

Review of recent development in Anti-Markovnikov addition reaction of olefins

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Abstract:

The regioselective functionalization of terminal olefins is of significant importance in organic synthesis. Based on the critical observations of Markovnikov, the types of addition products can be identified as Markovnikov or anti-Markovnikov products. In recent years, the anti-Markovnikov addition reaction of olefins has caught many scientists' eyes because of its broad application prospects in chemical and pharmaceutical industries and its perfectly compliant with green chemistry. Herein, we summarized the main methodologies developed for the functionalization of olefins and compared their advantages and disadvantages, hoping that this minireview can provide some inspiration for researchers to develop more effective pathways of functional group production based on olefins.

Keywords: Anti-Markovnikov, Olefins, Hydroboration, Hydration, Hydroxyoxygenation, Transition metals, Photocatalysts

1. Introduction

Markovnikov's rule [1], which was discovered by Russian chemist Markovnikov in 1870, was one of the most famous regional selective empirical rules in organic chemistry. The rule describes specific addition areas in electrophilic addition reactions and could be regarded as Matthew's effect in chemistry, which means when an electrophilic addition reaction occurs (such as the reaction between hydrogen halide and olefin), the positively charged group (such as hydrogen) in the electrophilic reagent is always added to the carbon atom with the most hydrogen connected (least substitution), while the negatively charged group (such as halogen) is added to the carbon atom with the least hydrogen connected (most substitution). The most typical reaction to prove Markovnikov's rule is the addition reaction of hydrogen iodide and vinyl bromide (shown in Figure 1a). The rule can be explained by electronic effects; when the positively charged part attacks the double bond, it prefers to add to the side with a relatively high electronic density and results in a stable carbocation to further combine with the substituent group. Markovnikov's rule is useful for quickly identifying the direction of electrophilic addition reactions and has been applied to produce many vital commodity chemicals, such

as alcohols and amines, in the modern global economy [2]. However, as people discovered more and more organic reactions, the rule became no more suitable in many occasions, which is called anti-Markovnikov reactions. In this case, the hydrogen is added to the double-bonded carbon atom with less hydrogen connected (shown in Figure 1b). The phenomenon often occurs when there are peroxide or strong electron-withdrawing groups participating in the reaction. Taking the existence of peroxide for example, the peroxide acts on the hydrogen bromide to produce bromide radical, and due to the hyperconjugation of two methyl groups, the stability of secondary carbon radicals is greater than that of primary carbon radicals, thus leading to the effects of anti-Markovnikov addition. The mechanisms of anti-Markovnikov additions are complicated and the relevant methods have been studied and developed for several decades [3]. Currently, there is no universally accepted approach for generating anti-Markovnikov products using the same initial substances, with the majority requiring the use of transition metal catalysts. In this article, we summarize and compare the present four methods of realizing anti-Markovnikov functionalization of olefins, and put forward our prospect for the future development of this novel methodology.

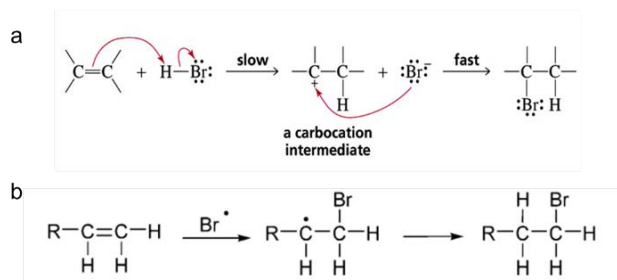


Figure 1. Typical models of Markovnikov's rule and anti-Markovnikov addition. (a) Addition reaction followed by Markovnikov's rule; (b) Addition reaction exhibited anti-Markovnikov selectivity.

2. Results and Discussion

Although the addition reactions of olefins may seem simple, it is still an enormous challenge to control the regioselectivity of such processes. Even now, achieving the anti-Markovnikov addition of amines, alcohols, and water to basic aliphatic olefins, materials of notable industrial importance, poses a challenging task. A typical and ideal instance of such a process is listed in Figure 2. Under certain catalysts, olefins react with water and directly generate anti-Markovnikov alcohols. This reaction fully conforms to the concept of green chemistry and is expected to gain an atom efficiency of 100%; with the efforts over the years, scientists have developed several methods to achieve this simple and complex reaction.

