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

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Abstract

The first Pd(II)-catalyzed alkylation of aryl C–H bonds is achieved without using a co-oxidant. The alkylation reaction was followed thereafter by an intramolecular lactonization to give broadly useful γ - and δ -benzolactones.

Pd(0)-initiated arylation of C–H bonds with aryl halides is among the earliest examples in Pd-catalyzed C–H activation/arylation chemistry.^{1–7} A single pioneering example of Pd(0)-catalyzed alkylation of aryl C–H bonds using a tethered alkyl chloride was also developed by Buchwald for highly efficient syntheses of oxindoles.⁸ In these reactions, no external oxidant other than the aryl halides or alkyl halides themselves are needed, affording this C–H functionalization process a practical advantage. Recently, Pd(II)-catalyzed arylation using Ar₂IX as the stoichiometric oxidant through a Pd(II)/Pd(IV) catalytic cycle has undergone major advances.^{9,10} Especially noteworthy is the broad range of arylation reactions using ArI/AgOAc.¹¹ To our knowledge, Pd-catalyzed intermolecular alkylation of C–H bonds with alkyl halides^{12,13} remains an unsolved problem, except for a single example of methylation of acetanilide via Pd(II)/Pd(IV) catalysis reported by Tremont (Scheme 1).¹⁴ However, in this case, the side reaction of AgOAc with methyl iodide prevented efficient catalysis with this protocol. Herein we report a sequential monoselective alkylation/lactonization reaction of benzoic acids with 1,2-dichloroethane, dichloromethane and dibromomethane. Alkylation with 1-chloropentane was also found to proceed, albeit in lower yield. For the first time, Pd-catalyzed alkylation of C–H bonds in the absence of Ag(I) oxidant is made possible. Preliminary mechanistic investigations have also been carried out to shed light into the nature of the catalytic cycle.

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Supporting Information Available: Experimental procedure and characterization of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

We recently established that the κ^2 -coordination of a cation with a carboxylate group forces Pd(II) 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 cleavage.¹⁵ The broad utility of carboxylate groups prompted us to develop a potentially useful catalytic system for alkylation of C–H bonds for these substrates.

In Tremont's Pd(II)/Pd(IV) catalytic cycle for methylation with MeI and arylation with ArI, the Pd–I species formed in each cycle needs to be converted to Pd(OAc)₂ by 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 displacement of chloride from the Pd–Cl species by a benzoate anion to close the catalytic cycle (Table 1). We were pleased to find that the presence of K₂HPO₄ alone is sufficient for the catalytic alkylation to proceed (Table 1, entry 1). As anticipated, the initially formed alkylation product underwent a S_N2 reaction to give the corresponding lactone. A control experiment showed that the Pd catalyst is essential (entry 2). The major competing side reaction is the S_N2 reaction between the substrate and 1,2-dichloroethane. For instance, the use of K₂CO₃ and Cs₂CO₃ resulted in predominant formation of the S_N2 product (entries 5 and 9). The use of K₂HPO₄ is decisively superior to Na₂HPO₄ with the latter giving a negligible amount of the desired product. This catalytic reaction can be performed under either air or argon with the latter giving a slightly lower yield (entry 3). The minor effect of O₂ suggests that a small amount of Pd(0) may have been formed through side reactions and that O₂ 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 due to an 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 (entries 4–8) proceeded to a noticeable extent when various carbonates were used. The alkylation of electron-deficient arenes afforded synthetically useful yields when KHCO₃ (entry 7) or Na₂CO₃ (entry 8) was used. Of particular mechanistic importance, it was found that alkylation with 1-chloropentane was feasible, albeit in only 26% yield due to significant formation of the S_N2 product (entry 9).

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. Keto and ester groups were also compatible, though they gave lower yields. Most importantly, the alkylation protocols with both dichloroethane and dibromomethane exhibit exclusive mono-selectivity at the less hindered *ortho*-position, partly due to rapid lactone formation. The catalyst loading can be reduced to 5 mol% (entry 2).

