

Oxidative Cyclization Synthesis of Tetrahydroquinolines and Reductive Hydrogenation of Maleimides under Redox-Neutral Conditions

Xiu-Long Yang, Jia-Dong Guo, Tao Lei, Bin Chen,[®] Chen-Ho Tung,[®] and Li-Zhu Wu^{*®}

Key Laboratory of Photochemical Conversion and Optoelectronic Materials, Technical Institute of Physics and Chemistry, the Chinese Academy of Sciences, Beijing 100190, P. R. China

Supporting Information

ABSTRACT: A redox-neutral reaction without using any external oxidant and reductant in one pot is described. By combining a $\text{Ru}(\text{bpy})_3^{2+}$ photocatalyst and cobaloxime catalyst, a number of tertiary anilines can be oxidized by $\text{Ru}(\text{bpy})_3^{2+}$ to realize oxidative cyclization of tetrahydroquinolines, and the electron and proton eliminated from the substrate anilines are captured by a cobaloxime catalyst to achieve hydrogen transfer *in situ* to maleimides, in good to excellent yields, under redox-neutral conditions.

he development of a mild, general, and efficient approach to build complex molecular structures is always an important concern of synthetic chemistry.¹ Photoredox catalysis, taking advantage of visible light as an energy input, has recently become a sought-after organic transformation. Although most organic molecules are transparent to visible light, a range of transition metal complexes and organic dyes have been exploited as efficient photocatalysts for the synthetically valuable reactions.² Thanks to the ability of photocatalysts to absorb visible light, numerous organic substrates, including unreactive C-H bonds, have been activated to undergo either oxidative or reductive reactions, respectively, with the aid of an external oxidant and reductant. Notwithstanding these advances, it is rather challenging to design a more atom- and step-economic reaction that avoids the use of an external oxidant and reductant for a redox-neutral reaction.

In this contribution, we report an oxidative cyclization of tertiary anilines with maleimides to synthesize tetrahydroquinolines, and simultaneously reductive hydrogenation of maleimides³ in one pot. Tetrahydroquinolines are significant structures existing in a number of natural products and synthetic drugs.⁴ With the aid of external oxidants, the oxidative cycloaddition synthesis of tetrahydroquinolines has been achieved. Our design here is to realize the oxidative cyclization without any external oxidant under visible light irradiation, and the electron and proton eliminated from the substrate tertiary anilines are captured by a cobaloxime catalyst to achieve hydrogen transfer *in situ* to maleimides. In contrast to those reports of oxidative cyclization to form tetrahydroquinolines in the presence of an oxidant,⁵ this is the first example of oxidative synthesis of tetrahydroquinolines in



conjunction with hydrogenation under redox-neutral conditions. This protocol utilizes commercially available substrates, avoids the use of any external oxidant and reductant in the reaction vessel, and produces the desired products in good to excellent yields (34 examples, up to 98%) under redox-neutral conditions.

Our investigations commenced with the reaction of N,Ndimethylaniline (1a, 0.2 mmol) with N-phenylmaleimide (2a, 0.4 mmol) in CH₃CN (4 mL). In the presence of 1 mol % Ru(bpy)₃Cl₂ and 10 mol % Co(dmgH)₂pyCl under an argon atmosphere, the reaction mixture of 1a and 2a was irradiated by 3 W blue LEDs at room temperature. The desired annulation product 3aa and hydrogenation product 4a were obtained in 88% and 91% yields (Table 1, entry 1). However, only a 30% yield of 3aa was obtained under air, along with the decomposition of most la into N-methylaniline (Table 1, entry 11).⁶ It was found that neither Acr⁺-MesClO₄⁻ (9mesityl-10-methylacridinium perchlorate) nor Ir(ppy)₃ was able to improve the transformation further (Table 1, entries 2 and 3). As reducing the amount of 2a in the reaction mixture decreased the yields of 3aa and 4a (Table 1, entry 6), and 5 mol % instead of 10 mol % of Co(dmgH)₂pyCl was not enough for the redox-neutral reaction (Table 1, entry 7 and Figure S2 in the Supporting Information), it is reasonable to consider that 2.0 equiv of 2a and the ratio of catalyst to substrate were essential for generation of 3aa and 4a in good yields. A set of control experiments suggested the necessity of $Ru(bpy)_3Cl_2$

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Table 1. Optimization of the Reaction Conditions⁴