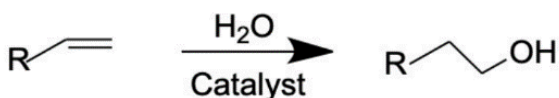


Figure 2. An ideal model of anti-Markovnikov addition of olefins

In 1933, M.S.Kharasch et al. [4] found that under the presence of light or peroxides, hydrobromic acid can react with asymmetric olefins, resulting in additional products that were exactly opposite to those predicted by Markovnikov's rule. Although, at that time, people were still uncertain about the mechanism of the reaction, chemists realized that free radicals might be involved in these reactions. Herbert C. Brown et al. [5-7] then started to make use of the organoboron compounds to develop new organic synthesis methods in the 1950s, and this kind of hydroboration is called Brown Hydroboration. Brown Hydroboration reaction refers to the synergistic *cis* addition of alkenes or alkynes by borane to obtain organic boron addition products. This process had high selectivity and stereospecificity, which meant boron mainly binds to carbon atoms in olefins with less substitutions, and through

further oxidation by peroxides, the olefins were finally turned into corresponding alcohols [5] (shown in Figure 3a). The mechanism of this reaction could also be divided into two parts: the addition reaction of B-H bond and the oxidative cleavage of B-C bond. Since in borohydride compounds, the electronegativity of boron was positive while the electronegativity of hydrogen was negative when they underwent an addition reaction with olefins, boron would be added to carbon atoms with more hydrogen content and presented an anti-Markovnikov semblance. In the next step, the conjugated base of hydrogen peroxide coordinated with the empty orbital of boron, after rearrangement and the remove of hydroxyl groups, the alkoxyboron further hydrolyzed and yielded a molecule of alcohol and one molecule of boric acid. The reaction has been widely applied in the manufacturing for synthetic drug intermediates. Notably, the difference in electronegativity between boron and hydrogen is relatively small, thus to achieve higher selectivity, it is recommended to induce larger substituents in borane, and for some reactions, the selectivity, stereoselectivity and functional group selectivity are not as high as expected, especially in nonactivated olefins [8]. Moreover, two factors are needed to be considered for the applications. First is the safety of using peroxides, as is known to all, peroxides have a high risk of fire and explosion. Second is the incomplete utilization of atoms, the byproduct-boric acid is difficult to recycle and reuse, which is not well matched the requirement of green chemistry. Thus, the reaction still has plenty rooms for further optimization.

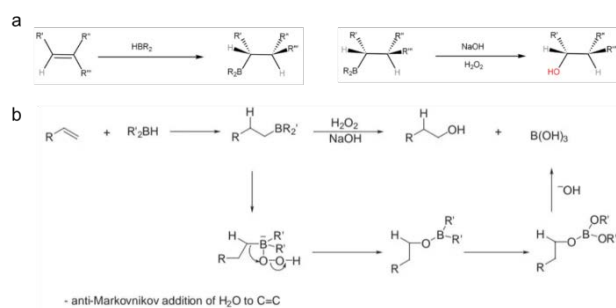


Figure 3. (a) Brown's method of anti-Markovnikov hydration of olefins; (b) The mechanism of hydroboration-oxidation reaction.

Since the synthesis of alcohols through hydroboration/oxidation is an indirect method, a more direct approach is urgently needed in chemical and pharmaceutical industries. In 2011, Grubbs et al. [9] reported a triple relay catalysis system to transfer aryl-substituted terminal olefins to primary alcohols. Compared with the limited success of traditional anti-Markovnikov olefin hydration, this reaction can be achieved in the nonactivated terminal

