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Regioselective Intramolecular Markovnikov and Anti-Markovnikov Hydrofunctionalization of Alkenes via Photoredox Catalysis

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Highly regioselective Markovnikov hydrofunctionalization of alkenes was successfully realized via photoredox catalysis by introducing a urea group and fine tuning the hydrogen atom transfer catalysts. The anti-Markovnikov hydroamination of alkenes was also achieved with high yields and stereoselectivities in this work.

The regioselective hydrofunctionalization of alkenes (HFA) represents an important strategy for the construction of high value-added molecules from feedstock materials with high atomic efficiency.¹ Over the past decades, extensive efforts have been focused on the development of regioselective HFA reactions via nobel metals and organocatalysts.² In particular, great advances have been made regarding the carbonylations,³ hydrocyanation,⁴ hydroamination,⁵ hydroxylation⁶ and hydroboration of alkenes.⁷ Despite the great importance of HFA reactions, "controlling the regioselectivity" is still a challenging topic in organic synthesis.

Recently, photoredox catalysis has become a powerful tool for constructing functionalized molecules, which also has wide applications in anti-Markovnikov HFA reactions employing a dual catalyst system including a photocatalyst and hydrogen atom transfer catalyst.8 Generally, a radical process was photocatalytic involved in the reactions. Taking oneintramolecular HFA reaction as an example (Scheme 1, Path a), a cation radical intermediate **B** was first generated via the oxidation of A by the excited photocatalyst, then the cyclization reaction proceeded, yielding the radical intermediate C. After a hydrogen atom transfer process, the desired product **D** was furnished. Compared with traditional noble-metals catalysis for HFA reactions, photoredox catalysis provides a sustainable, mild

Cyclization НΑ **Previous Work** Path a С D Anti-Markovnikov Product visible light Nu R' R Path h НАТ Cvclization Nυ Nu This work Е Markovnikov Product

Scheme 1. Photocatalyzed Markovnikov and anti-Markovnikov reactions. HAT: hydrogen atom transfer; Nu: nucleophile.

and environmentally benign strategy for the generation of anti-Markovnikov adducts.⁹ Although great advances have been made regarding anti-Markovnikov HFA via photoredox catalysis, minimal attentions has been focused on Markovnikov HFA reactions through photocatalysis. In light of the advantages of photoredox catalysis in organic synthesis, it is highly desirable to develop new methods to realize regioselective Markovnikov and anti-Markovnikov HFA reactions under visible light; this development would greatly expand the applications of photoredox catalysis in HFA reactions.

Based on the catalytic mechanism (Scheme 1, Path a), the functionalization of the alkenes first occurred via a cyclization process, that can be attributed to the properties of the radical intermediate **C**. Generally, this radical should be stabilized by electron-donating groups. We anticipated that if the HAT progress finished first, we would obtain cation intermediate **E** and then achieve a consequent cyclization process, and Markovnikov HFA reactions would be successfully realized (Scheme 1, Path b). Therefore, studies on the hydrogen transfer catalysts and suitable nucleophiles are important for realizing the above hypothesis. Recently, our group has focused on the applications of nitrogen radical cations in organic synthesis via

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Table 1. Screening the reaction conditions.^a



^aUnless otherwise noted, all the reactions were carried out with **1a** (0.1 mmol) in the presence of 4-MeOC₆H₄SH (20 mol%) catalysed by I (5 mol%) at -15 °C. For more details about the experimental procedures, see the Supporting Information.

photoredox catalysis, and found that urea groups exhibited excellent properties for controlling the regioselectivities via hydrogen binding interactions.¹⁰ Considering the excellent properties of urea groups, these groups might be ideal nucleophiles for exploring the Markovnikov HFA reaction. In addition, to accelerate the HAT process, strong electron-donating HAT catalysts are needed in the HFA reactions.

Initially, the Markovnikov reaction of 1a was examined under photocatalytic conditions. As shown in Table 1, a Z-isomer 2a can be obtained at 84% yield catalysed by Fukuzumi catalyst I under visible light. Furthermore, the structure of the spiro product 2a was confirmed by X-ray crystallographic analysis.¹¹ Subsequently, control experiments were examined including photocatalysts, blue light or 4-MeOC₆H₄SH (Table 1, entries 2-4). However, no product was formed when the reaction was carried out without any of these factors, which illustrated that the reaction was a photocatalysed Markovnikov HFA reaction. Furthermore, the influences of solvents continued to be investigated, while the reactions could be performed in chlorinated solvents such as CH_2Cl_2 and $CICH_2CH_2CI$ with low yield. However, no products were obtained when the reaction was carried out in other polar solvents (CH₃CN and DMF) (Table 1, entries 5-8). Then hydrogen atom transfer (HAT) catalysts were explored with regard to explaining the effects of hydrogen atom donors. Electron-poor thiols (4-CF₃C₆H₄SH) were detrimental to the reaction, and only low yields were obtained. $2,4,6^{-i}$ Pr₃C₆H₂SH was unfavourable for the yield because of the bulky steric influence of this complex. Moreover, the influences