^{*a*}Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), photocatalyst (1 mol %), and Co(dmgH)₂pyCl (10 mol %) were added in CH₃CN (4 mL) under an argon atmosphere and irradiation of 3 W blue LEDs for 24 h at rt. ^{*b*}Yield of isolated products based on 0.2 mmol of **1a**. ^{*c*}2 mL of CH₃CN. ^{*d*}4 mL of EtOH. ^{*c*}0.2 mmol of **2a** was used. ^{*f*}25% H₂ was detected by gas chromatography, using pure methane as an internal standard. ^{*g*}5 mol % Co(dmgH)₂pyCl. ^{*h*}In the dark. ^{*i*}Without Co(dmgH)₂pyCl ^{*j*}In open air. ^{*k*}In 1.0 mmol scale.

 $Co(dmgH)_2pyCl$, and visible light for this transformation (Table 1, entries 8–10).

To understand the primary process of the photocatalytic reaction, the luminescent spectra of $Ru(bpy)_3Cl_2$ in the presence of either 1a and $Co(dmgH)_2pyCl$ were examined. As shown in Figure 1a, both 1a and $Co(dmgH)_2pyCl$ quenched



Figure 1. (a) Luminescence spectra of Ru(bpy)₃Cl₂ (4 × 10⁻⁵ M) with Co(dmgH)₂pyCl (4 × 10⁻⁴ M) or **1a** (4 × 10⁻³ M) in degassed CH₃CN with excitation at 450 nm. (b) UV–vis absorption spectra of system containing 4 × 10⁻⁵ M Ru(bpy)₃Cl₂ and 4 × 10⁻⁴ M Co(dmgH)₂pyCl irradiated under blue LEDs for 0–3 min in degassed CH₃CN.

the luminescence of Ru(bpy)₃Cl₂, but the quenching extent by Co(dmgH)₂pyCl was much larger than that of **1a** (see Figures S5 and S6 in the Supporting Information for details). Considering the redox potential $[E_{1/2}^{\text{ox}} \text{ Ru(bpy)}_3^{3+}/*\text{Ru-(bpy)}_3^{2+} = -0.81 \text{ V vs SCE}, E_{1/2}^{\text{red}} *\text{Ru(bpy)}_3^{2+}/\text{Ru(bpy)}_3^{+} = +0.77 \text{ V vs SCE}, E_{1/2}^{\text{red}} \text{ Co}^{II} - 0.67 \text{ V vs SCE}, E_{1/2}^{\text{ox}}$ **1a^{+•}/1a** = +0.79 V vs SCE]^{2a,7} (Figure S3), the quenching behavior could be attributed to photoinduced electron transfer from Ru(bpy)₃Cl₂ to Co(dmgH)₂pyCl. The UV-vis absorption spectrum was further monitored to provide the intermediate information upon irradiation. Prior to irradiation, the absorption spectrum of Ru(bpy)₃Cl₂ and Co(dmgH)₂pyCl in degassed CH₃CN was simply the sum of the individual components. After irradiation, the system showed absorption bands at 440–500 nm and 550–650 nm (Figure 1b), which was consistent with the formation of Co^{II} and Co^I intermediate species.⁷ Evidently, the large luminescent quenching extent and reduced Co^{II} and Co^I intermediate formation indicated the preferred oxidative quenching pathway, i.e., photoinduced electron transfer from Ru(bpy)₃Cl₂ to Co(dmgH)₂pyCl.^{7,8} The generated Ru(bpy)₃³⁺ [$E_{1/2}^{\text{ox}}$ Ru(bpy)₃³⁺/Ru(bpy)₃²⁺ = +1.29 V vs SCE, $E_{1/2}^{\text{ox}}$ 1a^{+•}/1a = +0.79 V vs SCE]^{2a} is able to oxidize 1a to form radical cation 1a^{+•}, which eliminated a proton to form radical 1a[•] for the following photocatalytic reaction.

