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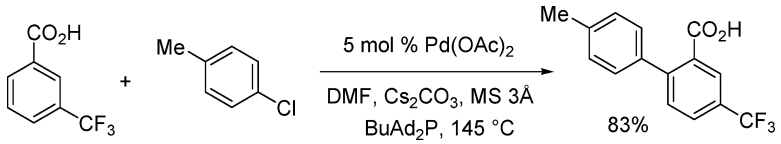

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Two Methods for Direct *ortho*-Arylation of Benzoic Acids

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Abstract: Two new palladium-catalyzed methods for the direct *ortho*-arylation of free benzoic acids have been developed. The first method employs stoichiometric silver acetate for iodide removal, aryl iodide as the coupling partner, and acetic acid solvent. This method is applicable to the arylation of electron-rich to moderately electron-poor benzoic acids and tolerates chloride and bromide substituents on both coupling partners. The second method involves the use of aryl chloride, cesium carbonate base, *n*-butyl-di-1-adamantylphosphine ligand, and DMF solvent and is suitable for both electron-rich and electron-poor benzoic acids. Mechanistic studies of the second method point to the heterolytic C−H bond cleavage as the rate-determining step.

1. Introduction

The selective functionalization of C−H bonds has attracted a substantial interest due to potential shortening of synthetic sequences.[1] At present, development of the methods for sp^2 C−H bond functionalization in directing-group containing arenes and electron-rich heterocycles has received the most attention. For a number of directing-group containing substances the conversion of aromatic *ortho*-C−H bonds to C−C bonds has been demonstrated. Compounds containing amide, pyridine, oxazoline, imine, ketone, and phenol directing groups have been *ortho*-arylated or alkylated under palladium, ruthenium, or rhodium catalysis.[2] We have developed a simple, palladium-catalyzed method for the arylation of anilides, benzamides, pyridines, and benzylamines.[3] This reaction likely proceeds via a Pd(II)−Pd(IV) catalytic cycle.[4] Only a few reports have dealt with the *ortho*-functionalization of free benzoic acids.[5a,6] Direct functionalization of C−H bonds in carboxylic acids is challenging. Stoichiometric *ortho*-metalation of carboxylic acids by transition metals is not known.[7a] The reactions may be complicated by decarboxylation.[5] Direct arylation of aromatic carboxylic acids would allow a one-step synthesis of 2-arylbenzoic acids. In contrast, the current methodology for the conversion of benzoic acids to the 2-arylated derivatives requires multiple steps (Scheme 1).[7b−d]

The carboxylate group may be removed after the arylation reaction.[8] It is well-known that transition-metal-catalyzed functionalization of arenes not possessing directing groups often results in the formation of regioisomer mixtures.[9] This may be avoided if the carboxylate substituent is used as a removable directing group. A few reports that describe the regioselective arylation of simple arenes rely on the use of either fluorine substituents that act by acidifying the *ortho*-hydrogens or substrates where the formation of regioisomers is not possible.[10] The direct functionalization of *ortho* C−H bonds in benzoic acids would have three important consequences: (1) achievement of the most direct functionalization of benzoic acids forming 2-arylbenzoic acids, compounds that are of pharma-

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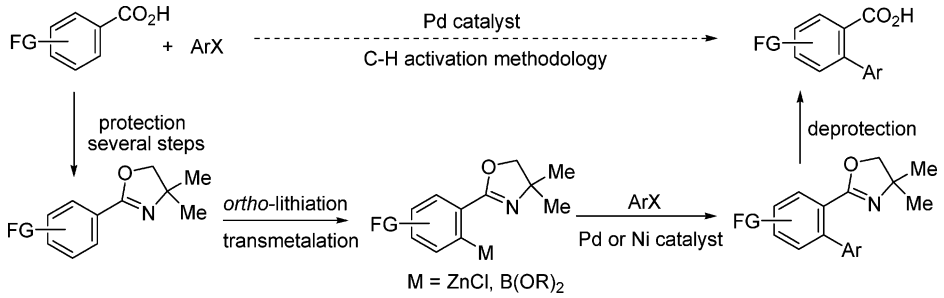
Scheme 1. Benzoic Acid Arylation

