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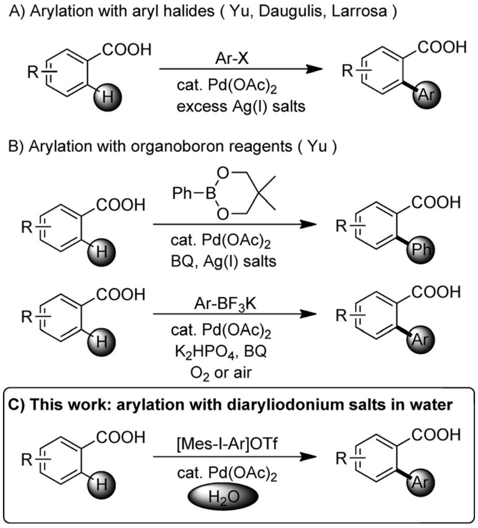
Palladium-Catalyzed C–H *ortho* Arylation of Benzoic Acids with Diaryliodonium Salts in Water

Zhiqing Wu,[a] Si Chen,[a] Chenxu Hu,[a] Zhengkai Li,[a] Haifeng Xiang,[a] and Xiangge Zhou*[a, b]

Palladium-catalyzed C–C bond-formation reactions between aryl halides or triflates and organometallic reagents are among the most useful methods to construct biaryls, which are usually structural motifs found in important nature products, pharmaceuticals, and organic materials.[1] The corresponding organometallic nucleophilic starting materials, however, are often not commercially available and sometimes lead to the formation of undesired side products. Over the past decade, extensive efforts have been made to explore the transition-metal-catalyzed direct arylation of C–H bonds as ecologically and economically friendly alternatives.[2] Furthermore, owing to the requirement of site selectivity, directing groups such as pyridyl, acylamino, hydroxy, and phenolic ester groups have been broadly introduced into substrates.[2d] The majority of these directing groups cannot be easily removed from the products, and a few of them have to be deprotected by further transformations.[3] In recent years, transition-metal-catalyzed decarboxylative coupling reactions have emerged as a powerful strategy to form carbon–carbon and carbon–heteroatom bonds from cheap, diverse, and readily available aryl carboxylic acids.[4] The carboxylic acid group can efficiently be removed or converted into a variety of useful functional groups, which makes the directed *ortho* C–H functionalization of carboxylic acids exceptionally practical for applications in organic synthesis.[5]

In 2007, the groups of Yu and Daugulis pioneered the direct *ortho*-arylation of benzoic acids with aryl halides by using palladium as a catalyst (Scheme 1 a).[6] Also, Yu and co-workers demonstrated that phenylboronic acid esters and aryltrifluoroborates can be utilized as coupling partners for the *ortho* functionalization of benzoic acids (Scheme 1 b).[6a, 7] Recent work has identified that diaryliodonium salts, which are commercially available or easily synthesized, are important alternatives that can be used as arylation reagents in palladium-catalyzed C–H arylation reactions.[8] However, application of diaryliodonium salts in the catalytic *ortho*-arylation of benzoic acids has not yet been reported.



Scheme 1. Palladium-catalyzed C–H *ortho* arylation of benzoic acids. Ac = acetyl, BQ = 1,4-benzoquinone, Mes = 2,4,6-trimethylphenyl, Tf = trifluoromethanesulfonyl.

The use of water as an environmentally benign, nonflammable, and nontoxic medium for organic transformations is strongly desired because of green chemistry.[9,10] As part of our continuous interest in aqueous catalysis,[11] herein we report an efficient and practical protocol for the palladium-catalyzed C–H *ortho* arylation of benzoic acids with diaryliodonium salts by using water as the solvent (Scheme 1 c).