Under the optimized conditions, the scope of the Markovnikov hydroxylation reactions continued to be investigated (Table 2). Different substituents on the urea were carefully investigated, electron-withdrawing groups are more favourable for the Markovnikov reaction (see Supporting Information for more details). For substrate 1b, 88% yield was obtained. The introduction of different substituents in the cyclohexane ring were tolerated well, with high yields such as methyl, ^t-Bu and phenyl (Table 2, entries 2-7). Moreover, trisubstituted cyclopentene and cycloheptane were also tested, and the spiro adducts 2i and 2j were obtained at yields of 78% and 75% respectively. Subsequently, trisubstituted cyclohexene 1k was examined, which could furnish the five membered ring 2k at a yield of 79%. Furthermore, linear alkene 1l was tolerated to provide the cyclization product 2l at an excellent yield (80% yield).

To explain the importance of thiols to the hydrogen atom transfer process, we tested the intramolecular hydroamination via tuning the electronic properties of thiols. After carefully screening the conditions of the reactions (see Supporting Information for more details), we found that the reaction can be successfully realized using 4-CF₃C₆H₄SH under room temperature (81% yield for cis-3a). In particular, excellent diastereoselectivity was obtained with >20:1 d.r.. The structure of **3a** was confirmed by X-ray crystallographic analysis.¹¹ For the best conditions, different substituents in the ring continued to be explored. As shown in Table 2, all the anti-Markovnikov hydroamination products could be produced with good to excellent yields and high diastereoselectivities. All the results illustrated that the Markovnikov and anti-Markovnikov reactions could be realized via tuning the electronic properties of hydrogen atom transfer catalysts and reaction temperature.

To expand the applications of the catalytic method, the gramscale experiment was then tested. As shown in Scheme 2a, the reaction can be performed using 3 mmol of **1a** with 71% yield. We primarily investigated the applications of the method in the late stage functionalization of stanolone. Intramolecular hydroxylation and hydroamination of the alkene were well tolerated with high yields (75% yield for **2o**, and 63% yield for **3o**).

To gain insight into the mechanism of the reaction, certain control experiments were performed. When the N-H of the urea was protected with benzyl group **1a'** or methyl group **1a''**, complex mixtures were observed under the optimized conditions. Replacing the urea groups with amides was detrimental to the reaction via photoredox catalysis (trace for **2p**, 24% yield for **2q**), so the nucleophilicity of the urea was important for the Markovnikov reaction. Based on the results and previous works, a possible mechanism was proposed as shown in Scheme 3b. The alkenes **1** was first oxidized by the excited photocatalyst to produce the radical cation intermediate **L**, which then proceeded via a hydrogen atom

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Table 2. Intramolecular anti-Markovnikov hydroamination of alkene via photocatalysis.



^aCondition A: all the reactions were carried out with **1** (0.1 mmol) in the presence of 4-MeOC₆H₄SH (20 mol%) catalyzed by I (5 mol%) at -15 °C. Condition B: all the reactions were carried out with **1** (0.1 mmol) in the presence of 4-CF₃C₆H₄SH (20 mol%) catalyzed by I (5 mol%) at r.t.. For more details about the experimental procedures, see Supporting Infromation.

transfer process to furnish the cation intermediate **M**. Subsequently, a cyclization reaction was performed to obtain the desired spiro products **2**.

In summary, highly regioselective intramolecular Markovnikov and anti-Markovnikov hydrofunctionalization of alkenes was successfully developed via photoredox catalysis. HAT catalysts and the urea groups played crucial roles in controlling the regioselectivities of these reactions. In which, Zisomers of spiro products were selectively prepared with high yields. Moreover, cis-stereoselective hydroamination of alkenes was realized via fine tuning of the HAT catalysts and reaction temperature. We believe that these results provide a new perspective on the application of photoredox catalysis in the functionalization of alkenes. In addition, further studies on the mechanism of the highly regioselective hydrofunctionalization of alkenes by photoredox catalysis are underway in our lab, and will be reported in due course.

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Scheme 2. Gram-scale synthesis and applications of the Markovnikov reaction via photoredox catalysis.



Scheme 3. Control experiments and the plausible catalytic mechanism.

a) Control experiments:



Conflicts of interest

The authors declare no competing financial interest.

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