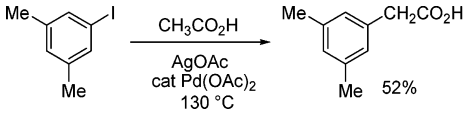


ceutical and other interest;[11] (2) possibility of subsequent decarboxylation; this sequence would be synthetically equivalent to regioselective arylation of unfunctionalized arenes; and (3) possibility of tandem reaction development by using carboxylate functionality in subsequent Heck and Suzuki couplings.[12]

We decided to investigate benzoic acid arylation by aryl iodides under Pd(II)−Pd(IV) catalytic cycle conditions and by aryl chlorides under Pd(0)−Pd(II) catalytic cycle conditions. The Pd(II)−Pd(IV) catalytic cycle would allow tolerance of halide substituents on both the benzoic acid and aryl iodide. Aryl chlorides are now routinely used for C−C bond creation under Pd(0)−Pd(II) catalytic cycle conditions.[13] As a consequence, use of cheaper ArCl in C−H bond functionalization should also be possible if appropriate ligands are used. Only a few examples of intermolecular C−H/C−Cl bond couplings have been reported so far.[14] We report here two complementary methods for direct palladium-catalyzed *ortho*-arylation of benzoic acids by (1) aryl iodides/AgOAc and (2) aryl chlorides/Cs_2CO_3/*n*-butyl-di-1-adamantylphosphine.[15] The decarboxylation of the arylated benzoic acid is also reported. Additionally, we report here the mechanistic studies of the arylation processes.

2. Results

2.1. Arylation Employing Aryl Iodides. Our initial efforts toward benzoic acid arylation employing aryl iodides and silver acetate focused on the use of acetic acid or trifluoroacetic acid as solvents under conditions previously utilized in our laboratory for anilide, benzamide, and benzylamine arylation.[3] The reactions proceed in both cases, but decarboxylation was observed to be faster in trifluoroacetic acid. The best results were obtained by using about 3.5 equiv of acetic acid as a solvent, although arylacetic acid byproduct was observed at longer reaction times. Heating 5-iodo-*m*-xylene with acetic acid in the presence of silver acetate and catalytic palladium acetate afforded a 52% yield of the corresponding arylacetic acid (eq 1).



(1)

The formation of this byproduct can be minimized by employing shorter reaction times and lower temperature. The arylation of benzoic acids proceeds with both electron-poor (entries 1, 3, 4, Table 1) and electron-rich (entries 2, 5, 6) aryl iodides. Chloride and bromide are tolerated on the coupling partners (entries 3 and 4). Both electron-rich and moderately electron-poor benzoic acids can be arylated. *ortho*-Substituted aryl iodides are unreactive, and attempted arylation of 2-furoic acid resulted in the formation of an intractable mixture.

2.2. Arylation Employing Aryl Chlorides. The second method required substantially more optimization. The reactions were optimized with respect to solvent, phosphine ligand, and the presence of molecular sieves. The best results were obtained in dry DMF in the presence of molecular sieves.[16] Wet DMF in the presence of wet molecular sieves resulted in slower reactions, omission of molecular sieves resulted in incomplete reactions, and no reaction was observed in DMA. A number of ligands that are routinely used for palladium-catalyzed ArCl coupling reactions were tested in phenylation of 2-naphthoic acid (Table 2). Use of trioctylphosphine, tri-*p*-tolylphosphine, and triphenylphosphine as ligands did not lead to efficient catalysis. Substantial conversions to product were observed with tricyclohexylphosphine, di-*tert*-butylmethylphosphine, and *tert*-butyldicyclohexylphosphine.