In our initial optimization study, *m*-toluic acid and phenyl(2,4,6-trimethylphenyl)iodonium triflate (**2 a**) were chosen as model substrates. As illustrated in Table 1, no desired product was found in the absence of catalyst by using water as the solvent (Table 1, entry 1). Gratifyingly, the substrates could be transformed into desired *ortho*-arylated product **3 a** in 85 % yield by using a catalytic amount of $Pd(OAc)_2$ (Table 1, entry 2). Next, a variety of organic solvents were tested; nevertheless, only a trace amount of the product was formed (Table 1, entries 3–10). The results suggest strongly that the choice of water as the solvent is crucial for this reaction. Replacing $Pd(OAc)_2$ by $PdCl_2$ resulted in a slightly lower yield of the product (78 %; Table 1, entry 11). Furthermore, low temperatures decelerated the reaction rate; product **3 a** was obtained in 54 % yield if the reaction was performed at 80 °C (Table 1, entry 12). A symmetrical iodonium salt was also compatible with the reaction, and it provided a similar result (Table 1, entry 13).

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[a] Z. Wu, S. Chen, C. Hu, Dr. Z. Li, Dr. H. Xiang, Prof. Dr. X. Zhou
Institute of Homogeneous Catalysis
College of Chemistry, Sichuan University
Chengdu 610064 (P.R. China)
Fax: (+86) 28-8541-2026
E-mail: zhouxiangge@scu.edu.cn

[b] Prof. Dr. X. Zhou
Key Laboratory of Organic Synthesis of Jiangsu Province
College of Chemistry, Chemical Engineering and Materials Science
Soochow University
Suzhou 215123 (P.R. China)

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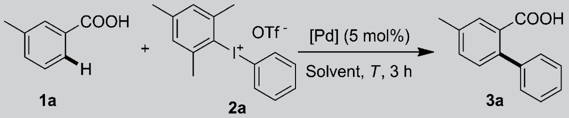
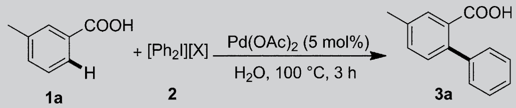
Table 1. Optimization of the reaction conditions.[a]



Entry	Pd catalyst	Solvent	T [°C]	Yield[b] [%]
1	–	H_2O	100	0
2	$Pd(OAc)_2$	H_2O	100	85
3	$Pd(OAc)_2$	1,2-dichloroethane	100	0
4	$Pd(OAc)_2$	AcOH	100	trace
5	$Pd(OAc)_2$	MeOH	100	trace
6	$Pd(OAc)_2$	toluene	100	trace
7	$Pd(OAc)_2$	1,4-dioxane	100	trace
8	$Pd(OAc)_2$	DMF	100	trace
9	$Pd(OAc)_2$	DMSO	100	0
10	$Pd(OAc)_2$	none	100	26
11	$PdCl_2$	H_2O	100	78
12	$Pd(OAc)_2$	H_2O	80	54
13	$Pd(OAc)_2$	H_2O	100	83[c]

[a] All reactions were performed with **1 a** (0.25 mmol), **2 a** (1.5 equiv.), and [Pd] (5 mol%) in solvent (0.5 mL) for 3 h. [b] Yield of isolated product. [c] Ph_2IOTf was used instead of **2 a**.

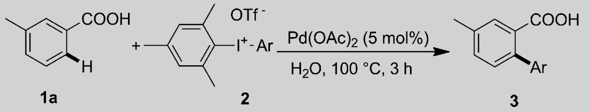
Table 2. Effect of the counteranions.[a]

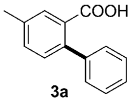
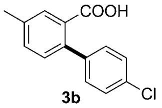
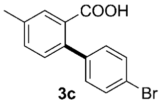
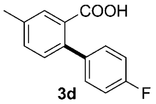
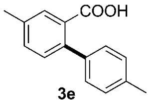
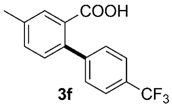
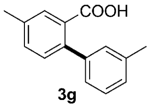
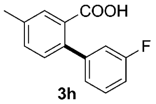
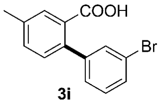


Entry	X	Yield [%][b]
1	OTf	83
2	BF_4	83
3	PF_6	79
4	Br	75

[a] All reactions were performed with **1 a** (0.25 mmol), **2** (1.5 equiv.), and $Pd(OAc)_2$ (5 mol%) in solvent (0.5 mL) for 3 h. [b] Yield of isolated product.

