C–H Activation

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Palladium(II)-Catalyzed *ortho* Alkylation of Benzoic Acids with Alkyl Halides**

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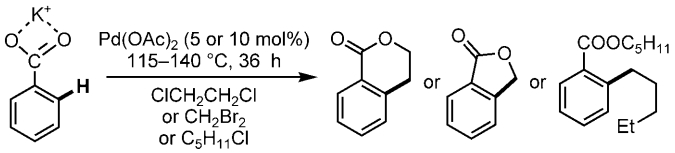
The Pd^0-initiated arylation of C–H bonds with aryl halides was among the earliest examples of Pd-catalyzed C–H activation/arylation chemistry.[1–6] A single pioneering example of the Pd^0-catalyzed alkylation of aryl C–H bonds using a tethered alkyl chloride was also developed by Buchwald and Hennessy for the highly efficient synthesis of oxindoles.[7a] Two examples of intra- and intermolecular alkylation of heterocycles have also been reported by Chang et al.[7b] and Hoarau et al.[7c] recently. In these reactions, no added oxidants other than the aryl halides or alkyl halides themselves are needed, which affords this C–H functionalization process a practical advantage. During the past five years, Pd^{II}-catalyzed arylation using Ar_2IX as the stoichiometric oxidant through a Pd^{II}/Pd^{IV} catalytic cycle has undergone major advances.[8,9] Especially noteworthy is the broad range of arylation reactions using ArI/AgOAc.[10] To our knowledge, the Pd^{II}-catalyzed intermolecular alkylation of C–H bonds with alkyl halides[11,12] remains an unsolved problem, except for a single example of methylation of acetanilide with MeI.[13,14] In addition, a large excess of AgOAc is required to scavenge the iodide from Pd–I species in this case. Herein we report a sequential monoselective alkylation/lactonization reaction of benzoic acids with 1,2-dichloroethane, dichloromethane, and dibromomethane (Scheme 1). Alkylation with 1-chloropentane was also found to proceed, albeit in lower yield. The use of alkyl chlorides instead of iodides allows the catalytic cycle to be closed in the presence of an inexpensive base without using stoichiometric amounts of Ag^+ salts.

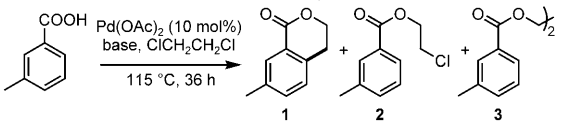
We recently established that the κ^2 coordination of a cation with a carboxylate group forces the Pd^{II} center to chelate in the proximity of the *ortho* C–H bonds (for benzoic acid and phenyl acetic acid substrates) and β C–H bonds (for aliphatic acids), a geometry that is essential for facile C–H bond cleavage.[15] The broad utility of carboxylate groups prompted us to develop a potentially useful catalytic system for the alkylation of C–H bonds in these substrates.

Although alkyl iodide is a more reactive oxidant for alkyl–palladium species, the subsequently formed Pd–I species in each cycle must be converted to $Pd(OAc)_2$ by reaction with AgOAc. Knowing that Pd–Cl or Pd–Br species would be generated when alkyl chlorides or bromides were used as the alkylating reagents, we began our screening efforts using 1,2-dichloroethane as the alkylating reagent with the aim of discovering conditions that would promote the displacement of chloride from the Pd–Cl species by a benzoate anion to close the catalytic cycle. We were pleased to find that the presence of K_2HPO_4 alone is sufficient for the catalytic alkylation to proceed (Table 1, entry 1). As anticipated, the initially formed alkylation product underwent an S_N2 reaction to give the corresponding lactone **1**. A control experiment showed that the Pd catalyst is essential (Table 1, entry 2). The major competing side reaction is the S_N2 reaction between the substrate and 1,2-dichloroethane. Since methylbenzoate is not reactive, we investigated the effect of the base on the S_N2 reaction. For instance, the use of K_2CO_3 and Cs_2CO_3 resulted in predominant formation of the S_N2 product (Table 1, entries 5 and 9). The use of K_2HPO_4 is decisively superior to Na_2HPO_4 with the latter giving only a negligible amount of the desired product. This catalytic reaction can be performed under either air or argon, although the latter gives a slightly lower yield (Table 1, entry 3). The minor effect of O_2 suggests



Scheme 1. Pd-catalyzed alkylation of aryl C–H Bonds.