olefins. The entire reaction was based on a two-catalyst cooperative system: an oxidation cycle and a reduction cycle (shown in Figure 4(a)). The oxidation cycle was established on Wacker oxidation reaction [10] by Pd(II) salts catalytic effect. In the presence of water, the catalyst could oxidize olefins to the corresponding aldehyde or carbonyl compounds and produce metal hydrides. In the reduction step, certain metal hydrides (metal: Ru, Ir, Fe, Ni, Pt, etc.) had the ability to reduce carbonyl compounds and form metal alkoxides, which could be protonated by acids and obtain the final alcohols. The authors optimized the design of the entire process in three aspects: the selectivity of the oxidation product, the compatibility between oxidation and reduction processes, and the successful transfer of hydrides from the Pd(II) salts to the second metal. In the selection of reaction substrates, styrene was chosen because of its reported relatively low anti-Markovnikov selectivity under traditional hydroboration/oxidation reactions [11, 12]. The increasing of phenylacetaldehyde production was achieved through the steric effect of *t*-BuOH and the catalysis of metal chlorides. In the reduction part, *i*-PrOH and Shvo's catalyst were selected. The existence of *i*-PrOH was beneficial for metal-catalyzed transfer hydrogenation, and Shvo's catalyst was a new catalyst composed of the diruthenium complex with catalytic hydrogenation of C=O. The reaction demonstrated a 77% yield of the primary product and was confirmed to yield significant amounts of primary alcohols from aryl-substituted terminal olefins via a triple relay catalysis pathway. This method had the disadvantages of high catalyst loadings, the use of stoichiometric benzoquinone, and the high cost of using transition metals, but the resulting high anti-Markovnikov effect of aryl-substituted terminal olefins was inspiring and encouraged more and more researchers to explore new ideas for catalytic alcoholization of olefins.

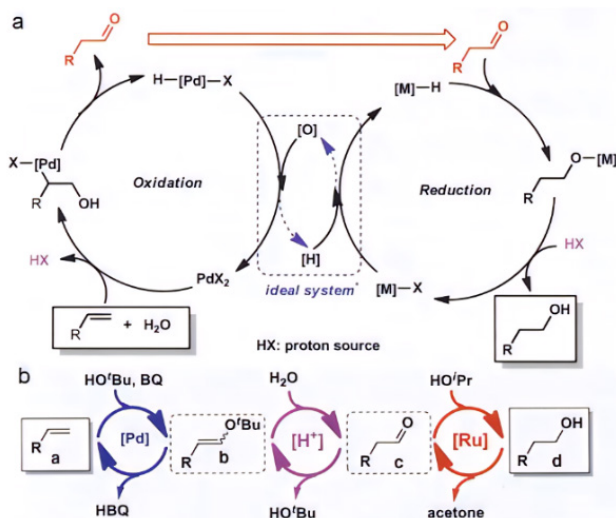


Figure 4. (a) The proposed two-catalyst

cooperative system; (b) The proposed mechanism.

Additional investigations were conducted on anti-Markovnikov addition reactions involving aliphatic alkenes. The emergence of photocatalysis has promoted the development of mild and selective synthetic methods. Nicewicz et al. [13] invented a photocatalyst-induced method to add carboxylic acids to alkenes and to generate carboxylic esters, which are one of the most significant and prevalent functional groups in synthetic chemistry. The research relied on a Fukuzumi acridinium photooxidant [14] and a stoichiometric amount of a hydrogen atom donor, as illustrated in Figure 5(a). The selection of a single electron photooxidant was critical for the production of an alkene radical cation intermediate. Acridinium photooxidants [15] were strong organic photocatalysts that have been commonly used for activating oxidation-reduction reactions and exhibited the characteristics of regioselectivity. Under visible light irradiation, acridinium salt took electrons from the substrate and converted them into acridine free radicals (Acr^\bullet); the photophysical and electrochemical properties could be regulated by functional group modification. Fukuzumi acridinium photooxidant ($\text{Acr}^+\text{-Mes}$) was reported [14, 16] to have a rather longer lifetime and higher energy among most acridinium photooxidants and was capable of high electron transfer efficiency. The achievement of high anti-Markovnikov regioselectivity was realized through the subsequent attack of nucleophiles. The work later evaluated several potential hydrogen atom donors and found that the employing of sodium benzene sulfinate could achieve a remarkable increase in reactivity and yield because the benzylic radical intermediate had the property of nucleophilicity and occupied the kinetic advantage. The reaction obtained good yields in *para* and *ortho* methoxy substitution and exhibited good tolerance of a phthalimide-protected amine. In the selection of reactant carboxylic acids, benzoic acid had a corresponding yield of 94%. The discovery that trisubstituted aliphatic alkenes, such as 1-methylcyclopentene, could undergo a reaction with acetic acid was particularly exciting. A deuterium-labeling experiment revealed that the rate-determine step was the hydrogen atom transfer process. The method could directly catalyst olefins to carboxylic esters, and more experiments needed to be carried out for mechanical studies.

