Palladium-catalyzed decarboxylative coupling of aromatic acids with aryl halides or unactivated arenes using microwave heating†

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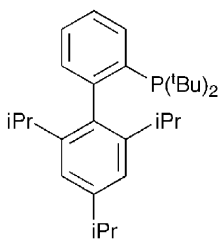
Microwave heating greatly accelerates Pd-catalyzed decarboxylative coupling of aromatic acids and aryl iodides, and allows the coupling of benzoic acids with unactivated arenes.

Aryl–aryl coupling reactions[1–11] generally rely on a stoichiometric organometallic reagent, such as a boronic acid, with an aryl halide as the other coupling partner.[1] New, greener coupling partners, such as carboxylic acids, are being explored[3] to replace the boronic acid.[6–8] ArH can also be coupled *via* C–H activation,[2] to replace the aryl halide. With carboxylic acids, regioselectivity is achieved because coupling occurs at the site of decarboxylation, but the reactions tend to be slow.[4] C–H activation is often limited by the need for a directing group to achieve high selectivity.[2] Heck[4] and Sonogashira reactions[5] involving ArCOOH decarboxylation are known. Coupling reactions between activated carboxylic acids and aryl bromides and chlorides, reported by Goossen,[7,8] use a Pd(II)/Cu(I) catalyst system for activated benzoic acids such as 2-nitrobenzoic acid. An alternative by Wagner uses catalytic Pd and a stoichiometric Ag salt to couple carboxylic acids and aryl iodides[9a] or diaryliodonium salts.[9b] Unactivated benzoic acids pose severe difficulties for current methods.

We now find that the reaction time can be significantly reduced by using ^{t}Bu-XPhos {P^{t}Bu$_2$(*o*-C$_6$H$_4$Ar)}[12] together with microwave heating, and with Ag_2O or Ag_2CO_3 as additive. Intramolecular coupling between ArCOOH and Ar′H now also becomes possible.

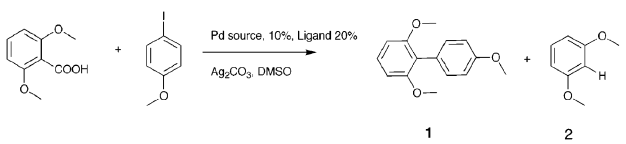


Buchwald phosphine
t-butyl XPhos

We first optimized the benzoic acid decarboxylative coupling with aryl halides as partners. Surprisingly, we find that

$$ArCOOH + Ar'I \rightarrow Ar\text{-}Ar' + CO_2 + HI \quad \text{(eq 1)}$$
$$ArCOOH + Ar'H \rightarrow Ar\text{-}Ar' + CO_2 + 2H^+ \quad \text{(eq 2)}$$

Scheme 1



Scheme 2

microwave heating under controlled and optimized conditions is superior to conventional heating. Reaction times are reduced from many hours to a few minutes. In the more challenging case of carboxylic acids and arenes as coupling partners, the reactions yielded no product under standard conditions, but under our new conditions, success was achieved for select cases (Scheme 1).

Even though prior work showed no significant microwave enhancement of decarboxylative coupling,[9] we now find a microwave protocol for the reaction in Scheme 2.

Initial results in a sealed microwave tube indicated that at 200 °C the coupling product was observed after 2 min, but heating was continued for a further 3 min to assure completion. Extension to a total time of 10 min gave no advantage. In all cases, a second product, ArH generated from ArCOOH, was also observed (Scheme 2, product **2**). Unlike some previous reports,[7] in our case there was no difference in the reactivity between the free acid and the potassium salt so the former was used in all subsequent reactions. The addition of K_2CO_3, along with the Ag_2CO_3, had no effect on the yield. Our procedure needs 1 equiv. of silver oxide or carbonate, not the excess (3 equiv.) previously reported for such reactions.[4,9]

Screening of palladium precursors showed palladium acetate gave the best yields. In contrast, Pd/C affords no coupling product, so decomposition to metal is not suspected. In the absence of any added ligand, we find low yields of **1** and **2** in approximately equal amounts. The effect of a number of ligands on the reaction was also studied (ESI Table 1†). N-donor ligands, such as pyridine, inhibited coupling, whereas phosphines were moderately active. P(iPr)Ph$_2$ and ^{t}Bu-XPhos gave the best yields among the phosphines. As previously reported,[9] $AsPh_3$ was also comparable in activity. Chelating ligands like bipyridine (bpy) and 1,2-bis(diphenylphosphino)-ethane (dppe) were significantly less active than their monodentate counterparts. $SbPh_3$ was likewise inactive.