The best results were obtained with *n*-butyl-di-1-adamantylphosphine[15] that was used in all subsequent reactions. Aryl bromides are also reactive, but because there are no substantial advantages in their use, all reactions were run with aryl chlorides.

Electron-poor benzoic acids react well, and it is possible to couple them with both electron-poor (entries 1−2, 4, 6, 9, 13; Table 3) and electron-rich (entry 3, 5, 11, 14) aryl chlorides. This result is somewhat surprising given that palladation is often slower for electron-deficient compounds.[17]

Both electron-poor (entry 13) and electron-rich (entry 14) aryl chlorides can be coupled with electron-rich benzoic acids. However, the combination of an electron-rich aryl chloride and an electron-rich benzoic acid is occasionally problematic due

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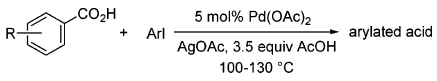
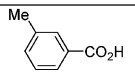
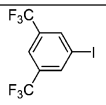
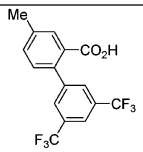
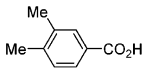
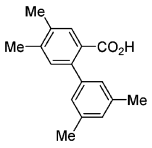
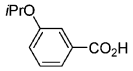
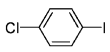
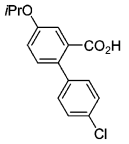
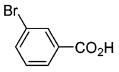
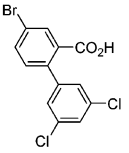
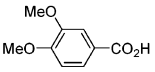
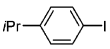
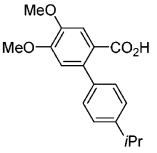
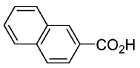
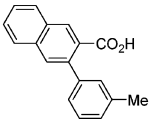
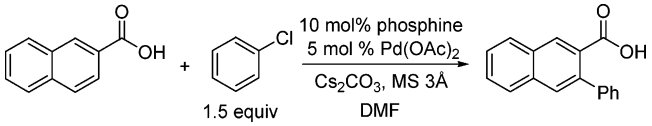
Table 1. Arylation of Benzoic Acids by Aryl Iodides[a]



Entry	Acid	Aryl Iodide	Arylated Acid	Yield
1				59%
2				54%
3				69%
4				53%
5				55%
6				67%

[a] $ArCO_2H$ (1 mmol), iodoarene (3 equiv), $Pd(OAc)_2$ (5 mol %), AgOAc (1.3 equiv), AcOH (0.2 mL), 4.5−7 h. Yields are isolated yields and are the average of three or four runs. See the Supporting Information for details.

Table 2. Ligand Optimization[a]



entry	phosphine	conversion, %
1	tricyclohexylphosphine	46
2	di-*tert*-butylmethylphosphine-HBF_4	58
3	tri-*n*-octylphosphine	7
4	triphenylphosphine	1
5	*tert*-butyldicyclohexylphosphine	57
6	*n*-butyl-di-1-adamantylphosphine	65
7	tri-*p*-tolylphosphine	2
8	1,3-bis(diphenylphosphino)propane	7
9	none	<1

[a] $Pd(OAc)_2$ (5 mol %), 2-naphthoic acid (0.5 mmol), chlorobenzene (0.75 mmol), phosphine ligand (10 mol %), Cs_2CO_3 (1.1 mmol), molecular sieves 3 Å (155 mg), and anhydrous DMF (2.5 mL), 145 °C, 24 h. Conversion determined by GC analysis using hexadecane internal standard.

to product decarboxylation or aryl halide hydrodehalogenation. The arylation of 2- and 3-phenylbenzoic acids proceeds well affording the *m*- and *p*-terphenyl derivatives (entries 11, 12). The nitro group is compatible with the reaction conditions, as

