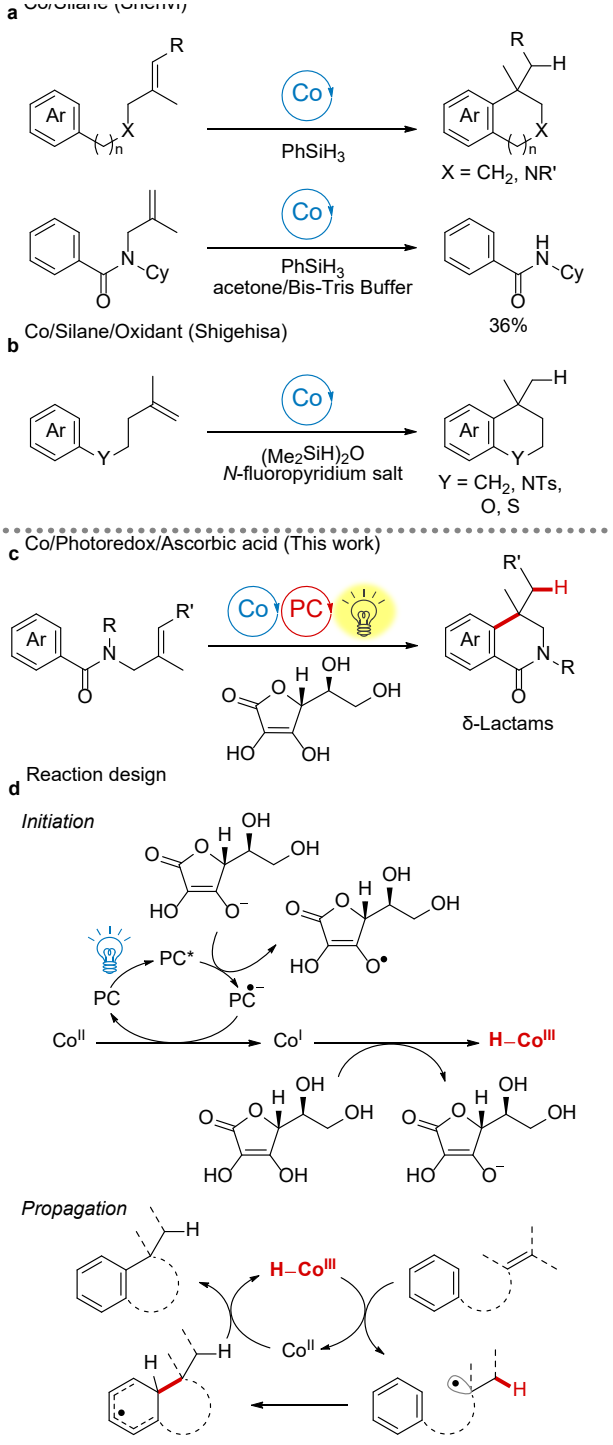


ABSTRACT: Intramolecular hydroarylation of alkenes through hydrogen atom transfer (HAT) represents a robust method to prepare benzo-fused heterocycles. However, the reported methods have limitations in a variety of accessible cyclic scaffolds. Here we report a dual cobalt- and photoredox-catalyzed HAT hydroarylation of alkenes which is characterized by higher efficiency in the synthesis of a δ-lactam compared to established protocols. The proposed mechanism is supported by experiments and DFT calculations.