Nicewicz's method was cost-effective and metal-free. However, it did not perform well in the construction of anti-Markovnikov alcohols. Aiwen Lei et al. [17] made enhancements to this method, broadening the application of visible-light-mediated anti-Markovnikov addition to include the direct hydration of olefins, as depicted in Figure

5(b). They used 1,1-diphenylethene as the model reaction substrate and the corresponding yield could be as high as 85%. The internal alkenes were also tested and exhibited good regioselectivity. The yield varied because of different steric effects and electronic effects of the substituent groups, but it was worth mentioning that this reaction could happen by only a small quantity of catalysts, and it further suggested that the rate-determine step was the protonation of PhS^- , the proposed mechanism was shown in Figure 5(c).

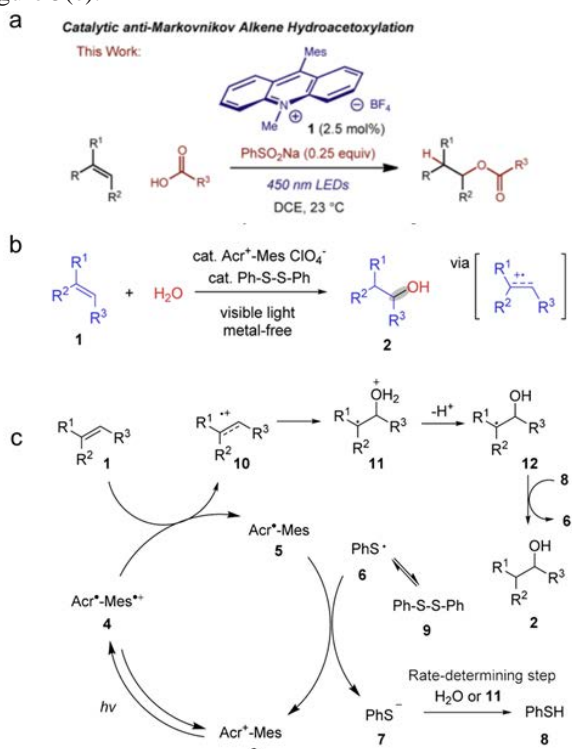


Figure 5. (a) Nicewicz's method of photocatalyzing olefins to carboxylic esters; (b) The direct hydration of olefins through visible-light-mediated anti-Markovnikov addition and (c) the possible mechanism.

Compared with electron-transfer (ET) photo-catalyzed anti-Markovnikov hydroxygenation, visible-light-mediated

energy-transfer (EnT) catalysis remains undeveloped. Huo et al. [18] reported an approach for the hydroxygenation of unactivated olefins through EnT, and the keypoint was to modify the reactivity of iminyl radicals and the solvent hydrogen-donating ability. The oxime esters were synthesized to function as the sources of iminyl radicals [19]. Oxime ester stands out as a crucial and versatile intermediate in organic synthesis, possessing diverse biological activities [20], including antibacterial properties, anti-inflammatory effects, and antioxidant capabilities, among others. The preparation of oxime ester was by simple and convenient raw material synthesis. They investigated the efficiency of anti-Markovnikov hydroxygenation by different photosensitizers and found that $\text{Ir}[\text{dF}(\text{CF}_3)\text{bpy}]_2(\text{dtbpy})\text{PF}_6$ [21] was the most useful catalyst and achieved the highest efficiency when the stoichiometric ratio to olefins was 3:1. The highest yield was obtained by taking NaOAc as the additive and chloroform as the solvent. The reaction was performed at room temperature and irradiation light for 12 hours. It was proved to be useful in terminal or internal alkenes with different functional groups, even in cyclic alkenes, but was not suitable for styrene. The reaction mechanism experiment was conducted by a radical-trapping experiment with TEMPO, and the main mechanism was proposed as follows: The N-O bond in oxime ester underwent homolytic cleavage and formed an iminyl radical and an acyloxy radical. Subsequently, the iminyl radical was added to the olefins and generated the radical intermediate. Finally, the intermediate absorbed the hydrogen in the CHCl_3 solvent and produced the end product. Unlike the previous methods, which chose carboxylic acid as the source of the ester group, this work made use of the delicate design of oxime ester, and the protocol could be suitable for various unactivated olefins with multi-functional groups, which was extremely important in practical applications. Within the paper, the authors carefully examined the potential for fabricating natural products or their derivatives with bioactivity, and this was a significant complement to the present methods of anti-Markovnikov hydroxygenation of olefins.

