C–H Activation

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Palladium-Catalyzed Alkylation with Alkyl Halides by C(sp^3)–H Activation

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Abstract: *Utilizing halogens as traceless directing goups represents an attractive strategy for C–H functionalization. A two C–H alkylation system, initiated by the oxidative addition of organohalides to Pd^0, has been developed. The first reaction involves an intermolecular alkylation of palladacycles to form C(sp^3)–C(sp^2) bonds followed by C(sp^2)–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_2Br_2, and 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 the C–H cleavage process. (Figure 1 a)[2] However, this strategy restricts the scope of

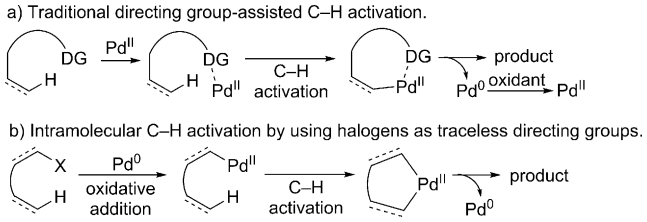

Figure 1. C–H functionalization using halogens as traceless directing groups.

accessible products. Although some directing groups can be manipulated after C–H functionalization, additional synthetic steps are often required.[3] 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 goups. For palladium-catalyzed reactions of this type, the catalytic cycles are usually initiated by the oxidative addition of organohalides to Pd^0 precatalysts. The resulting 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 resulting palladium–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 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 by 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 by C(sp^2)–H activation from aryl iodides and norbornene, in Catellani reactions, can react with alkyl halides efficiently.[9] 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^3)–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_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 details on screening reaction conditions see the Supporting Information.

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

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

Entry	Ligand	Yield [%][a]		
		3aa	**4a**	**5a**
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] Yield of the isolated product. DMF = *N*,*N*-dimethylformamide.

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

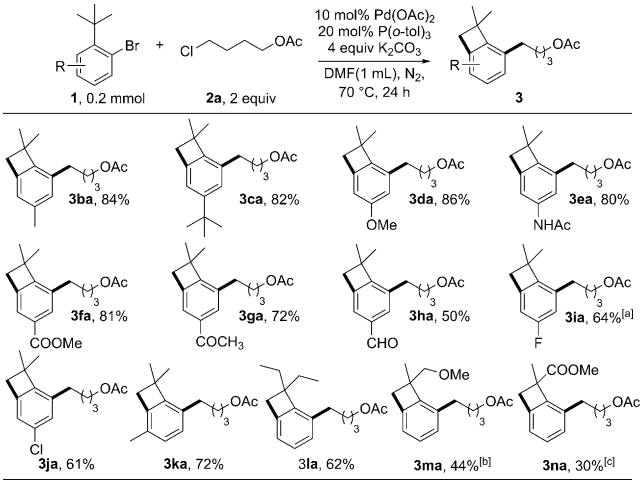


Figure 2. Scope with respect to the aryl bromide. Yield is that of the isolated product. [a] 90 °C. [b] 15 mol% $Pd(OAc)_2$, 30 mol% $P(o\text{-tol})_3$, 36 h. [c] 4 equiv **2a**, 100 °C, 12 h.

bearing a methyl, *tert*-butyl, methoxy, 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 an ester, carbonyl, and aldehyde, also underwent the domino reaction, thus giving the alkylated products in moderate to good yields (**3fa**, **3ga**, and **3ha**). Fluoro and chloro groups 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 the desired product **3ka** in 72% yield. Notably, bromobenzenes bearing derivatized *tert*-butyl groups were also reactive, albeit in lower yields (**3la**, **3ma**, and **3na**).

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, thus generating the desired products in good yields (**3ai**, **3aj**, **3ak**, and **3al**). Notably, 1,4-dichlorobutane was also compatible, with the second chloro group remaining 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**).

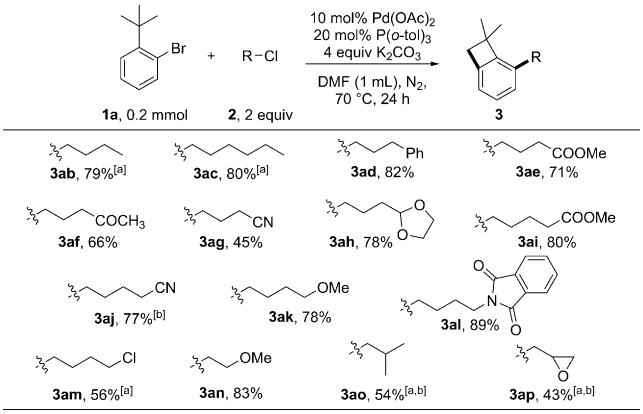
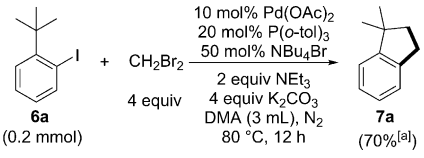


Figure 3. Scope with respect to the alkyl chloride. Yield is that of the isolated product. [a] 4 equiv **2**. [b] 90 °C.

The palladacycles in the above alkylation reaction consist of two carbon–metal bonds. The two carbon centers forming the palladacycle could be functionalized simultaneously, and thus 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 the Grignard reagent $Mg(CH_2CMe_2C_6H_5)Cl$, could react with either 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 materials 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 the desired indane prodcut **7a** in 13% yield. The yield was improved to 29% when the aryl iodide **6a** was employed. The optimal yield (70%) was achieved under reaction conditions as shown in Scheme 1. For details on screening reaction conditions see the Supporting Information.