Among solvents with good microwave absorptivity such as DMSO, DMF and water, a DMSO–DMF (1 : 9) mixture

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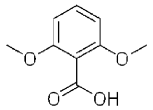
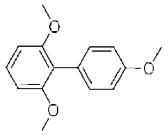
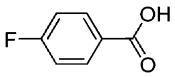
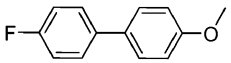
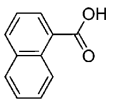
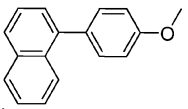
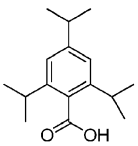
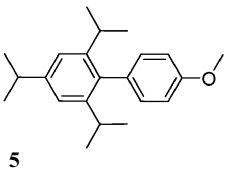
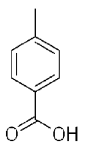
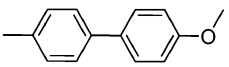
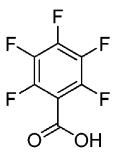
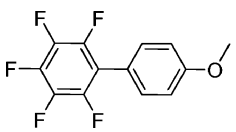
Table 1 Substrate scope ArCOOH for decarboxylative couplings[a]

Entry	Substrate	% yield[b]	Product
1		81	 **1a**
2		35	 **3**
3		61	 **4**
4		12	 **5**
5		15	 **6**
6		63	 **7**

[a] Conditions: 270 μmol substituted benzoic acid, 280 μmol iodoanisole, 10% $Pd(OAc)_2$ 20% ^{t}Bu-XPhos, 2 mL 9 : 1 DMF–DMSO, 0.100 g 4 Å molecular sieves, 200 °C microwave, 5 min. [b] Isolated yield with respect to benzoic acid.

proved best, however, in order to facilitate rapid NMR screening, we used d_6-DMSO alone, which led to slightly reduced yields of the desired coupling product **1**, but gave cleaner spectra. Water proved unsuitable, as at 200 °C the pressure of H_2O + CO_2 can exceed the set pressure limits of the microwave unit, and the presence of water increases the production of undesired ArH (**2**).

Silver carbonate and silver oxide were best. No other Cu^+ or Ag^+ sources screened were as successful. CuI, Cu_2O and $CuCO_3$ all gave low yields of coupling product **1** and increased yields of undesired product **2**, as shown in Table 2 (ESI†).

Table 2 Substrate scope of substituted aryl iodides for decarboxylative couplings[a]

Entry	Substrate	% yield **1**[b]	Product	% yield **2**[b]
1	4-iodoanisole	81	**1a**	18
2	3-iodotoluene	72	**1b**	36
3	4-iodoacetophenone	62	**1c**	29
4	9-iodoanthracene	68	**1d**	33
5	4-iodophenol	5	**1e**	44
6	3-iodopyridine	34	**1f**	52

[a] Conditions: 270 μmol 2,6-dimethoxybenzoic acid, 280 μmol substituted aryl iodide, 10% $Pd(OAc)_2$ 20% ligand, 270 μmol silver carbonate, 1 mL d_6-DMSO, 0.100 g 4 Å molecular sieves, 200 °C microwave heating, 5 min. [b] Reported yields with respect to the acid are based on NMR using 10 μL cyclooctane as internal standard.

The formation of product **2** was dependent on [H_2O]. Adding 100 μL water to a reaction identical to entry 1 (Table 1, ESI†) gave a 22% increase in **2**, and an equivalent decrease in **1**. An identical experiment with D_2O gave ArD (**2**). To maximize the coupling product, it is therefore desirable to eliminate water. With activated molecular sieves the yield of coupling product **1** increased from 59% to 75%.