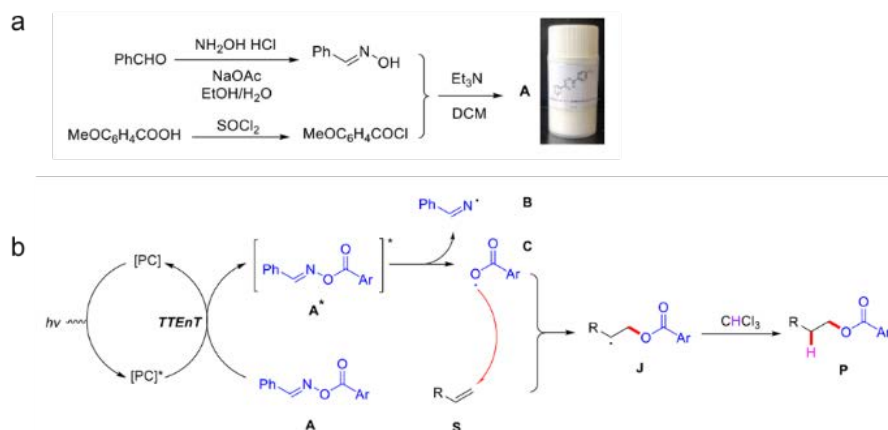


Figure 6. (a) the preparation of oxime ester; (b) The proposed reaction mechanism.

3. Conclusions

In summary, the regioselectivity of chemical reactions is beneficial to organic synthesis and production applications. Starting from olefins or alkynes to obtain functionalized products is a key link in green chemistry. Over the past 60 years, scientists have made great efforts to explore different approaches to realize the anti-Markovnikov addition reaction of olefins. For a long time, the synthesis of anti-Markovnikov alcohols from olefins involved a two-step hydroboration/oxidation reaction. This approach required substantial quantities of borane reagents, resulting in the generation of chemical waste. Additionally, the use of peroxide posed significant safety concerns in the large-scale production of this method. Another classical idea was to employ transitional metal catalysts to improve atom utilization. Grubbs' method went through a triple relay catalysis system and could transfer aryl-substituted terminal olefins to primary alcohols, but with the defect of expensive catalysts and limited substrate types. With further in-depth research, photocatalysis has been induced in the functionalization of olefins, through which carboxylic esters were successfully synthesized by adding carboxylic acids to olefins, and the primary alcohols could be directly produced by the hydration of olefins. This approach was cost-effective, metal-free, and allowed the reaction to proceed under mild conditions. However, it also had a limited range of applicable olefins, and the fully mechanisms were still remained unraveled. Unlike photocatalysis through electron transfer, the newly method of hydroxygenation of olefins was based on an energy transfer mechanism by using oxime esters as the donor of radicals. The entire reaction was catalyzed by an organic photocatalyst and has been proved to be suitable for anti-Markovnikov additions of multiple types of olefins, especially for unactivated olefins, which rendered the superiority of synthesizing natural bioactive drugs. Up till now, there is still no per-

fect method to realize regioselective functionalizations of olefins. For the chemical reaction design, the byproducts, reaction conditions, yield, etc. are important factors that need to be considered. In practical applications, the cost, safety, efficiency, large-scale production availability, etc. should also be carefully evaluated. The anti-Markovnikov addition reaction of olefins is not only a scientific concern but also an important involvement of the chemical economy. Based on the research above, we believe that the ideal direct hydration of olefins, especially the hydroxylation of terminal aliphatic olefins, will be achieved in the near future.

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