Coupling Reactions

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Decarboxylative Cross-Coupling of Aryl Tosylates with Aromatic Carboxylate Salts**

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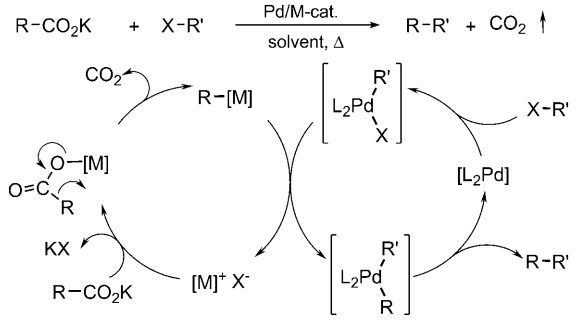
In memory of Keith Fagnou

Metal-catalyzed coupling reactions are effective synthetic tools for the formation of C–C bonds between nucleophilic and electrophilic substrates at positions predefined by leaving groups.[1] Recently, decarboxylative coupling reactions have emerged as powerful alternatives for regioselective C–C bond formation,[2] thus providing new protocols for Heck-type reactions,[3] oxidative arylations,[4] redox-neutral cross-coupling reactions,[5] and allylations.[6]

The redox-neutral decarboxylative coupling reactions that have been developed in our research group[5a] aim at replacing sensitive and costly organometallic reagents, which are traditionally used as nucleophilic coupling partners, with stable, inexpensive and widely available carboxylate salts.[5,7] In this type of reaction, a copper(I) or silver(I) catalyst mediates the extrusion of CO_2 from the carboxylates while a palladium complex catalyzes the coupling of the resulting carbon nucleophiles with carbon electrophiles (Scheme 1).

In view of the high performance level of traditional cross-couplings, a widespread practical application of decarboxylative couplings hinges on a broad substrate scope, the use of inexpensive and readily available carbon electrophiles, and mild reaction conditions. The early protocols allowed the coupling of diversely functionalized *ortho*-substituted benzoates, heterocyclic arenecarboxylates, and α-oxocarboxylates with a wide variety of aryl and heteroaryl halides.[5,8,9] However, the strongly coordinating halide ions that were formed in the process were found to impede the decarboxylation of other arenecarboxylates.[5b] A decisive extension of the substrate scope covering the full range of substitution patterns including *meta*- and *para*-substituted arenecarboxylates was achieved by new catalysts that allowed the use of aryl triflates as carbon electrophiles.[10] The coupling of these substrates releases only noncoordinating anions that do not hinder the decarboxylation at the copper center.[5b] Unfortunately, the practical utility of this protocol is limited by the expense and the sensitivity of aryl triflates.



Scheme 1. Cu/Pd-catalyzed decarboxylative cross-coupling. M = Ag, Cu; R = (hetero)aryl, vinyl, acyl; R′ = (hetero)aryl; X = I, Br, Cl, OTf. Tf = trifluoromethanesulfonyl.

The use of the inexpensive and more robust aryl *p*-toluenesulfonates (tosylates) is of profound interest for all types of cross-coupling reactions, and substantial effort has been devoted to the development of catalyst systems capable of activating them.[11] In earlier protocols, nickel complexes were mostly used as catalysts,[12] until a new class of bulky, electron-rich phosphines was discovered that strongly facilitates the oxidative addition of aryl tosylates to palladium catalysts.[13] In recent years, aryl tosylates have successfully been employed as substrates in, for example, Stille,[14] Suzuki,[15] and Kumada coupling reactions,[16] aminations,[17] and *ortho*-arylations.[18]

The use of aryl tosylates as substrates in decarboxylative coupling reactions should have an even higher synthetic impact, when considering that a low coordinating ability of the leaving group is an essential prerequisite for accessing the full range of carboxylic acid substrates.

We started the development of the catalyst for the desired decarboxylative cross-coupling (see Scheme in Table 1) with a series of protodecarboxylation reactions in the presence of phosphine ligands to identify phosphines that would not interfere with the decarboxylation step.[19] Fortunately, the conversion of 3-nitrobenzoic acid into nitrobenzene using Cu_2O/1,10-phenanthroline (phen) catalysts was not affected by the electron-rich, sterically demanding phosphines that are known to activate unreactive leaving groups (Scheme 2).

We next investigated the performance of palladium complexes with such ligands as catalysts in the decarboxylative coupling of potassium 2-nitrobenzoate (**1a**) with 4-tolyl tosylate (**2a**) in combination with a Cu_2O/phen co-catalyst (Table 1).