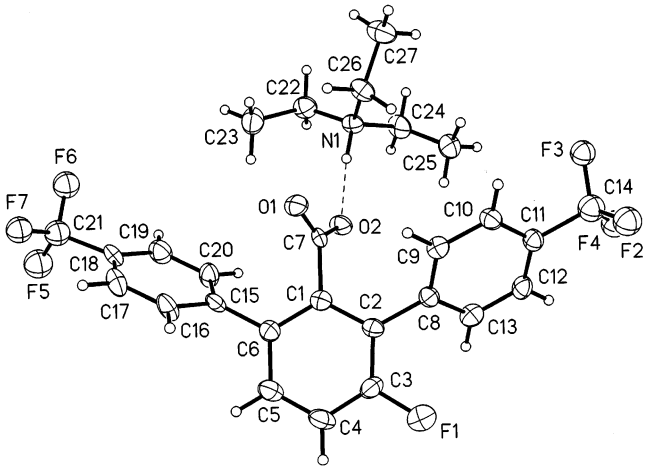
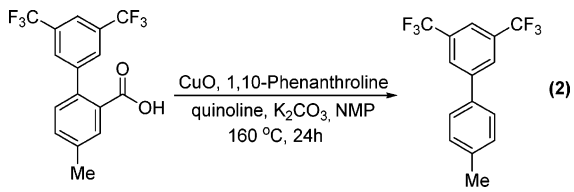


Figure 1. ORTEP view of triethylammonium 3-fluoro-2,6-bis(4-trifluoromethyl-phenyl)benzoate. Thermal ellipsoids are 40% equiprobability envelopes.

is the ester group (entries 6−8). Benzoic acid is diarylated (entries 9, 10). In general, 2- or 3-substituted benzoic acids are monoarylated, presumably due to steric interference of the substituent. It is well-known that the palladation of sterically hindered positions is unfavorable.[18] The exception is 3-fluorobenzoic acid, which is diarylated, presumably due to the small size of the fluorine substituent (entries 4, 5). There are two possible regiochemical outcomes of 3-fluorobenzoic acid diarylation. The fluorine can act as a directing group by increasing the acidity of the *ortho*-hydrogen substituent,[10b] or the carboxylate can direct the arylation. The X-ray crystallographic analysis of the diarylation product triethylammonium salt verified that the carboxylic acid group had directed the arylation (Figure 1).

2-Chlorotoluene was unreactive, and 4-chloroanisole suffered substantial hydrodehalogenation with all benzoic acids tested. Halogens other than fluorine are not compatible with the reaction conditions in contrast with the ArI/AgOAc method. For example, the coupling of 1,4-dichlorobenzene with 3-trifluoromethylbenzoic acid afforded 2-phenyl-5-trifluoromethylbenzoic acid as the major product.

It was also demonstrated that the arylation products can be decarboxylated by using the method developed by Goo*β*en and co-workers.[8] 2-(3,5-Bis(trifluoromethyl)phenyl)-5-methylbenzoic acid was decarboxylated in the presence of CuO/quinoline in NMP to afford 3,5-bis(trifluoromethyl)-4′-methylbiphenyl in 86% yield (eq 2). Two roles can be envisioned for the

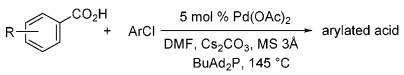


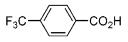
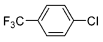
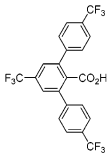
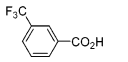
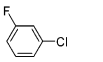
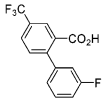
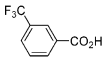
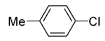
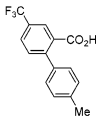
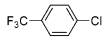
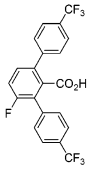
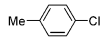
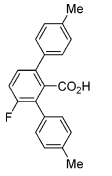
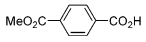
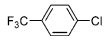
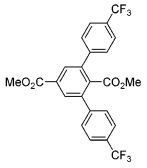
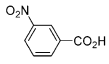
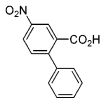
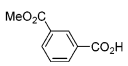
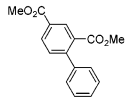
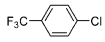
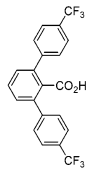
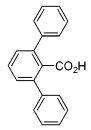
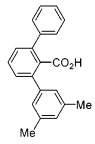
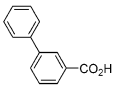
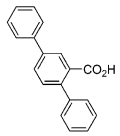
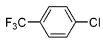
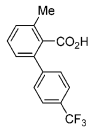
(2)