Table 1: Influence of the base on the alkylation reaction.



Entry	Base (equiv)	**1** [%][a]	**2** [%][a]	**3** [%][a]	Remaining substrate [%][a]
1	K_2HPO_4 (3)	82	10	4	0
2[b]	K_2HPO_4 (3)	0	16	33	16
3[c]	K_2HPO_4 (3)	67	16	8	0
4	$KHCO_3$ (2)	40	23	<1	35
5	K_2CO_3 (3)	32	58	<1	5
6	K_3PO_4 (3)	34	34	2	0
7	Na_2CO_3 (2)	17	<2	0	74
8	Na_2HPO_4 (3)	3	0	0	97
9	Cs_2CO_3 (2)	0	90	5	0

[a] Yield was determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [b] No $Pd(OAc)_2$ was used. [c] The reaction was carried out under an atmosphere of argon.

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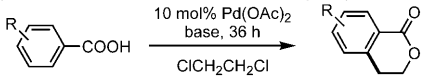
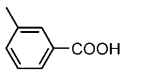
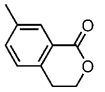
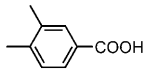
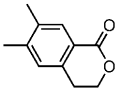
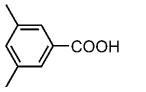
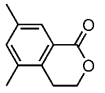
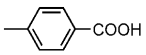
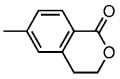
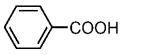
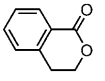
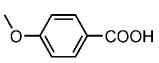
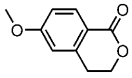
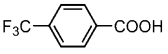
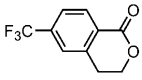
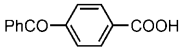
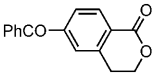
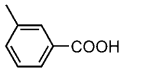
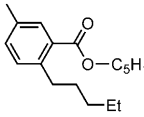
that a small amount of Pd^0 may form through side reactions and that O_2 could reoxidize the Pd^0 back into the catalytic cycle.

This optimized protocol was then tested with other substrates. Although alkylation of closely related benzoic acids (Table 2, entry 2) under identical conditions gave the desired products in comparable yields, further variation in substitution on the arene resulted in a significant decrease in the yields. In most cases the S_N2 reaction was predominant because of the increase in nucleophilicity of the carboxylate or an increase in the acidity of the parent carboxylic acid. We were pleased to find that careful selection of the base restored reactivity with a wider range of benzoic acids. For instance, alkylation of benzoic acids proceeded to a noticeable extent when various carbonates were used (Table 2, entries 4–8). The alkylation of electron-deficient arenes afforded synthetically useful yields when $KHCO_3$ (entry 7) or Na_2CO_3 (entry 8, Table 2) was used. Of particular mechanistic importance, it was found that alkylation with 1-chloropentane was feasible, albeit in only 26% yield owing to significant formation of the S_N2 product (Table 2, entry 9).

Table 2: Alkylation with 1,2-dichloroethane or pentyl chloride.[a]



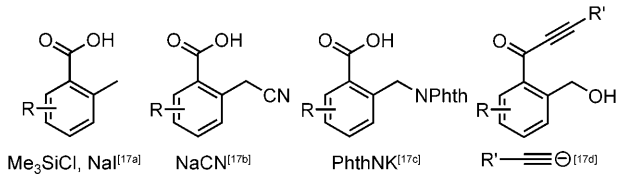
Entry	Substrate	Base (equiv)	T [°C]	Product	Yield [%][b]
1		K_2HPO_4 (3.0)	115		81 34[c]
2		K_2HPO_4 (3.0)	115		80
3		K_2HPO_4 (3.0)	115		55
4		$KHCO_3$ (2.5)	140		51
5		$KHCO_3$ (2.5)	140		42
6		Na_2CO_3 (3.0)	140		45
7		$KHCO_3$ (2.5)	140		67
8		Na_2CO_3 (3.0)	140		75
9[d]		K_2HPO_4 (3.0)	115		26