Kinetic isotopic effects (KIE) ascertained the dissociation of protons from the oxidized $1a^{+0}$. When all-deuterated D_{11} -1a was subjected to the reaction, D_2 -4a was obtained in 75% yield with 56% D along with D_9 -3aa in 78% yield (Scheme 1a). As a

Scheme 1. Kinetic Study and Radical Capture Experiments



result of proton exchange with a trace amount of water in CH₃CN or Ru(bpy)₃Cl₂·6H₂O, the ratio of D in **4a** also decreased in the hydrogen transfer process by Co-(dmgH)₂pyCl. When CD₃CN was used instead of CH₃CN as the solvent, **3aa** and **4a** decreased from 88% and 91% to 76% and 85% yields, respectively (Scheme 1b). All of the observations suggested that hydrogen transfer from tertiary anilines to maleimides occurred. The ($k_{\rm H}/k_{\rm D}$) intra- and intermolecular isotopic values were determined to be 2.1 and 2.2, respectively (Scheme 1c and 1d). The KIE values were much lower for the ($k_{\rm H}/k_{\rm D}$) intra- and intermolecular isotopic effects (6.4 and 4.0) determined under air conditions,^{Sb} suggesting that an electron/proton transfer⁹ instead of a

hydrogen atom transfer (HAT) process should occur predominantly for C-H bond cleavage. An obvious secondary kinetic isotope effect on the benzene ring (the intermolecular $k_{\rm H}/k_{\rm D} = 1.5$) indicated that the C–C bond formation occurs before C-H bond cleavage (Scheme 1e). Moreover, a series of radical inhibition experiments were conducted to confirm the radical formation for this reaction. With the addition of radical inhibitor 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) or 2,6di-tert-butyl-4-methylphenol (BHT), the cyclization reaction was gradually suppressed (Scheme 1f and 1g). When 2 equiv of 2-benzylidenemalononitrile 2x, a well-known radical scavenger of α -aminoalkyl radical, were added under the standard conditions, 5ax rather than the cyclization product 3ax was obtained in only 63% yield (Scheme 1h). Therefore, the photogenerated α -aminoalkyl radicals¹⁰ are significant and responsible for the addition/cyclization process.

Based on the aforementioned mechanistic studies, we proposed a plausible mechanism that is shown in Scheme 2.





Upon visible light irradiation of $\operatorname{Ru}(\operatorname{bpy})_3^{2+}$ by blue LEDs, *Ru(bpy)₃²⁺ in its excited state is oxidatively quenched by Co(dmgH)₂pyCl to afford Ru(bpy)₃³⁺ and Co^{II} via singleelectron transfer (SET). The formed Ru(bpy)₃³⁺ associates with 1a to regenerate Ru(bpy)₃²⁺ and produce radical cation 1a^{+•}, which is deprotonated to yield α -aminoalkyl radical 1a[•]. The resultant α -aminoalkyl radical intermediate 1a[•] undergoes an intermolecular radical addition/cyclization to form the radical intermediates A and B. As a result, the desired tetrahydroquinoline 3aa is generated through a rearomatization process. The released proton (H⁺) and electron (e), on the other hand, are immediately captured by Co(dmgH)₂pyCl to form the reduced species Co^{II} and Co^I as well as Co^{III}–H species, which achieves hydrogen transfer *in situ* to maleimides and regeneration of Co(dmgH)₂pyCl for the next catalytic cycle.

The generality of the redox-neutral reaction was well established with tertiary anilines substituted with electronwithdrawing, electron-donating, and bulky alkyl groups. As summarized in Scheme 3, *N*,*N*-dimethylanilines incorporating 4-Me, 4-OMe, 4-F, and 4-Cl on the phenyl ring reacted with **2a** to afford their corresponding tetrahydroquinolines **3aa–3ha** in 30–89% yields. However, the *N*,*N*-dimethylanilines bearing a strong electron-withdrawing group 4-CN (**1f**) with higher oxidation potential (Figure S4) did not produce any of the desired product. Irradiation of *N*,*N*-3-trimethylaniline (**1g**) and Scheme 3. Scope of Tertiary Anilines^{*a,b*}



^{*a*}Reaction conditions: 1 (0.2 mmol), 2a (0.4 mmol), 1 mol % $Ru(bpy)_3Cl_2$, and 10 mol % $Co(dmgH)_2pyCl$ were added in CH_3CN (4 mL) under an argon atmosphere and irradiation of 3 W blue LEDs for 24 h at rt. ^{*b*}Yield of isolated products based on 0.2 mmol 1. ^{*c*}The configuration of the diastereomer was determined by ¹H NMR. ^{*d*}3 mol % of $Ru(bpy)_3Cl_2$ and 5 mol % $Co(dmgH)_2pyCl$ were used.