carboxylate. First, it can be used as a directing group, allowing the functionalization of the benzoic acid moiety. Second, if desired, the carboxylate group can be removed, allowing the *regioselective* synthesis of bi- and polyphenyls. This would be attractive as arylation of arenes that do not contain directing groups is problematic due to the possibility of regioisomer

(18) Review: (a) Ryabov, A. D. *Synthesis* **1985**, 233. (b) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523.

Table 3. Arylation of Benzoic Acids by Aryl Chlorides[a]



Entry	Acid	Aryl Chloride	Arylated Acid	Yield
1				75%
2				72%
3				83%
4				91%
5				67%
6[b]				79%
7				65%
8[b]				75%
9				82%
10[c]				71%
11				67%
12				71%
13				72%
14				91%

[a] $ArCO_2H$ (0.5 mmol), chloroarene (2−3 equiv), $Pd(OAc)_2$ (5 mol %), *n*-$BuAd_2P$ (10 mol %), Cs_2CO_3 (2.2 equiv), MS 3 Å (155 mg), DMF (2.5 mL), 24 h, 145 °C. Yields are isolated yields. See the Supporting Information for details. [b]Isolated as the dimethyl ester after treatment with $TMSCHN_2$. [c]2-Phenylbenzoic acid (10%) also isolated.

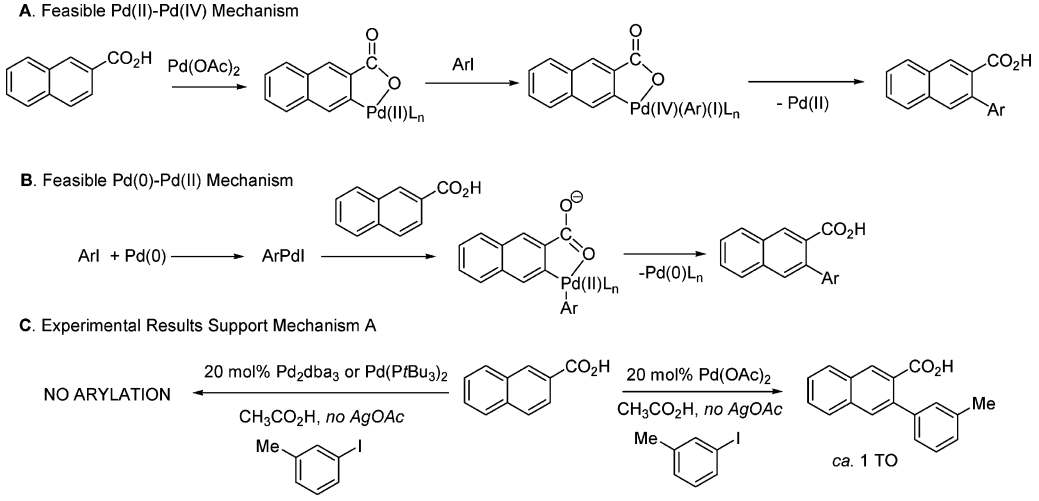
formation, unless unsubstituted benzene or very specifically substituted arenes are used.[10] The current examples of both palladium- and iridium-catalyzed or promoted functionalization of monosubstituted benzenes result in the formation of regioisomer mixtures that are difficult to separate due to similar chromatographic properties.[9]