The Markovnikov-selective hydrofunctionalization of alkenes via metal-catalyzed hydrogen atom transfer (HAT) has emerged as a versatile tool for the synthesis of complex molecules.[1] Among its ever-growing array of methodology developments,[2] the intramolecular hydroarylation of unactivated alkenes is recognized as a versatile method to access synthetically useful benzo-fused heterocycles from readily available acyclic starting materials.[3-5] Unlike classical Friedel–Crafts-type hydroarylations which require forcing acidic conditions for the activation of alkenes, the HAT-mediated hydroarylation proceeds via a radical mechanism at neutral pH, and thus tolerates a variety of Lewis-basic functional groups. In this context, Shenvi reported a pioneering cobalt-catalyzed HAT hydroarylation protocol for the isomerization of unactivated alkenes (Scheme 1a, top).[3a] In a typical reaction, the intramolecular hydroarylation of alkenes tethered to an aromatic ring proceeds in high yield in the presence of a cobalt catalyst and a catalytic amount of phenylsilane. The robustness of this cobalt-catalyzed method was further validated in aqueous media under highly diluted conditions, while the use of stoichiometric quantities of phenylsilane was preferred in certain cases.[3b] These cobalt-catalyzed HAT-mediated catalytic methods provide access to medicinally important *N*-heterocycles including tetrahydroisoquinolines and indolines. Interestingly, *N*-deallylation predominated instead of cyclization toward a respective δ-lactam when an acyclic *N*-allyl amide was subjected to the relevant reaction conditions (Scheme 1a, bottom). As an alternative HAT-mediated hydroarylation approach, Shigehisa reported an organosilane- and *N*-fluoropyridinium-salt-mediated hydroarylation of unactivated alkenes (Scheme 1b).[4] From a mechanistic perspective, the generation of a carbocation equivalent via HAT to the alkenes followed by one-electron oxidation of the resulting alkyl radical was proposed as a key intermediate in the C–C-bond-forming step. Shigehisa's protocol is characterized by access to a variety of heterocycles, including tetrahydroquinolines, dihydropyranes, and dihydrothiopyranes.

Against this background, we were motivated to devise a new HAT hydroarylation that facilitates the synthesis of benzo-fused heterocycles which are not readily accessible using the established protocols. Inspired by the recent development of metallaphotoredox catalysis,[6,7] our group has recently reported the hydrogenation of unactivated alkenes using ascorbic acid (also known as vitamin C) in combination with cobalt and photoredox catalysis.[8] We envisioned that an allied cobalt/photoredox catalytic system[9] might enable a HAT intramolecular hydroarylation of alkenes for the synthesis of benzo-fused heterocycles (Scheme 1c). Our reaction design for the silane-free[10] HAT hydroarylation is described in Scheme 1d. In the initiation step, H–Co^{III} is generated via one-electron reduction of the Co^{II} complex by a reduced photoredox catalyst (PC), while ascorbic acid serves as the source of one electron and a proton presumably along with the formation of dehydroascorbic acid. The thus formed H–Co^{III} enters the propagation step. HAT from the cobalt hydride to an alkene produces an alkyl radical intermediate along with the Co^{II} catalyst. Intramolecular radical addition to the aromatic ring then affords a cyclohexadienyl radical intermediate. We anticipated that the intramolecular C–C-bond-forming step should predominate over the intermolecular HAT between the alkyl radical and ascorbic acid, and undesired

Scheme 1. Intramolecular Hydroarylation of Alkenes via Metal-Catalyzed HAT

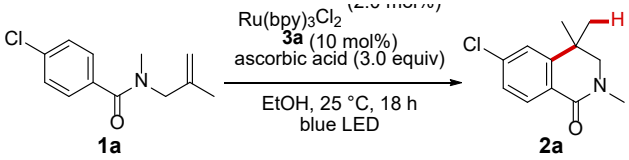


hydrogenation of an alkene would be circumvented. Hydrogen atom transfer between the cyclohexadienyl radical intermediate and the Co^{II} provides the cyclized product, and the H–Co^{III} complex is regenerated.

