A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201706418
Angew. Chem. 10.1002/ange.201706418

Link to VoR: http://dx.doi.org/10.1002/anie.201706418
http://dx.doi.org/10.1002/ange.201706418

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10.1002/anie.201706418

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Pd-Catalyzed Alkylation with Alkyl Halides via C(sp^3)−H Activation of Aryl Halides

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

Abstract: Utilizing halogens as traceless directing goups represents an attractive strategy for C−H functionalization. We have developed two C−H alkylation systems initiated by the oxidative addition of organohalides to Pd^0. The first reaction involved an intermolecular alkylation of palladacycles to form C(sp^3)−C(sp^2) bonds followed by C(sp^2)−H activation/cyclization, delivering alkylated benzocyclobutenes as the final products. In the second reaction, two C−C bonds were formed via the reaction of palladacycles with CH_2Br_2, which provides a facile and efficient method for the synthesis of indanes. The alkylated benzocyclobutene products can be transformed into tricyclic hyrocarbons, 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.[1] Most of the current C−H functionalization reactions rely on the use of directing groups, which can lead to great regioselectivity and accelerate C−H cleavage process.(Figure 1, A) [2] However, this strategy restricts the scope of accessible products. Although some directing groups can be manipulated after C−H functionalization, additional synthetic steps are often required.[3] Moreover, some directing groups have to be installed via complex synthetic steps.

An alternative method of activating C−H bonds is to utilize halogens as traceless directing goups. For Pd-catalyzed reactions of this type, the catalytic cycles are usually initiated by the oxidative addition of organohalides to Pd^0 precatalysts. The resulted Pd^{II} species then cleave proximal intramolecular C−H bonds and form palladacycles, which then undergo further transformations (Figure 1, B). The major advantage of this method is that the halo groups are removed and the resulted Pd-carbon bonds can be manipulated readily. Furthermore, halogens are ubiquitous functionalities in organic molecules and can be introduced comparatively readily. While Pd^{II}-initiated C−H functionalization reactions require the use of a stoichiometric amount of external oxidants, organohaldies act as oxidants themselves. Although some reactions of this type have been developed,[4] the majority of them are intramolecular cyclization reactions.[5] Notably, this strategy has also been applied to

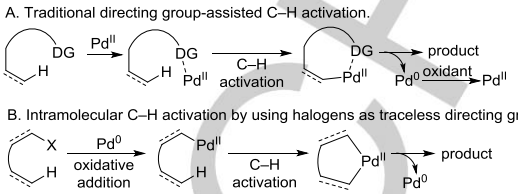
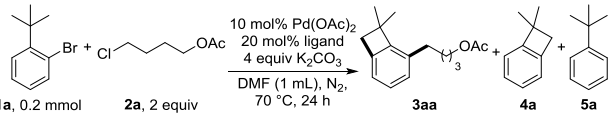


Figure 1. C−H functionalization using halogens as traceless directing groups .

C(sp^3)−H activation reactions. Likewise, the most of the reactions involve intramolecular cyclization[6] and very rare intermolecular reactions were reported.[7]

Recently, we found that dibenzometallacyclopentadiene prepared via C−H activaiton of 2-iodobiphenyl exhibited novel reactivity.[8] This palladacycle can selectively react with alkyl halides, whose reactions are usually challenging in transition-metal-catalyzed reactions. Actually, the palladacycles formed via C(sp^2)−H activation from aryl iodides and norbornene in Catellani reaction can react with alkyl halides efficiently.[9] Inspired by these reactions, we envisioned that palladacycles might be desirable models for the development of Pd-catalyzed alkylation with alkyl halides. In Catellani and our reactions, the palladacycles consist of two carbon-metal bonds, and the advantage of this type of palladacycles is that these two carbons can be functionalized. However, norbornene just functions as catalyst in Catellani reaction, and the C(sp^3)-Pd bond can usually not be manipulated. We were interested in the difunctionalization of the two carbon-metal bonds in the palladacycles, which 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 was a tandem process and provided alkylated benzocyclobutenes as the final products. A catalytic protocol for the reaction of the palladacycle with dibromomethane has also been developed.

Table 1. Survey of the reaction conditions for Pd-catalyzed alkylation of 1-bromo-2-*tert*-butylbenzene with 4-chlorobutyl acetate.



1a, 0.2 mmol **2a**, 2 equiv **3aa** **4a** **5a**

entry	ligand	**3aa** (%)[a]	**4a** (%)[a]	**5a** (%)[a]
1	---	0	0	0
2	PPh_3	16	0	8
3	**$P(o\text{-tol})_3$**	**85 (82[b])**	**2**	**3**

[a] The yields were determined by ^1H NMR analysis of the crude reaction mixture using $CHCl_2CHCl_2$ as the internal standard. [b] Isolated yield.

