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A mild and efficient carboxylate-directed C–H arylation of aryl carboxylic acids with iodobenzenes in water

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An efficient and environmental friendly Pd-catalyzed carboxylate-directed C–H arylation reaction of aryl carboxylic acids with iodobenzenes has been developed in water where Tween 20 was added (2% w/w) to form aqueous micelles to increase the solubility of starting materials. In this aqueous protocol, the reactions proceeded at a lower temperature (80 °C) compared with the traditional procedures using organic solvents (100 °C and above) and wide substrate scopes were demonstrated (15 examples, 62–92% yields).

During the past decade, C–H functionalization was extensively explored due to its high atom efficiency and potential to enable structural diversities without pre-functionalized starting materials such as iodines, triflates, boronic acids, etc.[1] To achieve the regioselectivity of the C–H activation, a number of directing groups containing nitrogen, sulfur, and phosphine were discovered to bind with the transition metal catalysts and position them at the desired site for the C–H bond cleavage.[1] Recently, the 'weakly coordinating directing groups' were developed for regio-selective C–H functionalization including ketones, aldehydes, ethers, and carboxylic acids.[2] Among them, carboxylic acids deserved special attention due to their ready availability and greater flexibility for removal after the reaction completes.[3] The palladium-catalyzed C–H arylation using carboxylic acid as the directing group was pioneered in 2007 when the Yu group and the Daugulis group independently developed the *ortho*-arylation of C–H bonds in benzoic acids.[4] High temperature (100–130 °C) was reported in the reaction conditions from both groups, and moderate to low yields were observed in Yu's protocol[4a] while in Daugulis' protocol acetic acid had to be used as the solvent for arylations with aryl iodides as starting materials.[4b] Since then, the carboxylate-directed C–H arylation reactions have attracted tremendous interests from the synthetic chemistry community and significant progress has been made to optimize the conditions.[5] Recently, the Zhou group has reported the C–H *ortho*-arylation of benzoic acids in the environmentally friendly solvent, water, where diaryliodonium salts were used for arylation.[6] Even though palladium-catalyzed C–H bond activation/cross-coupling reaction cascades were known to happen in water for several cases,[7] the carboxylate-directed C–H *ortho*-arylation in water was rarely reported. Zhou's protocol, to the best of our knowledge, was the only example reported but it suffered from the inconvenience of the preparation of diaryliodonium salts as the required starting materials.[6] Furthermore, high reaction temperature (100 °C) was required in order to achieve reasonable yields (70–91%). Herein, we reported the carboxylate-directed C–H arylation of aryl carboxylic acids in water with readily available iodobenzenes and at a lower temperature (80 °C).

The common challenge to organic reactions in water is the insolubility of starting materials/catalysts, and one potential solution for this issue relies on adding surfactants to form aqueous micelles to improve solubility.[8] The Lipshutz group developed a palladium-catalyzed C–H activation/cross-coupling reaction cascade of aryl ureas in water using Brij 35 as the surfactant to form aqueous micelles.[9] A C–H acylation of anilides in aqueous solution was also reported by Stirling and co-workers using sodium dodecyl sulfate (SDS) as the surfactant.[10] However, the C–H arylation of aryl carboxylic acids, which are readily available but less reactive, in aqueous solutions has not yet been developed.

We started our exploration using 2-naphthoic acid (**1**) and 1-chloro-4-iodobenzene (**2**) as starting materials and polysorbate 80 (Tween 80) as the surfactant (Table 1). To our delight, we observed a moderate conversion (50%) of the desired C–H arylation product (**3a**) using $Pd(OAc)_2$ as the catalyst and AgOAc as the

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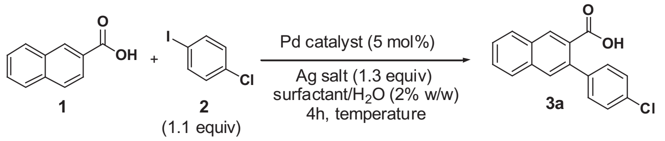
0040-4039/