[a] Unless otherwise noted, the reaction was carried out on a 0.5 mmol scale in 2.0 mL of 1,2-dichloroethane. [b] Yield of isolated product. [c] 10 mol% $PdCl_2$. [d] *n*-Pentyl chloride (2.0 mL) was used instead of 1,2-dichloroethane.

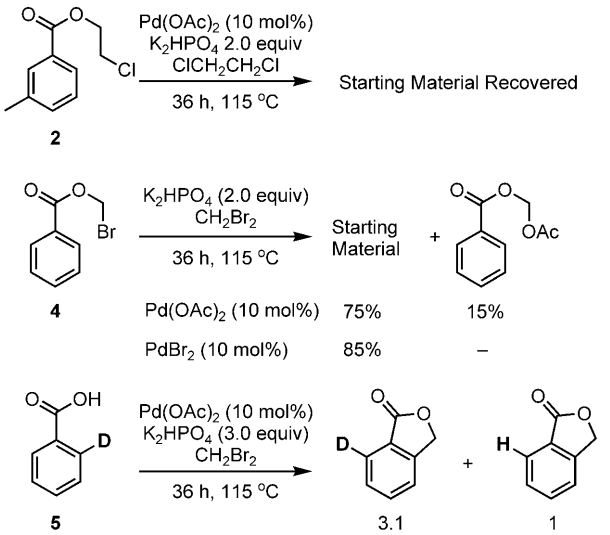
To further expand the scope of this alkylation reaction, we tested dichloromethane and dibromomethane as the alkylating reagents. Although dichloromethane only worked well with a few substrates (Table 3, entry 2), the use of dibromomethane substantially improved the reaction yields and expanded the substrate scope. Electron-withdrawing halo and trifluoromethyl groups were well tolerated (Table 3, entries 4–8 and 11). Keto and ester groups were also compatible, though these substrates gave lower yields (Table 3, entries 12 and 13). Most importantly, the alkylation protocols with both dichloroethane and dibromomethane exhibit exclusive monoselectivity at the less hindered *ortho* position, partly because of rapid lactone formation. The catalyst loading can be reduced to 5 mol% (Table 3, entry 2).

From the viewpoint of synthetic applications, δ-benzolactones (Table 2) can be readily converted into coumarins under dehydrogenative oxidations.[16] Although alkylation with dibromomethane introduces only one carbon unit into the arene, the excellent reactivity of the new benzylic carbon allows for versatile chain extension using a broad range of nucleophiles to afford valuable building blocks for synthesis (Scheme 2).[17]

To gain insight into the reaction mechanism and catalytic cycle, further experimental studies were performed. The observation that **2** and **4** were unreactive to both $Pd(OAc)_2$ or $PdBr_2$ (Scheme 3) speaks against a mechanism in which