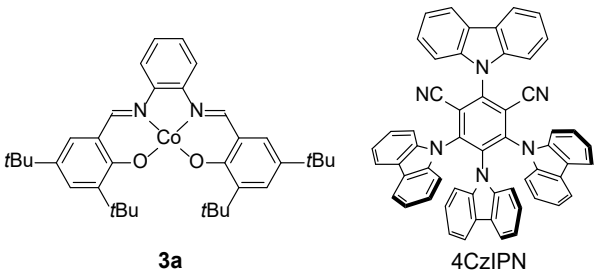
Based on the reaction design, we began our investigation with the aim of cyclizing allyl amide **1a** into 3,4-dihydroisoquinolin-1(2*H*)-one **2a** via intramolecular hydroarylation. HAT hydroarylation of *N*-allyl amides toward benzo-fused δ-lactams has not been addressed in previous studies, and we anticipated that studying this transformation should provide new insight into HAT chemistry. After several trials, a dual catalytic system consisting of $Ru(bpy)_3Cl_2$ as a photocatalyst and cobalt salophen complex **3a** as a cocatalyst was found to be generally suitable for the hydroarylation of alkenes. The results of our investigations into the reaction conditions for the hydroarylation of **1a** are summarized in Table 1. The hydroarylation took place in high yield when a substoichiometric amount of ascorbic acid was used (entry 2). This observation is in accordance with the reaction design in Scheme 1d, in which a catalytic amount of ascorbic acid is sufficient to initiate the catalytic cycle. Product **2a** was still obtained in 71% yield when the amount of the cobalt catalyst **3a** was reduced to 3 mol% (entry 3). It is worth noting here that the reaction was almost equally efficient when the organophotocatalyst 4CzIPN was used (entry 4), suggesting that the reaction can be performed under noble-metal-free conditions. The hydroarylation proceeded in good yield in an aqueous medium (entry 5), and this mixed solvent system is suitable for the cyclization of some substrates studied in Scheme 2 (*vide infra*). In terms of the photon source, the widely used Kessil lamp provided an efficiency that was as high as that of our standard LED setup (entry 6). Control experiments revealed that the reaction did not occur in the absence of the cobalt catalyst, the photocatalyst, or light (entry 7), demonstrating that all these reaction components are of critical importance for this reaction, as proposed in Scheme 1d.

With the optimized reaction conditions in hand, the scope of the intramolecular hydroarylation was evaluated, and the results are summarized in Scheme 2. Intramolecular hydroarylation proceeded in the presence of the aromatic ring with varying electronic properties (**2a**-**2i**). The cyclization of **1b** can be conducted at the 1.0 mmol scale in excellent yield (**2b**), which

Table 1. Evaluation of the Reaction Conditions for the Intramolecular Hydroarylation of **1a**

