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Advances and challenges in palladium-catalyzed intermolecular selective allylic C–H functionalization of alkenes

Xiaoxu Qi, Pinhong Chen & Guosheng Liu*

State Key Laboratory of Organometallic Chemistry; Shanghai Institute of Organic Chemistry, Chinese Academy of Scieneces, Shanghai 200032, China

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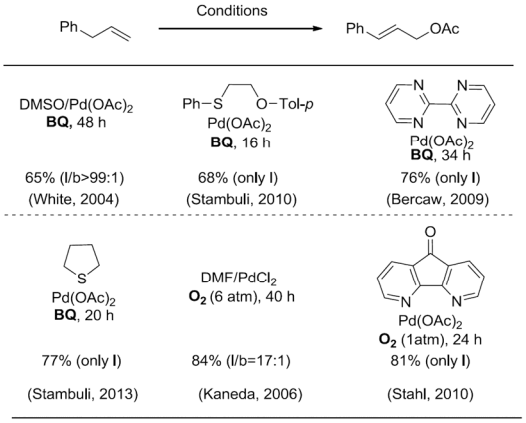
During the past decade, there was increased interest in the functionalization of the allylic C–H bond of alkenes. As opposed to traditional Trost-Tsuji reactions, this strategy avoids the prefunctionalization of the alkene. Many transition metals have been used to promote such processes, and palladium has proved to be one of the best catalysts as it offers great advantages from the point of view of substrate scope and selectivity. Therefore, many groundbreaking results obtained with Pd-catalyzed processes have been reported, including allylic C–H oxygenation, amination, alkylation, and other transformations, which have been well documented in reviews [1]. However, there remain some challenges to overcome, such as regio- and enantioselective functionalizaiton. Future studies should concentrate on the development of new concepts and strategies to address these problems. This perspective article will focus on the recent developments and perspectives of this growing field.

Pioneering studies on the allylic C–H bond functionalization date back to 1959, but they were limited to the acetoxylation of cyclic alkenes [2]. In the case of acyclic terminal alkenes, the reactions generally proceeded through Wacker-type oxidation to yield ketone or vinyl acetate compounds. Recent studies have demonstrated that the addition of ligands such as sulfoxides [3], sulfides [4], and bipyrimidine [5] to the previously used palladium/*p*-benzoquinone (Pd^{II}/BQ) systems dramatically changes the reaction pathway, leading to major linear product (Scheme 1). In this case, BQ plays a dual role: (1) it acts as an oxidant, promoting palladium catalyst regeneration (from Pd(0) to Pd(II)); (2) it acts as a π-acidic ligand, promoting the nucleophilic substitution of π-allyl Pd(II) species. Later on,



Scheme 1 Pd-catalyzed allylic acetoxylation to give linear product.

Kaneda *et al.* [6] and Stahl *et al*. [7] independently demonstrated that the Pd-catalyzed acetoxylation of terminal alkenes could be achieved under aerobic conditions in the absence of BQ, in a reaction where the dimethyl fromamide (DMF) solvent and the 4,5-diazafluorenone ligand are essential for the allylic C–H bond functionalization. Such catalytic systems were also successfully used in allylic C–H aminations [8,9] and alkylations [10]. However, there are two notable limitations of these processes: first, these catalytic systems are only efficient in the case of terminal alkenes, and second, long reaction times are required. These limitations are possibly due to the weak interactions between the alkenes and the palladium catalysts. Recently, Szabó *et al.* [11], Liu *et al.* [12] and Stambuli *et al.* [13] independently used hypervalent iodine as the oxidant to achieve allylic C–H oxygenation and amination. These reactions were significantly faster, while the alkene substrate could be an internal or cyclic alkene (Scheme 2). Although

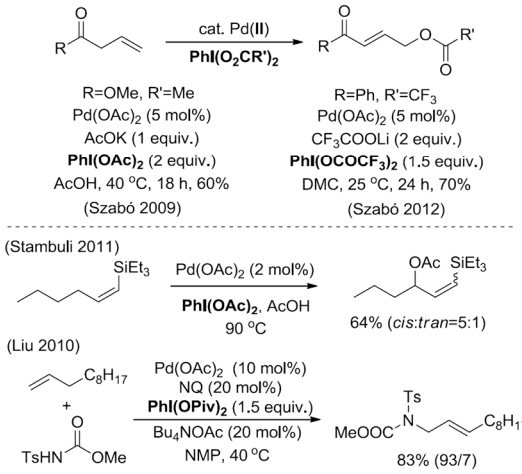
*Corresponding author (email: gliu@mail.sioc.ac.cn)

a Pd(II/IV) catalytic cycle was proposed by Szabó and coworkers, the detailed mechanism is still unclear and might be worth investigating.