From the viewpoint of synthetic applications, δ -benzolactones (Table 2) can be readily converted into coumarins through 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 elongation using a broad range of nucleophiles to afford valuable building blocks for synthesis (Scheme 2).¹⁷

To gain insights into the reaction mechanism and catalytic cycle, further experimental studies were performed. The observation that **1** and **2** were unreactive using both Pd(OAc)₂ or PdBr₂ (Scheme 3) speaks against a mechanism whereby nucleophilic substitution occurs first, followed by C–H activation which is initiated by oxidative addition to the intramolecular halide.⁸ This data combined with that of the 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, the *ortho*-C–H insertion intermediate **4** obtained with *o*-toluic acid¹⁵ allowed us to test the reactivity of such aryl palladium species with alkyl halides. We found that treatment of **4** with dibromomethane afforded the anticipated lactone as the major product (eq 1).

(1)

The alkylation of the arylpalladium intermediate **5** may involve oxidation of Pd(II) to Pd(IV) by alkyl halides as proposed by Tremont¹⁴ and a subsequent reductive elimination occurs to give the desired product. However, in light of previous discoveries that arylpalladium species react as a nucleophile with electrophiles such as aldehydes and ketones,¹⁸ we believe that direct σ -bond metathesis⁸ between the aryl–Pd and the alkyl halide is also possible (eq. 2). In both cases, Pd–halide species are formed. Although alkylation using 10 mol% PdCl₂ and PdBr₂ gave the desired product in 34% and 68% respectively, the formation of palladium benzoate *in situ* could still be responsible for the catalytic C–H activation reactivity.

(2)

In summary, we have developed the first Pd(II)-catalyzed alkylation of aryl C-H bonds without using co-oxidants. This reaction provides a very simple and efficient synthetic method for benzolates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Methylation via Pd(II)/Pd(IV) catalysis **Our alkylation/lactonization reaction**

Scheme 1.
Pd-Catalyzed Alkylation of Aryl C–H Bonds

Scheme 2.
Building Blocks Derived from Benzolactones

Scheme 3.
Preliminary Mechanistic Studies

Table 1

Influence of Bases on the Alkylation Reaction

Entry	Base (equiv)	a % ^a	b % ^a	c % ^a	Remaining Substrate % ^a
1	K ₂ HPO ₄ (3)	82	10	4	0
2 ^b	K ₂ HPO ₄ (3)	0	16	33	16
3 ^c	K ₂ HPO ₄ (3)	67	16	8	0
4	KHCO ₃ (2)	40	23	<1	35
5	K ₂ CO ₃ (2)	32	58	<1	5
6	K ₃ PO ₄ (2)	34	34	2	0
7	Na ₂ CO ₃ (2)	17	<2	0	74
8	Na ₂ HPO ₄ (3)	3	0	0	97
9	Cs ₂ CO ₃ (2)	0	90	5	0

^aYield was determined by ¹H NMR analysis of crude product using CH₂Br₂ as the internal standard;^bNo Pd(OAc)₂;^cThe reaction was carried out under an atmosphere of argon.

Yield % ^b	Product	Base	Temperature
81		K ₂ HPO ₄	115 °C
34 ^c		3.0 equiv.

Base	Temperature	Product	Yield % ^b
K ₂ HPO ₄ 3.0 equiv.	115 °C		80

Base	Temperature	Product	Yield % ^b
K ₂ HPO ₄ 3.0 equiv.	115 °C		55

Base	Temperature	Product	Yield % ^b
KHCO ₃ 2.5 equiv.	140 °C		51

Base	Temperature	Product	Yield % ^b
KHCO ₃ 2.5 equiv.	140 °C		42

Base	Temperature	Product	Yield % ^b
Na ₂ CO ₃ 3.0 equiv.	140 °C		45

KHCO₃
2.5 equiv.

140 °C

67

Base	Temperature	Product	Yield % ^b
Na ₂ CO ₃ 3.0 equiv.	140 °C		75

Base	Temperature	Product	Yield % ^b
K ₂ HPO ₄ 3.0 equiv.	115 °C		26

Table 3

Substrate	Product	Yield % ^d
62

Product

Substrate

Substrate	Product	Yield % ^d
47

Substrate	Product	Yield % ^d
55

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Substrate	Product	Yield % ^d
	87

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Yield %^d

68

Product

Substrate

^a Unless otherwise noted, the reaction was carried out on a 0.5 mmol scale in 2.0 mL dibromomethane;

^b 3.0 equiv. K₂HPO₄, 140 °C;

^c 2.5 equiv. KHCO₃, 140 °C;

^d Isolated yield;

^e 115 °C;

^f 2.0 mL Dichloromethane instead of dibromomethane;

^g 10 mol% PdBr₂;

^h 5 mol% Pd(OAc)₂.