Table 3. Scope of the diaryliodonium triflate substrate.[a]



Entry	Ar	Product	Yield [%][b]
1	Ph	 **3a**	85
2	p-ClC_6H_4	 **3b**	91
3	p-BrC_6H_4	 **3c**	85
4	p-FC_6H_4	 **3d**	80
5	p-$CH_3C_6H_4$	 **3e**	88
6	p-$CF_3C_6H_4$	 **3f**	83
7	m-$CH_3C_6H_4$	 **3g**	80
8	m-FC_6H_4	 **3h**	70
9	m-BrC_6H_4	 **3i**	75

[a] All reactions were performed with **1 a** (0.25 mmol), **2** (1.5 equiv.), and $Pd(OAc)_2$ (5 mol%) in H_2O (0.5 mL) at 100 °C for 3 h. [b] Yield of isolated product.

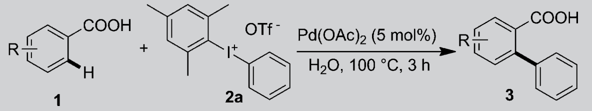
We then investigated the effect of the counter anions of the diaryliodonium salts, as summarized in Table 2. Diphenyliodonium salts containing diverse anions were evaluated and all provided satisfactory yields, which demonstrated that the counter anions did not play an important role in this aqueous C–H arylation reaction.

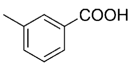
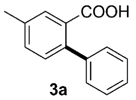
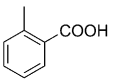
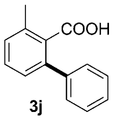
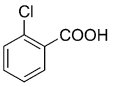
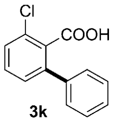
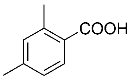
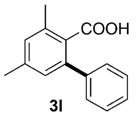
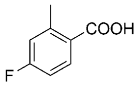
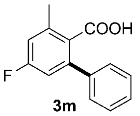
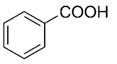
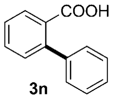
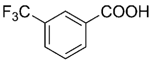
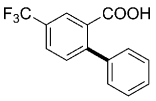
Next, the substrate scope of the diaryliodonium salt was examined in the reaction with *m*-toluic acid under the optimized reaction conditions. As shown in Table 3, diversely substituted and readily accessible diaryliodonium salts could be successfully used; exclusive transfer of the smaller aryl group to give the desired products in moderate to good yields ranging from 70 to 91% was observed. Notably, Cl and Br substituents were well tolerated in this protocol, which is crucial for further synthetic manipulations (Table 3, entries 2, 3, and 9).

Also, the aromatic acid substrates were investigated. We were delighted to observe that different substituted benzoic acids could be arylated smoothly with high efficacy. As shown in Table 4, high chemoselectivity was observed, and monoarylated benzoic acids were the main products; no diarylated products were observed. Importantly, the aqueous system is suitable for large-scale synthesis. For example, upon performing the reaction with 10 mmol of *o*-toluic acid, 1.7 g of **3 j** was obtained (82% yield; Table 4, entry 2). However, 3-trifluoromethylbenzoic acid was inert in this protocol, and this might be the result of the highly electron-deficient nature of the substrate, which is unfavorable for C–H activation (Table 4, entry 7).

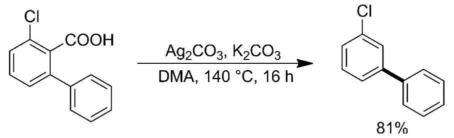
We next sought to demonstrate that the carboxyl group could be removed, which would allow the regioselective synthesis of biaryls. 2-Chloro-6-phenylbenzoic acid (**3 k**) was decarboxylated by using known methods to afford 3-chlorobiphenyl in 81% yield, as shown in Scheme 2.[12]

Table 4. Scope of the aromatic acid substrate.[a]