Table 1
Optimization of the Pd-catalyzed carboxylate-directed C–H arylation conditions



Entry	Pd catalyst	Ag salt	Surfactant	Temp (°C)	Conv[a] (%)
1	$Pd(OAc)_2$	AgOAc	Tween 80	80	50
2	$Pd(OAc)_2$	Ag_2O	Tween 80	80	44
3	$Pd(OAc)_2$	AgOTf	Tween 80	80	59
4	$Pd(OAc)_2$	AgTFA	Tween 80	80	82
5	$Pd(OAc)_2$	Ag_2CO_3	Tween 80	80	53
6	$Pd(OAc)_2$	None	Tween 80	80	Trace
7	$Pd(OAc)_2$	AgTFA	Tween 20	80	87
8	$Pd(OAc)_2$	AgTFA	Tween 40	80	77
9	$Pd(OAc)_2$	AgTFA	Tween 60	80	55
10	$Pd(OAc)_2$	AgTFA	Brij 35	80	67
11	$Pd(OAc)_2$	AgTFA	SDS	80	10
12	$Pd(OAc)_2$	AgTFA	HTAB	80	40
13	$Pd(OAc)_2$	AgTFA	None	80	0
14	$Pd(TFA)_2$	AgTFA	Tween 20	80	80
15	$PdCl_2$	AgTFA	Tween 20	80	70
16	$Pd(dppf)Cl_2$	AgTFA	Tween 20	80	15
17	$Pd_2(dba)_3$	AgTFA	Tween 20	80	0
18	$Pd(OAc)_2$	AgTFA	Tween 20	60	Trace
19[b]	$Pd(OAc)_2$	AgTFA	Tween 20	80	95

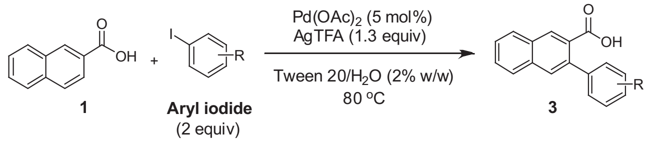
[a] Conversion was measured using LC–MS.
[b] 2 equiv of 1-chloro-4-iodobenzene was added.

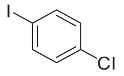
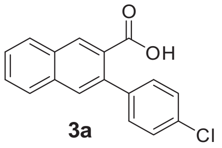
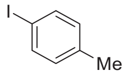
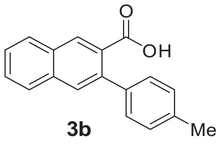
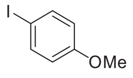
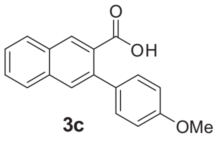
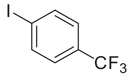
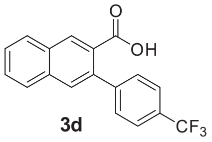
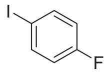
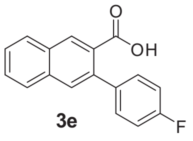
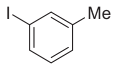
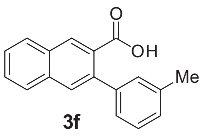
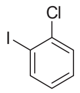
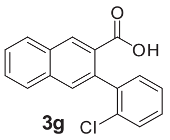
additive (entry 1). We firstly investigated the effect of different silver(I) salts and discovered the silver(I) trifluoroacetic acid salt (AgTFA) to be the most effective additive, providing the highest conversion (82%) to product **3a** (entries 2–5). Without the silver(I) salt, there was only a trace amount of product (entry 6), suggesting the critical role of the silver(I) additives which was reported for the removal of iodide from coordination with palladium in the catalytic cycle.[11] The type of surfactants used also demonstrated a significant impact on the C–H arylation (entries 7–12). Polysorbate 20 (Tween 20) was somewhat more effective than Tween 80, and it was the most effective surfactant among all the polysorbates.[12] Another non-ionic surfactant Brij 35 was also effective for the reaction, albeit resulted in a lower conversion compared with that of Tween 20. On the other hand, ionic surfactants such as sodium dodecyl sulfate (SDS) and hexadecyltrimethylammonium bromide (HTAB) provided low conversions to the C–H arylation product **3a**. Without the addition of surfactant, no desired product was observed (entry 13) probably due to the insolubility of starting materials in water. Pd-catalysts were also screened, and $Pd(OAc)_2$ proved to be the most effective catalyst (entries 7, 14–17). It is noteworthy that $Pd_2(dba)_3$ was totally inactive in catalyzing the C–H arylation (entry 17), suggesting a Pd(II)/Pd(IV) mechanism.[4] When the reaction temperature was decreased to 60 °C, only a trace amount of the C–H arylation product (**3a**) was detected (entry 18). Instead, we observed a significant amount of bi-product 4,4′-dichloro-1,1′-biphenyl which was formed from the homo-coupling of the starting material 1-chloro-4-iodobenzene (**2**). Indeed, the homo-coupling bi-product was also observed in reactions at the elevated temperature (80 °C) to a less extent but this might be the reason why the reaction could not proceed to full conversion when a stoichiometric amount of **2** was used. Increasing the amount of **2** (two equivalents) in the reaction mixture provided much improved conversion (95%, entry 19).