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[**] The work was supported by the National Natural Science Foundation of China (No. 21372176) and Shanghai Science and Technology Commission (14DZ2261100). We thank Prof. Jin-Quan Yu (The Scripps Research Insitute) for helpful discussions.

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We commenced our study by investigating the reaction of 1-bromo-2-*tert*-butylbenzene (**1a**) with 4-chlorobutyl acetate (**2a**). Unexpectedly, the reaction formed alkylated benzocyclobutenes **3aa** in the presence of PPh_3 (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)$_3$ was used (entry 3). (For detailed condition screening, see SI).

The substrate scope was next examined. We first investigated the performance of a range of 1-bromo-2-*tert*-butylbenzene derivatives. As shown in Figure 2, the substrates bearing a methyl, *tert*-butyl, methoxyl, or acetamido group were suitable, and the desired products were formed in good yields (**3ba**, **3ca, 3da**, and **3ea**). The derivatives bearing electron-withdrawing groups such as ester, carbonyl, and aldehyde also underwent the domino reaction, giving the alkylated products in moderate or good yields (**3fa**, **3ga**, and **3ha**). Fluoro and chloro were also tolerated (**3ia** and **3ja**). The substrate bearing a methyl group at the position *meta* to the *tert*-butyl group was also transformed into desired product **3ka** in 72% yield. Notably, bromobenzenes bearing derivatized *tert*-butyl groups were also reactive, albeit in lower yields (**3la**, **3ma**, and **3na**).

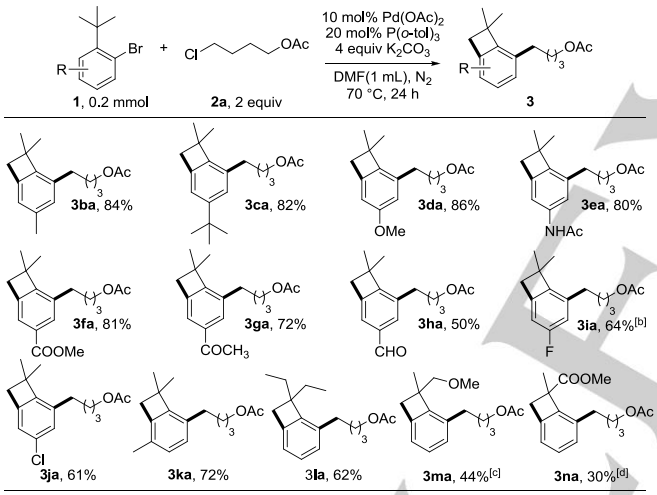


Figure 2. Aryl bromide scope. [a] Isolated yields. [b] 90 ℃. [c] 15 mol% Pd(OAc)$_2$, 30 mol% P(*o*-tol)$_3$, 36 h. [d] 4 equiv **2a**, 100 ℃, 12 h.

Subsequently, we investigated the substrate scope with respect to alkyl chlorides. As shown in Figure 3, *n*-butyl and *n*-hexyl chlorides were reacitve, and a variety of functionalities including phenyl, ester, carbonyl, cyano, and acetal on *n*-propyl chloride were tolerated in the reaction (**3ad**, **3ae**, **3af**, **3ag**, and **3ah**). The performance of *n*-butyl chloride derivatives was also examined, and a range of butyl chlorides proved to be effective alkylating reagents, generating the desired products in good yields (**3ai**, **3aj**, **3ak**, and **3al**). Notably, 1,4-dichlorobutane was also compatible with the second chloro group intact during the reaction (**3am**), and the reaction of 1-chloro-2-methoxyethane was high-yielding (**3an**). Finally, sterically hindered 1-chloro-2-methylpropane and 2-(chloromethyl)oxirane could alkylate **1a**, albeit in lower yields (**3ao** and **3ap**).

The palladacycles in the above alkylation reaction consist of two carbon-metal bonds. The two carbons forming the

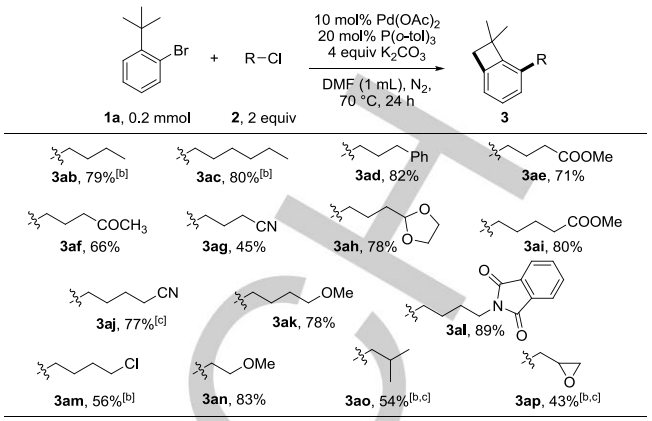
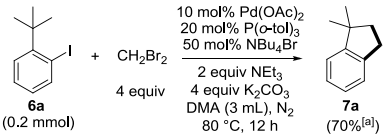