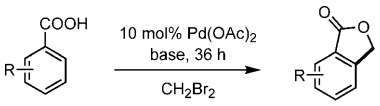


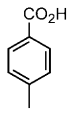
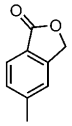
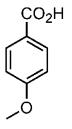
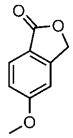
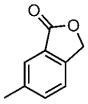
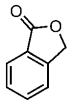
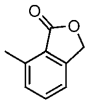
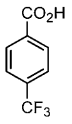
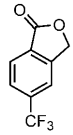
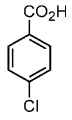
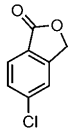
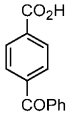
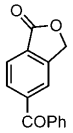
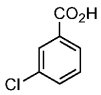
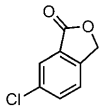
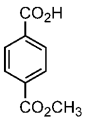
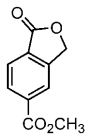
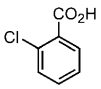
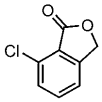
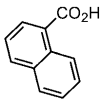
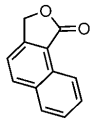
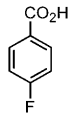
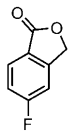
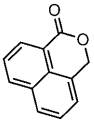
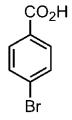
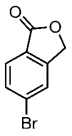
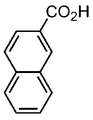
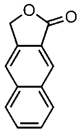
Scheme 2. Building blocks derived from benzolactones. Nucleophiles used and literature references are listed under each product. Phth = phthaloyl.



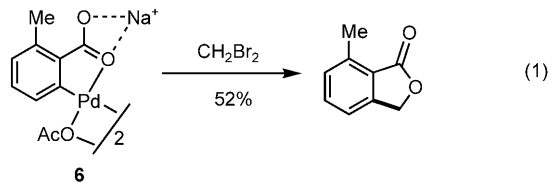
Scheme 3. Preliminary mechanistic studies.

Table 3: Alkylation with dibromomethane.[a]

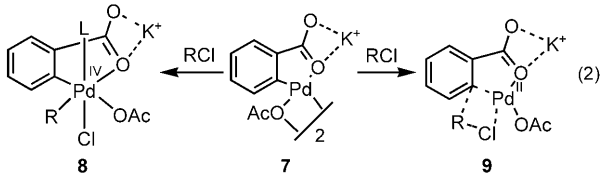


Entry	Substrate	Product	Yield %[d]	Entry	Substrate	Product	Yield %[d]
1[b]			81	9[c]			62
2[b,e]			92 83[f] 68 [g] 80 [h]	10[b]			90
3[b]			62	11[b]			71
4[c]			81	12[c]			47
5[c]			75	13[c]			55
6[c]			59	14[b]			87
7[c]			81				7
8[c]			72	15[b]			68

[a] Unless otherwise noted, the reaction was carried out on a 0.5 mmol scale in 2.0 mL of dibromomethane. [b] 3.0 equiv K_2HPO_4, 140 °C. [c] 2.5 equiv $KHCO_3$, 140 °C. [d] Yield of isolated product. [e] 115 °C. [f] Dichloromethane (2.0 mL) was used instead of dibromomethane. [g] 10 mol% $PdBr_2$. [h] 5 mol% $Pd(OAc)_2$.



6 (1)



8 **7** **9** (2)

nucleophilic substitution occurs first, followed by C–H activation initiated by oxidative addition to the intramolecular halide.[8] This finding combined with data from kinetic isotope effect studies also do not support a Friedel–Crafts-type reaction mediated by the Pd^{II} catalyst or by trace quantities of HCl generated from Pd^{II} salts (Scheme 3).

Finally, intermediate **6**, obtained by *ortho* C–H insertion with *o*-toluic acid,[15] was used to test the reactivity of such arylpalladium species with alkyl halides. We found that treatment of **6** with dibromomethane afforded the anticipated lactone as the major product [Eq. (1)].

Although the oxidation of the arylpalladium(II) intermediate by MeI to Pd^{IV} was previously proposed (intermediate **8**),[14] in light of previous discoveries that arylpalladium species react with electrophiles such as aldehydes and ketones,[18] direct σ-bond metathesis[8] between the aryl–Pd bond and the alkyl halide cannot be ruled out (intermediate **9**) [Eq. (2)]. In both cases, Pd–halide species are formed. Although alkylation using 10 mol% $PdCl_2$ and $PdBr_2$ gave the desired product in yields of 34% and 68%, respectively, the formation of palladium benzoate in situ could still be responsible for the catalytic C–H activation reactivity.

In summary, we have developed a Pd^{II}-catalyzed alkylation of aryl C–H bonds with alkyl chlorides without using Ag^+ salts as the iodide scavengers. This reaction provides a new synthetic method for benzolactones.

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