With the optimized reaction condition in hand, the scope of iodobenzenes was examined in the C–H arylation reactions with 2-naphthoic acid (**1**). As shown in Table 2, iodobenzenes with a variety of different substitutions were well tolerated for the reaction and the mono-arylated products (**3**) were the main products observed. *Para*-substituted iodobenzenes bearing both electron-withdrawing and electron-donating substitutions resulted in the C–H arylation products (**3a**–**3e**) in moderate to good isolated yields (67–88%). Iodobenzene with *meta*-substitution (1-iodo-3-methylbenzene, entry 6) demonstrated similar reactivity to provide the C–H arylation product (**3f**) in a reasonable yield (78%). Increasing the steric hindrance of the iodobenzene by introducing the chlorine atom at the *ortho*-position (1-chloro-2-iodobenzene, entry 7) resulted in a slower reaction and product **3g** was obtained in 72% yield after a prolonged reaction (24 h).

The scope of the aryl carboxylic acid substrate was also investigated (Table 3). To our delight, different substituted benzoic

Table 2
Scope of iodobenzenes for Pd-catalyzed carboxylate-directed C–H arylation in water[a]

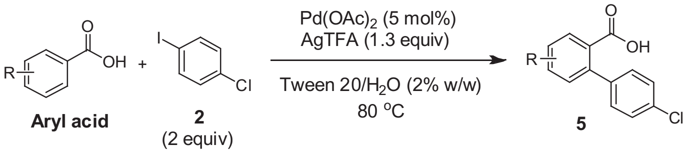


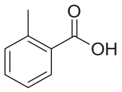
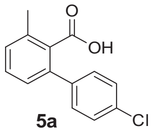
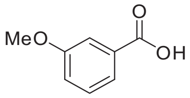
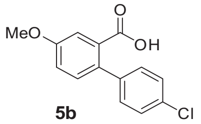
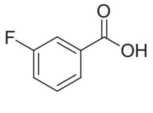
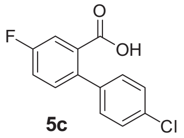
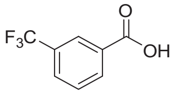
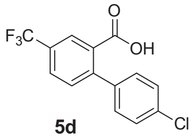
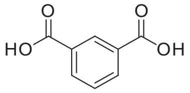
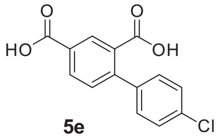
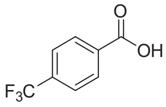
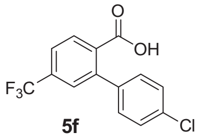
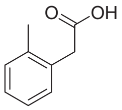
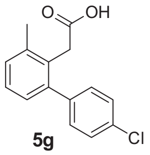
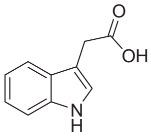
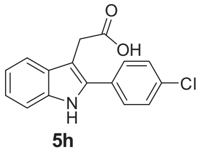
Entry	Aryl iodide	Product	Yield[b] (%)
1		 **3a**	88
2		 **3b**	75
3		 **3c**	67
4		 **3d**	70
5		 **3e**	85
6		 **3f**	78
7		 **3g**	72[c]