Figure 3. Alkyl chloride scope. [a] Isolated yields. [b] 4 equiv **2**. [c] 90 ℃.

palladacycle could be functionalized simultaneously, which offers opportunities to develop new synthetic methods. We envisioned that if the alkyl chlorides were replaced with dihaloalkanes, the palladacycles could react with the dihaloalkanes to form benzocycloalkanes. Notably, the same palladacycles, which were obtained from Grignard reagent Mg($CH_2CMe_2C_6H_5$)Cl, could react with CH_2Br_2 or CH_2I_2 to form α α-dimethylindane.[10] Indanes are very important carbocyclic derivatives. They are ubiquitous in various drugs and natural products and find applications in material science and asymmetric catalysis.[11] Therefore, we sought to develop a catalytic process for the synthesis of indanes starting from 1-bromo-2-*tert*-butylbenzenes and dihalomethanes. Gratefully, by subjecting **1a** and CH_2Br_2 to the above alkylation reaction conditions, we obtained desired indane prodcut **7a** in 13% yield. The yield was improved to 29% when aryl iodide **6a** was employed. The optimal yield (70%) was achieved under reaction conditions as shown in Scheme 1. (For detailed condition screening, see SI).



Scheme 1. Synthesis of indane from 1-iodo-2-*tert*-butylbenzene and CH_2Br_2. [a] Isolated yield.

We then explored the substrate scope of the catalytic protocol (Figure 4). The tolerance of functional groups was examined by investigating the reactivity of substrates bearing a substituent at the position *para* to the *tert*-butyl group. Gratefully, a range of functional groups, including alkyl, methoxyl, ester, ketone, aldehyde, and chloro, were compatible (**7b**-**7g**). Next, we examined the performance of substrates bearing a *meta* substituent. Whereas **7h** was formed as a single isomer, two regiomers **7i-1** and **7i-2** were obtained in a ratio of 1 : 1 in the reaction of **6i**. The formation of isomers **7i-2** implied that the palladacycle tended to decompose to form C(sp^3)-Pd species, which could activate the other C-H bond *ortho* to the *tert*-butyl group due to the small size of fluoride and formed a second palladacycle. Interestingly, whereas the substrate bearing two methoxyl groups (**6j**) yielded a single product **7j**, **6k** formed two

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isomers **7k-1** and **7k-2**. The substrates bearing derivatized *tert*-butyl groups could be converted into corresponding indane derivatives, the yields were lower, though (**7l**-**7o**).

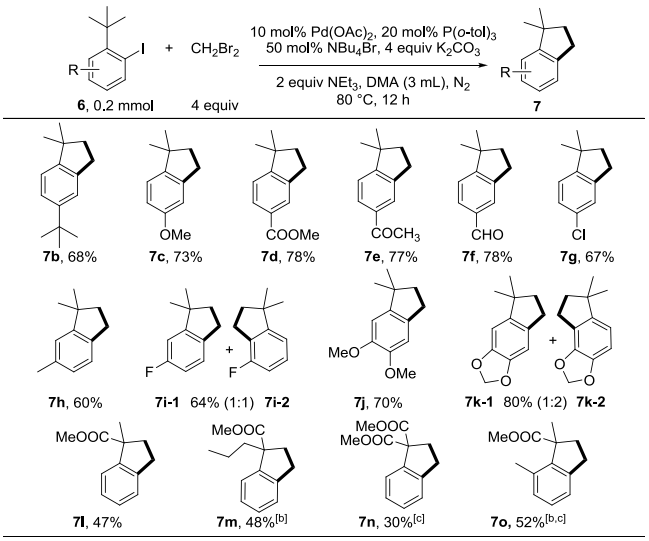
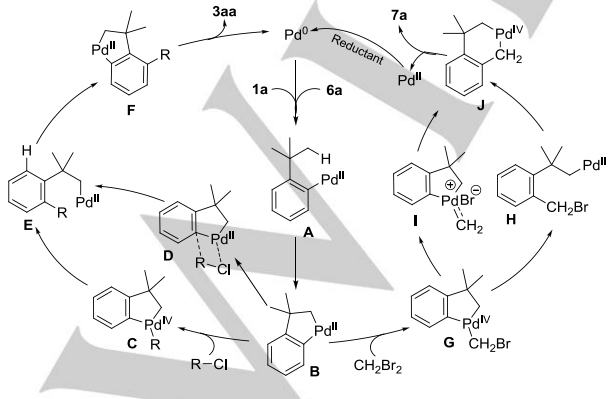