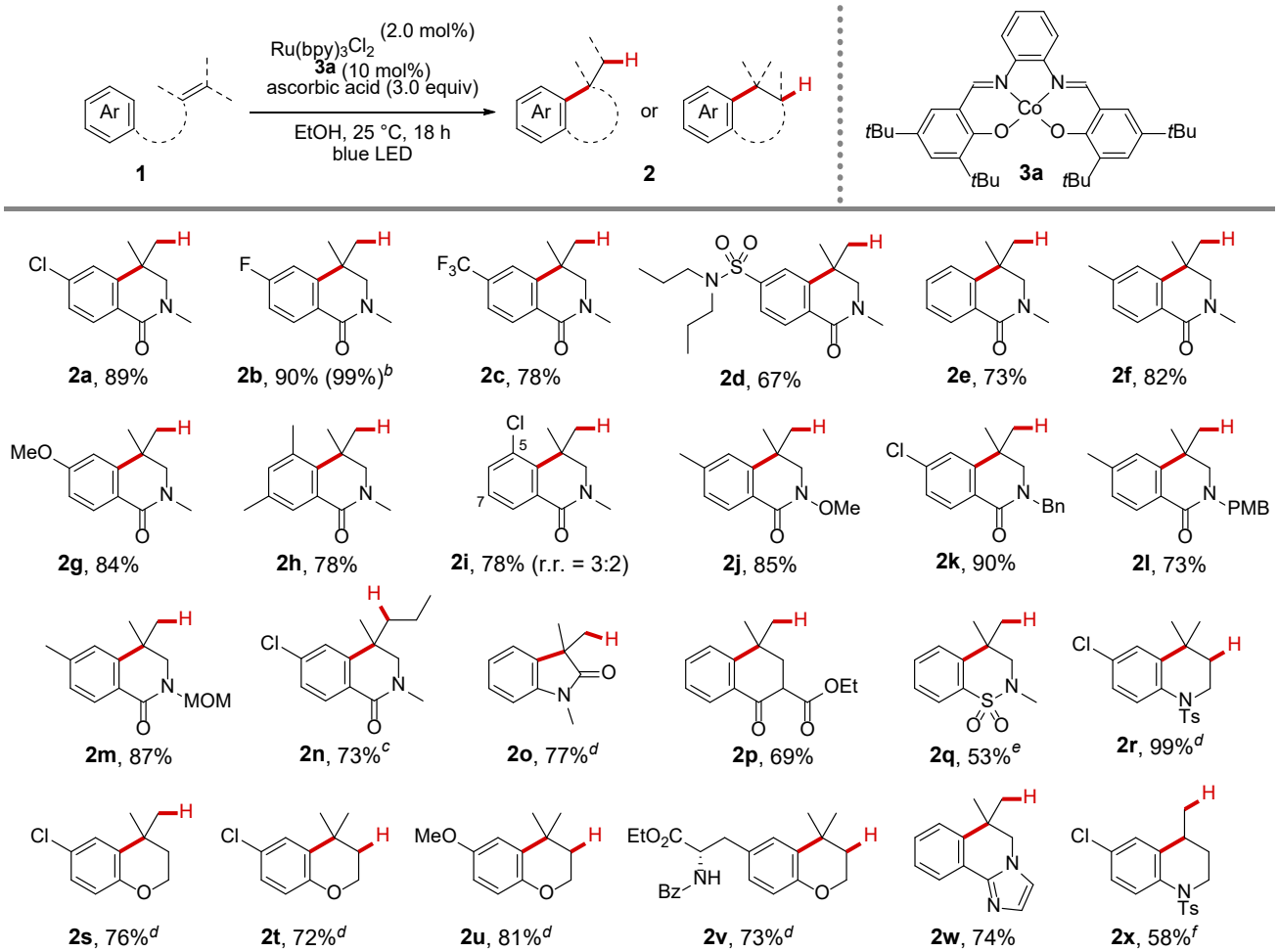


entry	deviation from the reaction conditions	yield (%)[a]
1	None	89[b]
2	0.5 equiv ascorbic acid instead of 3.0 equiv	83
3	3.0 mol% **3a** instead of 10 mol%	71
4	4CzIPN instead of $Ru(bpy)_3Cl_2$	82
5	*t*BuOH/H_2O instead of EtOH	72
6	Kessil blue LED as a photon source instead of our standard LED setup	88
7	without **3a**, $Ru(bpy)_3Cl_2$ or blue LED	< 5



[a]Unless otherwise noted, determined by ^{1}H NMR analysis. [b]Isolated yield.

Scheme 2. Substrate Scope of the Intramolecular HAT Hydroarylation of Alkenes



[a]Reaction conditions (unless otherwise noted): **1** (0.20 mmol), $Ru(bpy)_3Cl_2$ (0.0040 mmol, 2.0 mol%), **3a** (0.020 mmol, 10 mol%), and ascorbic acid (0.60 mmol) in EtOH (3.0 mL) at 25 °C under irradiation from blue LEDs (CCS). Isolated yields are shown. [b]1.0 mmol scale. [c]At 50 °C for two cycles. [d]**1** (0.20 mmol), $[Ru(bpy)_3][PF_6]_2$ (0.0040 mmol, 2.0 mol%), **3a** (0.020 mmol, 10 mol%), and ascorbic acid (0.40 mmol) in *t*BuOH/H_2O (3:1, 3.0 mL) at 25 °C under irradiation from blue LEDs (CCS). [e]45 h. [f]**1x** (0.20 mmol), 4CzIPN (0.0040 mmol, 2.0 mol%), **3a** (0.020 mmol, 10 mol%), and ascorbic acid (0.40 mmol) in *t*BuOH/H_2O (3:1, 6.0 mL) at 40 °C for 20 h under irradiation from blue LEDs (Kessil).