[a] The reaction was conducted with 2-naphthoic acid (100 mg), substituted iodobenzene (2 equiv), silver(I) trifluoroacetate (1.3 equiv), and diacetoxypalladium (0.05 equiv) in Tween 20/H_2O (3 mL, 2% w/w) at 80 °C for 4 h.
[b] Isolated yield.
[c] Reaction run for 24 h.

Table 3

Scope of aryl carboxylic acids for Pd-catalyzed carboxylate-directed C–H arylation in water[a]



Entry	Aryl acid	Product	Yield[b] (%)
1		 **5a**	88
2		 **5b**	86
3		 **5c**	82
4		 **5d**	68
5		 **5e**	80
6		 **5f**	62
7		 **5g**	92
8		 **5h**	75[c]

[a] The reaction was conducted with acid (100 mg), 1-chloro-4-iodobenzene (2 equiv), silver(I) trifluoroacetate (1.3 equiv), and diacetoxypalladium (0.05 equiv) in Tween 20/H$_2$O (3 mL, 2% w/w) at 80 °C for 4 h.

[b] Isolated yield.

[c] Reaction run for 30 min.

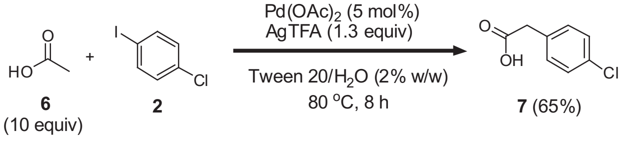


Figure 1. Pd-catalyzed C–H arylation of acetic acid in water.

acids (with electron-donating or electron-withdrawing substitutions at *ortho*-, *meta*-, or *para*-positions) underwent C–H arylation smoothly with moderate to good yields (entries 1–6). The main products formed were the mono-arylated products at the *ortho*-position of the carboxylic acid. In addition, 2-(*o*-tolyl)acetic acid (entry 7) could also be arylated with high efficiency. Carboxylate-directed C–H arylation of indole (entry 8) proceeded much faster and the reaction was completed in 30 min. In addition, **5f** and **5h** were scaled up to ~1 g scales and good yields were observed (63% and 71%, respectively). These results further demonstrated the practicality of this catalytic procedure.

Pd-catalyzed C–H arylation of aliphatic acids with **2** was explored. Encouragingly, coupling product (**7**) of acetic acid with **2** was isolated in 65% yield after stirring in the Tween 20/H$_2$O aqueous micelles for 8 h at 80 °C (Fig. 1). Small amount of bis-coupling product with **2** was also observed. We are currently optimizing the reaction conditions for improved yields at the same time expanding the aliphatic acid substrate scope to make the reaction more synthetically appealing.

In summary, we have developed a mild and efficient Pd-catalyzed carboxylate-directed C–H arylation reaction of aryl carboxylic acids with iodobenzenes in water, where Tween 20 was added (2% w/w) to form micelles to improve the solubility of starting materials. In our protocol, the C–H arylation reactions proceeded at a lower temperature (80 °C) compared with the reported procedures (100 °C and above) wherein organic solvents were used as solvents. A wide scope of substrates of both aryl carboxylic acids and iodobenzenes were demonstrated (15 examples, 62–92% yields). Further investigation of this protocol on C–H arylation of aliphatic acids is ongoing.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.001.

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