2.3. Mechanistic Considerations. 2.3.1. Arylation by Aryl Iodides. There are several possible mechanistic pathways for this reaction (Scheme 2). The reaction may proceed by a Pd(II)−Pd(IV) mechanism (Scheme 2A). Cyclometallation followed by oxidative addition of ArI would afford a Pd(IV) intermediate. Fast reductive elimination would produce the arylated carboxylic acid and regenerate Pd(II) species. Alternatively, a Pd(0)−Pd(II) mechanism may be considered (Scheme 2B). After reduction of Pd(II) to Pd(0)[19] oxidative addition of aryl iodide would afford arylpalladium iodide. Cyclometallation followed by reductive elimination would produce the arylated carboxylic acid and regenerate a Pd(0) species. To distinguish between these possibilities, 2-naphthoic acid was reacted with 3-iodotoluene in the presence of a 20 mol % palladium source (Scheme 2C). If palladium acetate was used, about one turnover to the arylated product was observed. Reactions in the presence of Pd_2dba_3 or $Pd(PtBu_3)_2$ did not afford tolylnaphthoic acid. This result points to a Pd(II)−Pd(IV) catalytic cycle; however, a σ-bond metathesis mechanism suggested by Tremont cannot be excluded.[2d]

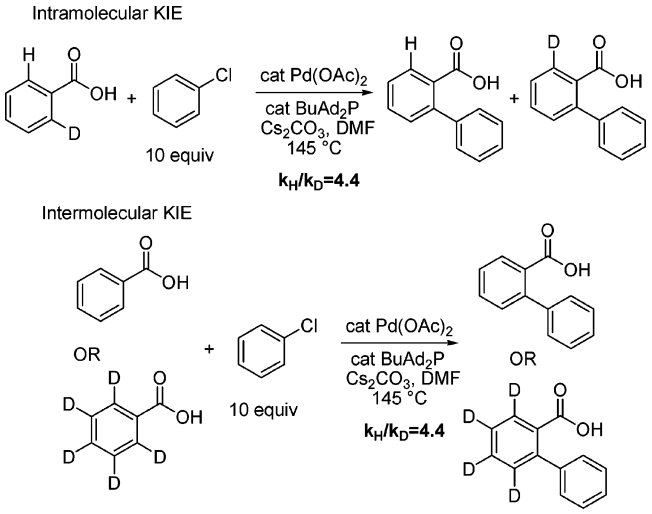
2.3.2. Arylation by Aryl Chlorides. As mentioned before, the arylation reaction proceeds well with both electron-rich and electron-poor benzoic acids. The palladation reactions often proceed faster for electron-rich arenes.[17] Recent work by Echavarren

(19) A reviewer suggested that a Pd(0)−Pd(II) catalytic cycle might be accessed by cyclometallation of the substrate followed by reductive elimination of *o*-acetoxyarenecarboxylic acid. Under the conditions of Scheme 2C the formation of 1-hydroxy-2-naphthoic, 3-hydroxy-2-naphthoic, 1-acetoxy-2-naphthoic, and 3-acetoxy-2-naphthoic acids was not observed (GC analysis of crude reaction mixtures; comparison with authentic samples).

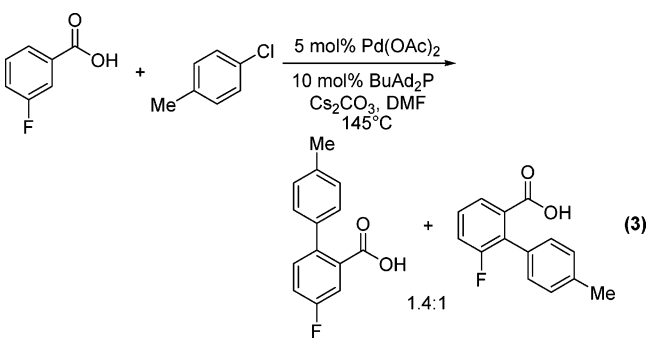
Scheme 2. Illustration of Two Possible Reaction Mechanisms: Pd(II)/Pd(IV) and Pd(0)/Pd(II)