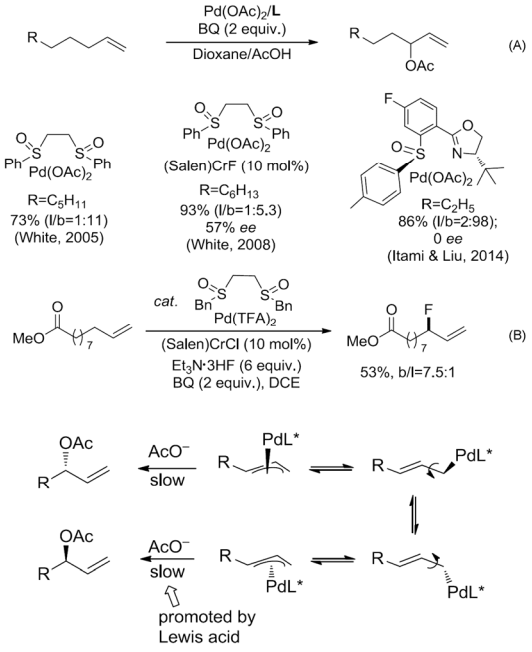
Another noteworthy point is that the linear compound was, in the most cases, the major or the sole product. Regioselective reactions leading to branched compounds are more challenging. White *et al*. [14] has reported a Pd/disulfoxide catalytic system yielding branched allylic acetate as the major product (Scheme 3(A)). Recently, Doyle and coworkers [15] reported that a similar catalytic system was used in the oxidative allylic C–H fluorination of alkenes, with $Et_3N\cdot 3HF$ as the source of fluoride. Branched allylic fluorides were obtained as major products in moderate to good yields, with good regioselectivity (Scheme 3(B)). However, when a chiral disulfoxide ligand was introduced, the reaction could not deliver enantiomeric excess (*ee*). It is possible that the coordination between sulfur and palladium is not strong enough to control the stereoselectivity of the reaction. For testing the possibility of enantioselective allylic acetoxylation, Itami *et al*. [16] introduced an oxazoline moiety to the sulfoxide ligand, in order to enhance the coordination ability of the ligand toward Pd. Although the chiral sulfoxide-oxazo-line (sox) ligand showed high efficiency, with excellent regioselectivity toward branched compounds, the reaction afforded a racemic mixture as the product (Scheme 3(A)) [16]. White and coworkers [17] found that the addition of a chiral Lewis acid could help induce an asymmetric reaction, and (Salen)CrF was found to be the best in affording branched allylic acetates with moderate *ee* (54%–63%, Scheme 3(A)). One possible explanation for the increasing in *e.e* after the addition of (Salen)CrF is that, in the catalytic cycle, the final nucleophilic substitution of the π-allylic Pd(II) is a slow step. In that case, the fast isomerizaiton between η^1 and η^3-allylic Pd complexes could result in an erosion on the chiral center, leading to the racemic product. The addition of Lewis acids could enhance the Lewis acidity of the palladium center, thus promoting the final nucleophilic substitution (Scheme 3).

Alternative new strategy leading to enantioselective allylic C–H functionalization involves the use of a prechiral nucleophile. For instance, Trost and coworkers [18] reported the first Pd-catalyzed enantioselective allylic C–H alkylation for the synthesis of various allylated 1,3-diketones with good yields, where chiral phosphoramidite was found to be the best ligand that afforded excellent regio- and enantioselectivity (first reaction in Scheme 4). Quite recently, Gong and coworkers [19] also reported a palladium-catalyzed asymmetric allylic C–H alkylation using chiral phosphonic acid as the counter anion at the palladium center to control the stereochemistry (last reaction in Scheme 4).

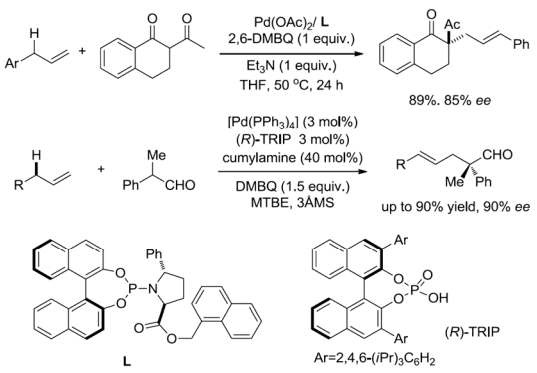
Another successful enantioselective allylic C–H functionalization of terminal alkenes was reported by Shi and coworkers [20]. In this case, the reaction was initiated by the oxidative-addition of di-*tert*-butyldiaziridinone by Pd(0)



Scheme 2 Allylic oxygenation and amination with hypervalent iodine as the terminal oxidizing agent.

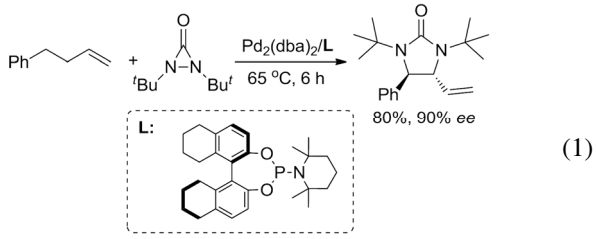


Scheme 3 Pd-catalyzed allylic functionalization leading to branched products.



Scheme 4 Asymmetric intermolecular allylic alkylation.

species to generate diamine-Pd(II) catalyst, and H_8-BINOL-derived phosphoramidite was used as an efficient chiral ligand. Allylic and homoallylic C–H bond diamination products could be obtained in good yields with excellent regio-, diastereo-, and enantioselectivites (Eq. (1)) [20].



(1)

So far, various palladium-catalyzed C–C, C–N, and C–O bond forming reactions via allylic C–H activation have been developed for the synthesis of allylic derivatives from easily available alkenes. However, the following limitations still remain: (1) most of the reactions were compatible with the acidic nucleophilic reagents only within a narrow pK_a range; (2) linear allylic compounds were the major/sole products; (3) low efficiency was observed in most cases, resulting in long reaction times and high catalyst loading. Compared to the Tsuji-Trost reactions, allylic substitution via allylic C–H activation is more effective and directive, but still far from successful, especially on the regio- and enantioselective control. Therefore, further investigations are required to address the aforementioned issues, and the exploration of new type of catalytic systems, including new ligands, metal complexes, and additives, is essential. In addition, further mechanistic investigations are important for improving the efficiency of the reactions. Thus, the development of straightforward and selective methods for direct allylic C–H functionalization is anticipated.

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