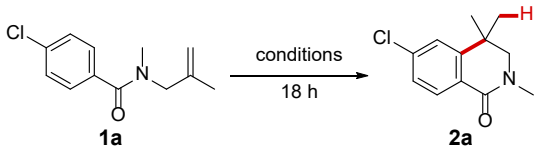
highlights the potential scalability of the reaction. The modest regioselectivity of **2i** (5-Cl/7-Cl =3:2) is in consistent with the insensitivity of the radical intermediate in the cyclization step. Several kinds of *N*-functionalized allyl amides smoothly underwent the hydroarylation (**2j**-**2m**). Hydroarylation of a trisubstituted alkene was also possible at 50 °C, and **2n** was obtained in 73% yield. Preparation of a γ-lactam, a carbocycle, a δ-sultam and a tetrahydroquinoline were also possible (**2o**-**2r**). The hydroarylation of 4-substituted phenols proceeded smoothly using either terminal or internal alkenes under the aqueous conditions (**2s**-**2v**). The hydroarylation afforded **2w** in 74% yield when the alkene and the arene were tethered with an imidazole ring. The hydroarylation of a simple terminal alkene can be performed in 58% yield under the relevant reaction conditions (**2x**).

Regarding the construction of 3,4-dihydroisoquinolin-1(2*H*)-one skeleton,[11] several thermally demanding radical reactions have afforded the 3,4-dihydroisoquinolones from acyclic *N*-allyl amides.[12] However, the respective hydroarylation via HAT has remained elusive. To evaluate the feasibility of the synthesis of benzo-fused δ-lactams via metal-mediated HAT, the efficiency of the transformation of **1a** using reported protocols for intramolecular HAT hydroarylation was compared (Table 2). Under the dual cobalt- and photoredox-catalyzed conditions, **2a** was obtained in 71% yield using 3 mol% of the cobalt catalyst **3a** (entry 1). On the other hand, the reported protocol for the phenylsilane-mediated hydroarylation[3a] resulted in a lower yield of **2a** and 69% of unreacted **1a** was recovered without noticeable byproducts (entry 2). When **1a** was subjected to the organosilane- and *N*-fluoropyridinium-salt-mediated conditions,[4] **2a** was obtained in 11% yield within a complex product mixture (entry 3). These results suggest that the cobalt/photoredox-catalyzed HAT hydroarylation has an advantage for the preparation of δ-lactams compared to previous protocols.[13,14]

In summary, we have developed an intramolecular hydroarylation of alkenes using cobalt/photoredox dual catalysis. This system is featured by higher efficiency for the synthesis of medicinally relevant benzo-fused δ-lactams compared to existing metal-catalyzed HAT protocols.[15] Further studies of the unique

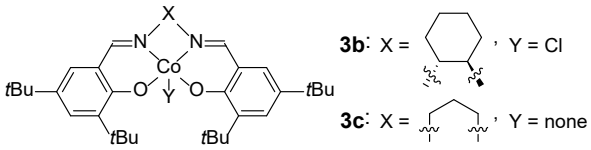
utility of the cobalt/photoredox system compared to thermal HAT reactions as well as applications to other alkene isomerization reactions are currently under investigation in our group.

Table 2. Comparison of the Reactivity of Reported Protocols for the Intramolecular Hydroarylation of **1a**



1a **2a**

entry	conditions	yield (%)[a]
1	$Ru(bpy)_3Cl_2$ (2.0 mol%), **3a** (3.0 mol%), ascorbic acid (3.0 equiv), EtOH, 25 °C, blue LEDs	71
2[b]	**3b** (3.0 mol%), $PhSiH_3$ (6.0 mol%), benzene, 22 °C	18
3[c,d]	**3c** (3.0 mol%), *N*-fluoro-2,4,6-trimethylpyridinium triflate (2.0 equiv), $(Me_2SiH)_2O$ (2.0 equiv), $PhCF_3$, rt	11



[a]Determined by ^1H NMR analysis. [b]Ref. 3a. [c]Ref. 4. [d]20 h.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures, characterization of the synthesized compounds, details of DFT calculations, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(13) Stoichiometric phenylsilane in the presence of **3b** improved the efficiency of the hydroarylation, yet the yield of **2a** remained modest (34–43%). See Table S1 in the Supporting Information for details

(14) Both the structure of **3a** and photoirradiation are responsible for the difference in reactivity. See Section 3 of the Supporting Information for additional comparative experiments and discussions.

(15) For mechanistic studies including DFT and detection of alkyl radical intermediates, see Section 4 of the Supporting Information.