We then explored the substrate scope of the catalytic protocol (Figure 4). The tolerance of functional groups was



Scheme 1. Synthesis of indane from 1-iodo-2-*tert*-butylbenzene and CH_2Br_2. [a] Yield of isolated product. DMA = *N*,*N*-dimethylacetamide.

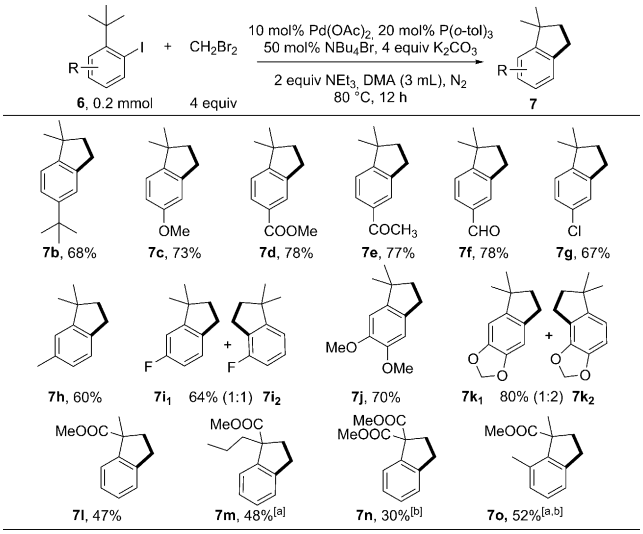
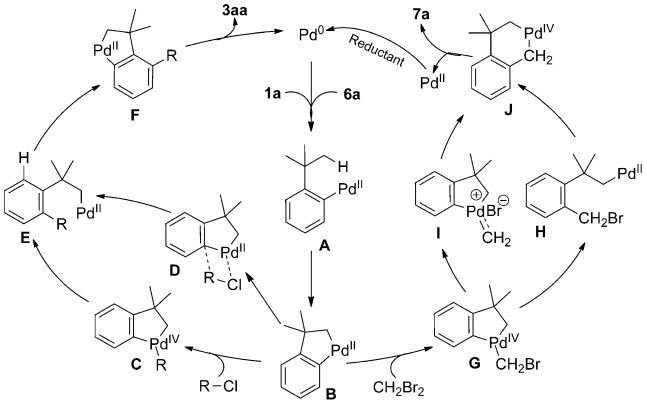


Figure 4. Scope with respect to the aryl idoide. Yield is that of the isolated product. [a] 24 h. [b] 15 mol% $Pd(OAc)_2$, 30 mol% P(*o*-tol)$_3$.

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–g**). Next, we examined the performance of substrates bearing a *meta* substituent. Whereas **7h** was formed as a single isomer, two regiomers, $\mathbf{7i_1}$ and $\mathbf{7i_2}$, were obtained in a ratio of 1:1 in the reaction of **6i**. The formation of the isomers $\mathbf{7i_2}$ implied that the palladacycle tended to decompose to form a C(sp^3)–Pd species, which could activate the other C–H bond *ortho* to the *tert*-butyl group, because of the small size of fluoride, and form a second palladacycle. Interestingly, whereas the substrate bearing two methoxy groups (**6j**) yielded a single product (**7j**), **6k** formed two isomers, $\mathbf{7k_1}$ and $\mathbf{7k_2}$. The substrates bearing derivatized *tert*-butyl groups could be converted into corresponding indane derivatives, but the yields were lower (**7l–o**).

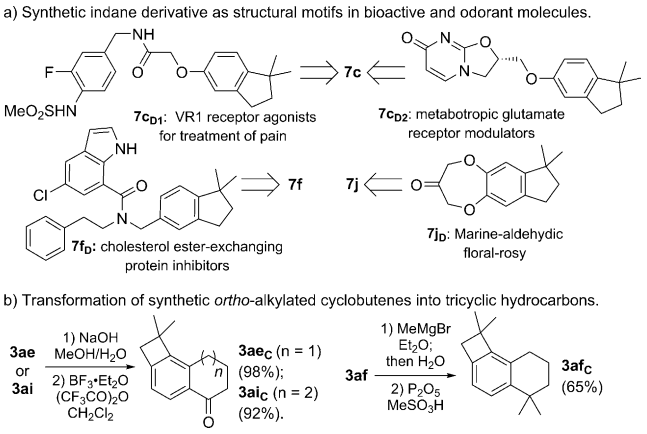
On the basis of the products fromed in the reactions and the previous reports,[6e,7b,8a,10] tentative mechanisms for these two alkylation reactions are proposed (Scheme 2). The key palladacycle **B** is formed by intramolecular C(sp^3)–H activation. For the reaction with simple alkyl chlorides, **B** undergoes either 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 **3aa**. For the reaction with CH_2Br_2, the oxidative addition of CH_2Br_2 to **B** forms **G**, which is then transformed into the palladacycle **J** via either the intermediate **H** or carbene complex **I**. The reductive elimination of **J** generates the 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, and implies that C–H bond cleavage is the rate-determining step in both of the alkylation reactions.

Notably, α,α-disubstituted indanes are essential structural motifs in many bioactive and odorant molecules, and also find



Scheme 2. Proposed mechanisms.

applications in materials science[12,13] (Scheme 3a). In contrast, the reactions with alkyl chlorides provide a simple method for the synthesis of alkylated cyclobutarenes. The



Scheme 3. Applications of the synthetic products.

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 3b).[14]

In conclusion, we have developed tandem palladium-catalyzed C(sp^3)–H activation/alkylation reactions. The iodo and bromo groups functioned as the traceless direcitng groups, and 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 in a tandem process, thus 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.

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Conflict of interest

The authors declare no conflict of interest.

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