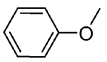
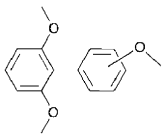
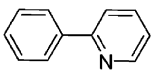
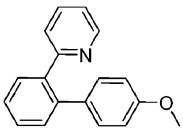
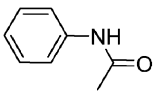
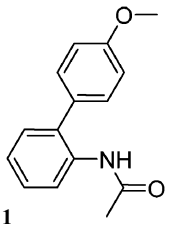
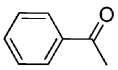
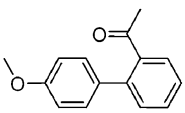
Table 1 shows several substrates screened using optimized reaction conditions. Previously reported procedures involved highly activated substrates. Wagner *et al.*[9] observed that all the successful substrates had either electron-withdrawing 2,6-substituents, such as nitro, or electron-donating methoxy and fluoride substituents. Goossen[7,8] has shown that 2-nitrobenzoic acid is an excellent substrate for decarboxylative coupling to aryl bromides using a Pd/Cu system. In addition, a computational thermodynamic study[8] indicates that decarboxylation of a select group of substituted benzoic acids is non-spontaneous, except for highly activated substrates, which are close to thermoneutral. With microwave heating under our conditions coupling of less activated carboxylic acids now proves possible. Naphthoic acid shows similar reactivity to 2,6-dimethoxybenzoic acid. The less reactive *p*-toluic acid is significantly less effective (15% yield) and 2,4,6-triisopropylbenzoic acid also gives only 12% desired product.

The substrate scope for the ArI coupling partner is shown in Table 2. Electron-donating substituents are preferred. Aryl iodides with coordinating substituents such as hydroxyl groups (entry 5), or *N*-heterocyclic arenes, such as 3-iodopyridine (entry 6) are poor substrates. The mechanism is under study and will be discussed in the full paper.

We have been able to replace the toxic aryl iodides by simple arenes, providing a greener coupling procedure (Scheme 1, (eqn 2)). These substrates must now react *via* C–H activation pathways (Scheme 3). Goossen recently reported the use of a similar phosphine for coupling to aryl chlorides.[8b] ^{t}Bu-XPhos also proved to be the best ligand for decarboxylative coupling *via* C–H activation. Triphenylarsine was comparable in activity, but was again avoided due to high toxicity.

^{t}Bu-XPhos gave >95% conversion of acid, and a ratio of products **1** : **13** : **3** of 3 : 1 : 5. Selectivity was lacking, thus we moved to the chelating substrates in Table 3. Of these, 2-phenylpyridine performed best, while the others afforded only modest yields of the desired coupling product (Table 3).

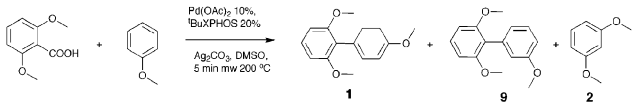
Table 3 Substrate scope for decarboxylative coupling with simple arenes[a]

Entry	Substrate	Yield (% Ar-Ar′)	Product	Yield (% ArH)
1		53 (2 isomers)	 *para* - **9a** *meta* - **9b**	46
2		69	 **10**	36
3		31	 **1**	68
4		25	 **12**	72

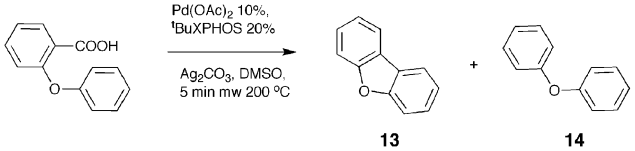
[a] Conditions: 350 μmol 2,6-dimethoxybenzoic acid, 280 μmol arene substrate, $Pd(OAc)_2$ 10%, Ag_2CO_3 (350 μmol), ^{t}Bu-XPhos (20%) and in 2 mL 9 : 1 DMF–DMSO, 0.200 g crushed 4 Å molecular sieves. The isolated yields reported are the average of two reactions.

For 2-phenylpyridine, the ^{t}Bu-XPhos was slightly superior to $AsPh_3$. Unlike the ArX–ArCOOH coupling reactions, the reproducibility of this reaction was somewhat variable, possibly due to heterogeneity as a result of the presence of the molecular sieves.

In an intramolecular case that would be expected to have enhanced selectivity, 2-phenoxybenzoic acid was chosen. As



Scheme 3



Scheme 4

shown in Scheme 4, this reaction yields the desired annulated product, dibenzofuran (**13**, 44% yield), as well as the protonated product, diphenyl ether (**14**, 52% yield).

In summary, microwave heating greatly enhances yields and shortens reaction time in decarboxylative coupling of substituted aromatic acids and either aryl iodides or arenes.

Notes and references

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