Scheme 3. Intra- vs Intermolecular KIE

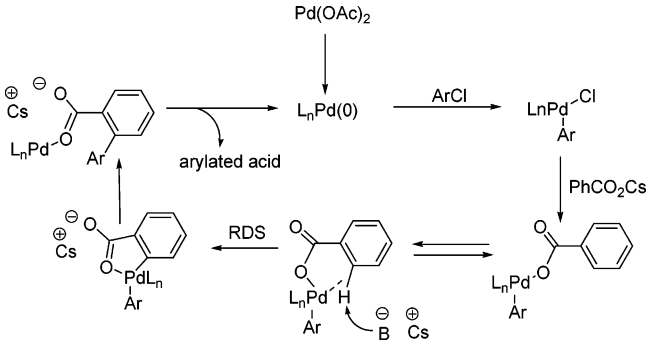


and Fagnou has shown that for electron-poor fluoroarenes complete inversion of reactivity may be achieved.[10b,20a] Accessibility of this mechanistic pathway is dependent on the acidity of the C−H bond that is being functionalized. To evaluate the mechanism of the benzoic acid *ortho*-arylation, several experiments were carried out. First, 3-fluorobenzoic acid was arylated under the usual reaction conditions with *p*-tolyl chloride. The reaction was stopped at very low conversion, before the formation of the diarylation product was observed (eq 3). Low



selectivity of the arylation was observed, with preferential arylation (1:1.4) observed at the *para*-position to the fluorine

Scheme 4. Proposed Catalytic Cycle



substituent. In the arylation of fluorobenzene derivatives, preferential reaction is observed at positions *ortho* to fluorine that are more acidic.[10b]

Both inter- and intramolecular deuterium isotope effects were obtained for the reaction of *p*-tolyl chloride and benzoic acid (Scheme 3). The intramolecular and intermolecular isotope effects are the same, 4.4. The magnitude of the isotope effect is close to the one observed by Echavarren[20a] and is within the expected range for turnover-limiting C−H bond cleavage.[20b] It may be concluded that the exchange of benzoate on the palladium center is rapid compared with the C−H cleavage step. Given the magnitude of the isotope effect, insensitivity of reaction to electronic properties of benzoic acid, and lack of selectivity in the monoarylation of 3-fluorobenzoic acid, we believe that the most likely mechanism for the C−H bond cleavage is the one proposed by Macgregor[21] and Echavarren.[20a] The reaction is initiated by reduction of Pd(II) to Pd(0) (Scheme 4). Oxidative addition of aryl chloride to Pd(0) is facilitated by an electron-rich, bulky ligand. The halide in the coordination sphere of palladium may be replaced by the benzoate followed by the rate-limiting C−H bond cleavage step. The initial formation of an agostic complex is favored by electron-rich C−H bonds.[21] This may explain the slight predominance of arylation at the more electron-rich position of 3-fluorobenzoic

(20) (a) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (b) Reactions proceeding by electrophilic aromatic substitution mechanisms typically have k_H/k_D of around 1. Zollinger, H. *Adv. Phys. Org. Chem.* **1964**, *2*, 163.

(21) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754.

acid. The deprotonation step, on the other hand, may be more facile for more acidic protons allowing the arylation of electron-poor benzoic acids. The equilibrium isotope effect for the agostic bond formation is expected to be relatively small (less than 2).[22] As a consequence, it appears that the deprotonation of the agostic complex is the overall rate-determining step of the reaction. Reductive elimination followed by fast ligand exchange affords the product.

