

## C–H Activation

International Edition: DOI: 10.1002/anie.201706418

German Edition: DOI: 10.1002/ange.201706418

Palladium-Catalyzed Alkylation with Alkyl Halides by C(sp<sup>3</sup>)–H Activation

Zhuo Wu, Ding Ma, Bo Zhou, Xiaoming Ji, Xiaotian Ma, Xiaoling Wang, and Yanghui Zhang\*

**Abstract:** Utilizing halogens as traceless directing groups represents an attractive strategy for C–H functionalization. A two C–H alkylation system, initiated by the oxidative addition of organohalides to Pd<sup>0</sup>, has been developed. The first reaction involves an intermolecular alkylation of palladacycles to form C(sp<sup>3</sup>)–C(sp<sup>2</sup>) bonds followed by C(sp<sup>2</sup>)–H activation/cyclization to deliver alkylated benzocyclobutenes as the final products. In the second reaction, two C–C bonds are formed by the reaction of palladacycles with CH<sub>2</sub>Br<sub>2</sub>, and provides a facile and efficient method for the synthesis of indanes. The alkylated benzocyclobutene products can be transformed into tricyclic hydrocarbons, and the indane derivatives are essential structural motifs in bioactive and odorant molecules.

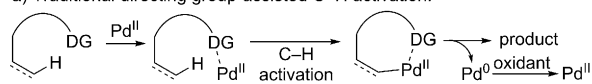
In the past few decades, transition metal catalyzed C–H functionalization has made noticeable progress and is emerging as a novel and valuable strategy in organic synthesis.<sup>[1]</sup> Most of the current C–H functionalization reactions rely on the use of directing groups, which can lead to great regioselectivity and accelerate the C–H cleavage process. (Figure 1a)<sup>[2]</sup> However, this strategy restricts the scope of

precatalysts. The resulting Pd<sup>II</sup> species then cleave proximal intramolecular C–H bonds and form palladacycles which then undergo further transformations (Figure 1b). The major advantage of this method is that the halo groups are removed and the resulting palladium–carbon bonds can be manipulated readily. Furthermore, halogens are ubiquitous functionalities in organic molecules and can be introduced comparatively readily. While Pd<sup>II</sup>-initiated C–H functionalization reactions require the use of a stoichiometric amount of external oxidants, organohalides act as oxidants themselves. Although some reactions of this type have been developed,<sup>[4]</sup> the majority of them are intramolecular cyclization reactions.<sup>[5]</sup> Notably, this strategy has also been applied to C(sp<sup>3</sup>)–H activation reactions. Likewise, the most of the reactions involve intramolecular cyclization<sup>[6]</sup> and very rare intermolecular reactions were reported.<sup>[7]</sup>

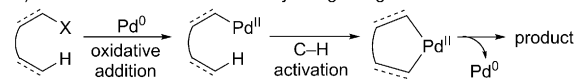
Recently, we found that dibenzometallacyclopentadiene, prepared by C–H activation of 2-iodobiphenyl, exhibited novel reactivity.<sup>[8]</sup> This palladacycle can selectively react with alkyl halides, whose reactions are usually challenging in transition metal catalyzed reactions. Actually, the palladacycles formed by C(sp<sup>2</sup>)–H activation from aryl iodides and norbornene, in Catellani reactions, can react with alkyl halides efficiently.<sup>[9]</sup> Inspired by these reactions, we envisioned that palladacycles might be desirable models for the development of palladium-catalyzed alkylation with alkyl halides. In Catellani reactions, as well as our reactions, the palladacycles consist of two carbon–metal bonds, and the advantage of this type of palladacycle is that these two carbon atoms can be functionalized. However, norbornene just functions as catalyst in the Catellani reaction, and the C(sp<sup>3</sup>)–Pd bond can usually not be manipulated. We were interested in the difunctionalization of the two carbon–metal bonds in the palladacycles, as it may offer opportunities to develop novel organic reactions. Herein, we report the alkylation reaction of the palladacycle derived from 2-*tert*-butylaryl halides with alkyl chlorides and dibromomethane. The reaction with alkyl chlorides is a tandem process and provides alkylated benzocyclobutenes as the final products. A catalytic protocol for the reaction of the palladacycle with dibromomethane has also been developed.

We commenced our study by investigating the reaction of 1-bromo-2-*tert*-butylbenzene (**1a**) with 4-chlorobutyl acetate (**2a**). Unexpectedly, the reaction formed the alkylated benzocyclobutene **3aa** in the presence of PPh<sub>3</sub> (Table 1, entry 2). Inspired by this exciting result, we sought to improve the yield of **3aa** by screening phosphine ligands, and found that the yield increased dramatically to 85% when P(*o*-tol)<sub>3</sub> was used (entry 3). For details on screening reaction conditions see the Supporting Information.

a) Traditional directing group-assisted C–H activation.



b) Intramolecular C–H activation by using halogens as traceless directing groups.



**Figure 1.** C–H functionalization using halogens as traceless directing groups.

accessible products. Although some directing groups can be manipulated after C–H functionalization, additional synthetic steps are often required.<sup>[3]</sup> Moreover, some directing groups have to be installed by complex synthetic steps.

An alternative method of activating C–H bonds is to utilize halogens as traceless directing groups. For palladium-catalyzed reactions of this type, the catalytic cycles are usually initiated by the oxidative addition of organohalides to Pd<sup>0</sup>

[\*] Z. Wu, D. Ma, B. Zhou, X. Ji, X. Ma, X. Wang, Prof. Dr. Y. Zhang  
School of Chemical Science and Engineering, Shanghai Key Laboratory of Chemical Assessment and Sustainability, Tongji University  
1239 Siping Road, Shanghai 200092 (China)  
E-mail: zhangyanghui@tongji.edu.cn

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:  
<https://doi.org/10.1002/anie.201706418>.