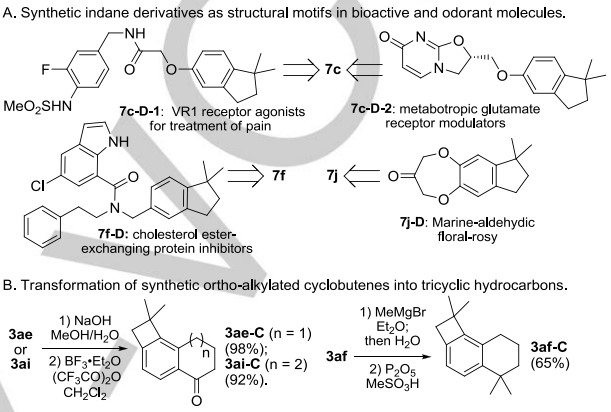
Figure 4. Aryl Idoide Scope. [a] Isolated yields. [b] 24 h. [c] 15 mol% $Pd(OAc)_2$, 30 mol% P(*o*-tol)$_3$.

On the basis of the products fromed in the reactions and the previous reports,[6e, 7b, 8a, 10] tentative mechanisms for these two alkylation reactions are proposed. The key palladacycle **B** is formed via intramolecular C(sp^3)-H activation. For the reaction with simple alkyl chlorides, **B** undergoes oxidative addition/reductive elimination or metathesis with the alkyl chlorides to generate **E.** Next, intramolecular C(sp^2)-H activation forms a second palladacycle **F**, and final reductive elimination yields product **3aa**. For the reaction with CH_2Br_2, the oxidative addition of CH_2Br_2 to **B** forms **G**. **G** is transformed into palladacycle **J** via intermediate **H** or carbene complex **I**. The reductive elimination of **J** generates final product **7a** and releases Pd^{II}, which is reduced to Pd^0. Furthermore, isotope effect experiments were conducted using deuterated **1n** and **6l** (with one of the methyl groups fully deuterated). The kinetic isotope effects were 5.9 and 6.1 for the reaction with **2a** and CH_2Br_2 respectively, which implies that C–H bond cleavage was the rate determining step in both of the alkylation reactions.



Scheme 2. Proposed mechanisms.

It should be noted that α,α-disubstituted indanes are essential structural motifs in many bioactive and odorant molecules and also find applications in material science.[12,13] (Scheme 3, A). On the other hand, the reactions with alkyl chlorides provide a simple method for the synthesis of alkylated cyclobutarenes. The products can undergo cyclization to form tricyclic hydrocarbons with a central benzene ring fused to two saturated carbocyclic rings, which are not only important intermediates in organic synthesis but also interesting molecules for bonding studies (Scheme 3, B).[14]



Scheme 3. Applications of the synthetic products.

In conclusion, we have developed tandem Pd-catalyzed C(sp^3)–H activation/alkylation reactions. The iodo and bromo groups functioned as the traceless direcitng groups, which represents an advantageous strategy for C–H functionalization. In the reaction of 1-bromo-2-*tert*-butylbenzenes with alkyl chlorides, two C(sp^2)–C(sp^3) bonds were formed via a tandem process, yielding alkylated benzocyclobutenes as the final products. A catalytic protocol for the reaction of 1-iodo-2-*tert*-butylbenzenes with CH_2Br_2 was also developed.

Keywords: C–H activation • alkylation • alkyl halides • palladium catalysis

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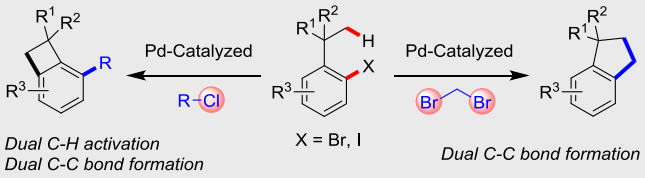

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Pd-Catalyzed Alkylation with Alkyl Halides via C(sp^3)-H Activation of Aryl Halides

Pd-catalyzed intermolecular alkylation reactions with alkyl halides via C(sp^3)-H activation of aryl haldies have been developed. The reactions involved a tandem process and two C(sp^2)-C(sp^3) bonds were formed, yielding alkylated benzocyclobutenes as the final products. A catalytic protocol for the reaction with CH_2Br_2 was also developed, which provides a facile and efficient method for the synthesis of indanes.