3. Summary

We have developed two methods for direct *ortho*-arylation of benzoic acids. The first method involves the use of catalytic palladium acetate, stoichiometric silver acetate, and an aryl iodide coupling partner. This method is tolerant of chloride and bromide substitution and most likely proceeds through a Pd(II)−Pd(IV) coupling cycle. Moderately electron-poor to electron-rich benzoic acids are reactive, and aryl iodides of any electronic properties may be used. The second method involves the use of catalytic palladium in combination with *n*-butyl-di-1-adamantylphosphine, cesium carbonate base, and an aryl chloride coupling partner. The reaction requires the presence of molecular sieves. Benzoic acids of any electronic properties are reactive. Inter- and intramolecular isotope effects for the benzoic acid arylation by aryl chlorides have been determined and were found to be the same with a magnitude of 4.4 pointing toward heterolytic C−H bond cleavage as the turnover-limiting step.

4. Experimental Section

4.1. General Procedure for Coupling of Iodoarenes with Benzoic Acids. Without special precautions, a 2-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (5 mol %), silver acetate (1.3 equiv), $ArCO_2H$ (1 equiv), iodoarene (3 equiv), and acetic acid (200 μL per mmol of $ArCO_2H$). The sealed vial was placed in a preheated oil bath (100−130 °C) and heated until all benzoic acid starting material had been consumed as determined by TLC or GC (*ca.* 4.5 to 7 h). The reaction mixture was allowed to cool to room temperature, diluted with dichloromethane (2 mL), and filtered through a pad of Celite. The reaction vessel and Celite pad were rinsed with dichloromethane (2 × 1 mL). The filtrate was concentrated under reduced pressure, and the residue was suspended in 5% aqueous KOH. The mixture was extracted with dichloromethane (3 × 10 mL) after which the aqueous layer was acidified with concentrated HCl to pH = 2 followed by extraction with dichloromethane (3 × 10 mL). After filtering through a pad of Celite the dichloromethane layer was concentrated to a volume of about 2 mL. The mixture was adsorbed on silica gel and was subjected to flash chromatography (hexanes then dichloromethane−ethyl acetate 95:5). After the removal of the solvent and trituration with hexanes, the residue was dried under reduced pressure (50 °C) to give the product.

4.2. General Procedure for Coupling of Chloroarenes with Benzoic Acids. Outside the glovebox a 2-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (5 mol %), $ArCO_2H$ (0.5 mmol), and chloroarene (2−3 equiv). The vial was flushed with argon, capped, and placed inside a glovebox. To this mixture was added *n*-butyl-di-1-adamantylphosphine (10 mol %), Cs_2CO_3 (2.2 equiv), molecular sieves 3 Å (155 mg), and anhydrous DMF (2.5 mL). The sealed vial was taken out of the glovebox, stirred at room temperature for 2 h, and placed in a preheated oil bath (145 °C) for 24 h. The reaction mixture was cooled to room temperature and quenched with 15% aqueous HCl (4 mL). The resulting suspension was extracted with ethyl acetate (3 × 3 mL), and the organic layer was filtered through a pad of Celite. The filtrate was concentrated under vacuum to a volume of about 2 mL. The mixture was adsorbed on silica gel and subjected to flash chromatography (hexanes then CH_2Cl_2−EtOAc 95:5). The CH_2Cl_2−EtOAc fraction was concentrated, and the residue was triturated with distilled water (3 × 2 mL) and dried under reduced pressure. The residue, after trituration with hexanes (2 × 2 mL) and/or purification by preparative HPLC and drying under reduced pressure (50 °C), yielded the product.

Acknowledgment. We thank the Welch Foundation (Grant No. E-1571) for supporting this research. Q.P. is grateful to University of Houston for an undergraduate research scholarship (PURS). We thank Dr. James Korp for collecting and solving the X-ray structures. We also thank Prof. Maurice Brookhart for helpful comments.

Supporting Information Available: Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA071845E

(22) (a) Brookhart, M.; Green, M. L. H.; Wong, L.-L. *Prog. Inorg. Chem.* **1988**, *36*, 1. (b) Jones, W. D. *Acc. Chem. Res.* **2003**, *36*, 140. However, a substantial isotope effect ($k_H/k_D = 3.0$) observed in the palladium-catalyzed dimerization of arylacetylenes was explained by an agostic interaction. (c) Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 11107.