2a resulted in the formation of a mixture of regioisomers 3ga and 3ga' in a ratio of 1.8:1 and 46% combined yield. When *N*-ethyl-*N*-methylaniline 1i was used as the substrate, the reaction took place mainly at the *N*-methyl carbon with the less sterically hindered position (3ia and 3ia'). Though the same selectivity was observed using *N*-isopropyl-*N*-methylaniline (3ja), *N*-phenyl or benzyl substituted tertiary anilines hardly gave the desired products 3ka and 3la. Significantly, the use of *N*-aryltetrahydroisoquinolines (THIQ) as the partners afforded the desired heterocyclic scaffolds (3na-3pa) as diastereoisomers in 30%-78% yields. Mifepristone (1q), a representative pharmaceutical containing *N*,*N*-dimethylaniline, enabled the formation of 3qa as a complex mixture of diastereomers in a combined 62% yield.

Having successfully achieved the reaction with various tertiary anilines, we shifted our attention to the scope of electron-deficient olefins (Scheme 4 and 5). Remarkably, N-aryl maleimides substituted with electron-donating or -withdrawing groups gave tetrahydroquinolines 3ab-3ak in good yields. Due to the atropisomeric ortho-substituted acrylamide, N-(o-tolyl) maleimide and N-(2-bromophenyl) maleimide were suitable for the reaction, giving rise to 3aj and 3ak as a mixture of diastereomers in combined 96% and 68% yields, respectively. Furthermore, reactions of the N-aliphatic (methyl, n-propyl, tert-butyl, cyclopentyl, cyclohexyl, and benzyl) maleimides also proceeded smoothly to afford their corresponding tetrahydroquinolines in excellent yield (3al-3ar). However, 1a failed to react with the other olefins (2s-2w) (Table S3) and decomposed partly into H₂ and N-methylaniline due to its unfavored cyclization under the reaction conditions. Interestingly, the redox-neutral reaction, i.e., an oxidative cyclization

Scheme 4. Scope of Electron-Deficient Olefins^{*a,b*}



^{*a*}Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), 1 mol % $Ru(bpy)_3Cl_2$, and 10 mol % $Co(dmgH)_2pyCl$ were added in CH_3CN (4 mL) under an argon atmosphere and irradiation of 3 W blue LEDs for 24 h at rt. ^{*b*}Yield of isolated products based on 0.2 mmol of **1a**. ^{*c*}The configuration of diastereomer was determined by ¹H NMR. ^{*d*}95% of **2** was recovered.



"Reaction conditions: **1a** (0.2 mmol), **6** (0.2 mmol), 1 mol % $Ru(bpy)_3Cl_2$, and 10 mol % $Co(dmgH)_2pyCl$ were added in CH_3CN (4 mL) under an argon atmosphere and irradiation of 3 W blue LEDs for 24 h at rt. ^bYield of isolated products based on **1a**. ^c3 mol % of $Ru(bpy)_3Cl_2$ and 5 mol % $Co(dmgH)_2pyCl$ were used.

and reductive hydrogenation, was also amenable to commercially available bismaleimide 7 and N,N-dimethylaniline 1a (Scheme 5). When 1a (1.0 equiv) and di-N-substituted maleimides 6 (1.0 equiv) were irradiated for 24 h under the optimized conditions, reduced monocyclized compound 7 and bicyclized compound 8 were formed.

In conclusion, we have successfully developed a redox-neutral reaction to achieve oxidative cyclization synthesis of tetrahydroquinolines in conjunction with hydrogenation. Upon visible light irradiation of a catalytic amount of photocatalyst $Ru(bpy)_3Cl_2$ and cobaloxime catalyst $Co(dmgH)_2pyCl$, various tetrahydroquinolines have been synthesized from tertiary anilines and maleimides in good to excellent yields, and simultaneously, the electron and proton eliminated from tertiary anilines are captured by a cobaloxime catalyst to achieve hydrogen transfer *in situ* to the maleimides. It is anticipated that exploitation of photoredox/cobalt catalytic systems¹¹ would represent a more step- and atom-economic approach for organic transformation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b00977.

Experimental procedures, methods and product characterizations (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: lzwu@mail.ipc.ac.cn.

ORCID 💿

Bin Chen: 0000-0003-0437-1442 Chen-Ho Tung: 0000-0001-9999-9755 Li-Zhu Wu: 0000-0002-5561-9922

Notes

The authors declare no competing financial interest.

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