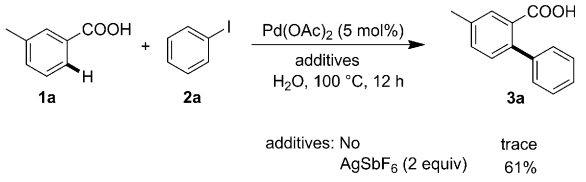


Entry	Substrate	Product	Yield [%][b]
1		 **3a**	85
2		 **3j**	88 82[c]
3		 **3k**	70
4		 **3l**	75
5		 **3m**	70
6		 **3n**	76
7			0

[a] All reactions were performed with **1** (0.25 mmol), **2a** (1.5 equiv.), and $Pd(OAc)_2$ (5 mol%) in H_2O (0.5 mL) at 100 °C for 3 h. [b] Yield of isolated product. [c] Reaction was performed on a 10 mmol scale.



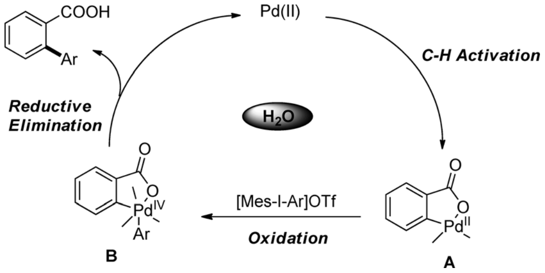
Scheme 2. Protodecarboxylation of a carboxylic acid. DMA = dimethylacetamide.



Scheme 3. Arylation with iodobenzene.

To gain some insight into the reaction process, comparative experiments were performed (Scheme 3). The reaction between *m*-toluic acid and iodobenzene provided a trace amount of the desired product under the optimized aqueous conditions. This result demonstrated that the aryl iodide, which may come from the decomposition of the diaryliodonium salt, is not the actual arylating species in this reaction. We suspected that the addition of silver salts could promote the C–H arylation with iodobenzene in water.[13] After extensive screening, we found that the reaction between *m*-toluic acid and iodobenzene provided the arylated product in a moderate 61% yield in the presence of water-soluble $AgSbF_6$.

On the basis of the work of Sanford and co-workers, who suggested that palladium-catalyzed C–H arylation with diaryliodonium salts might proceed through a high-valent palladium pathway,[8e,h] a proposed mechanism is shown in Scheme 4.



Scheme 4. Proposed catalytic cycle.

The carboxyl-directed insertion of Pd^{II} into the C–H bond affords Pd^{II} species **A**, which is subsequently oxidized to Pd^{IV} intermediate **B** by the diaryliodonium salt. Following reductive elimination, the arylated product is produced and the Pd^{II} species is regenerated to complete the catalytic cycle.[14]

In summary, we have disclosed an efficient and practical protocol for the C–H *ortho* arylation of benzoic acids by using water as an environmentally benign, nontoxic reaction medium. Remarkably, the diaryliodonium salts were first utilized as arylating reagents for C–H arylation of benzoic acids. The choice of water as the solvent is crucial for this reaction, which sets the stage for the broad application of aqueous conditions in C–H functionalization reactions. Overall, this simple catalytic system represents an important complement to previous reports for the preparation of biaryls. Further investigations of this system for use in other reactions as well as the study of a detailed mechanism are currently ongoing in our laboratory.

Experimental Section

General experimental procedure for the C–H arylation of benzoic acids with diaryliodonium salts

Benzoic acid (0.25 mmol), [Mes-I-Ar]OTf (0.375 mmol), and $Pd(OAc)_2$ (0.0125 mmol) were combined in water (0.5 mL) in a 10 mL vial. The vial was sealed with a Teflon-lined cap, and the reaction mixture was stirred in a 100 °C oil bath for 3 h without an inert gas atmosphere. After cooling to room temperature, the mixture was acidified with 2 N HCl (2 mL) and extracted with ethyl acetate (3× 10 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to afford the corresponding product.

Acknowledgements

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Keywords: biaryls · C–H activation · diaryliodonium salts · palladium · water chemistry

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