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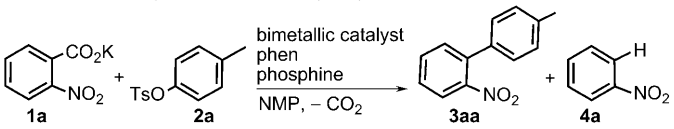
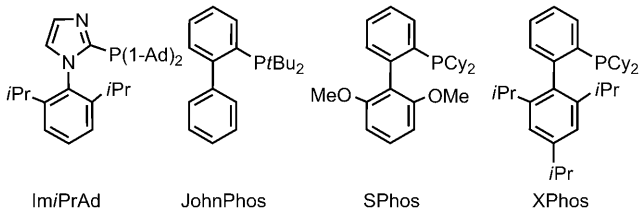
Table 1: Development of the catalyst system.[a]



Entry	Bimetallic catalyst		Phosphine	*t* [h]	**3aa** [%]	**4a** [%]
1	5% Cu_2O	$[Pd(acac)_2]$	*p*-tolBINAP	16	4	69
2	5% Cu_2O	$[Pd(acac)_2]$	Im*i*PrAd	16	9	86
3	5% Cu_2O	$[Pd(acac)_2]$	JohnPhos	16	7	87
4	5% Cu_2O	$[Pd(acac)_2]$	SPhos	16	21	66
5	5% Cu_2O	$[Pd(acac)_2]$	XPhos	16	48	39
6[b]	5% Cu_2O	$NiBr_2$	PPh_3	16	0	99
7	5% Cu_2O	$[NiBr_2(PPh_3)_2]$	PPh_3	16	0	99
8	5% Cu_2O	$[(1\text{-Np})NiBr(PPh_3)_2]$	PPh_3	16	0	92
9	2.5% Cu_2O	$[Pd(acac)_2]$	XPhos	16	63	0
10	1.3% Cu_2O	$[Pd(acac)_2]$	XPhos	16	65	10
11	2.5% Cu_2O	$[Pd(acac)_2]$	XPhos	8	72	0
12	2.5% Cu_2O	$[Pd(acac)_2]$	XPhos	4	76	0
13	2.5% Cu_2O	$PdBr_2$	XPhos	4	29	0
14	2.5% Cu_2O	$PdCl_2$	XPhos	4	58	0
15	2.5% Cu_2O	$Pd(OAc)_2$	XPhos	4	40	59
16	2.5% Cu_2O	$[Pd(dba)_2]$	XPhos	4	31	0
17[b]	2.5% Cu_2O	$[Pd(acac)_2]$	XPhos	16	0	0
18[c]	7.5% Cu_2O	$[Pd(acac)_2]$	XPhos	16	11	0
19[c,d]	7.5% Cu_2O	$[Pd(acac)_2]$	XPhos	0.1	52	0

[a] Reaction conditions: 1.00 mmol of **1a**, 2.00 mmol of **2a**, Cu/phen (1:1 ratio), 5 mol% of Pd- or Ni-source, 7.5 mol% of phosphine, 4 mL of NMP, 170°C. Yields determined by GC analysis using *n*-tetradecane as the internal standard. [b] 15 mol% of PPh_3. [c] 1.00 mmol of **1b**. [d] μW at 190°C/150 W/5 min. dba = *trans*,*trans*-dibenzylideneacetone, NMP = *N*-methylpyrrolidone, 1-Np = 1-naphthyl, phen = 1,10-phenanthroline, *p*-tolBINAP = 2,2′-bis(di(4-tolyl)phosphino)-1,1′-binaphthyl, Ts = 4-toluenesulfonyl.



Scheme 2. Electron-rich, sterically demanding phosphines. Cy = cyclohexyl.

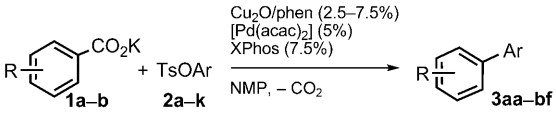
Even though all reactions were performed under rigorous exclusion of moisture, our first attempts mainly gave the protodecarboxylation product nitrobenzene (**4a**). A catalyst system generated from Cu_2O/phen and $[Pd(acac)_2]$/*p*-tolBINAP, which is very effective in the analogous transformation of aryl triflates, gave only trace quantities of the desired biaryl (**3aa**; Table 1, entry 1). Better yields were obtained with particularly bulky phosphines such as Beller's Im*i*PrAd ligand (entry 2).[20] With Buchwald's XPhos ligand,[13] biaryl **3aa** was formed in an encouraging 48% yield (entry 5). No product was obtained using nickel-based catalysts (entries 6–8).

We gradually lowered the copper/palladium ratio to achieve a better balance between the two catalytic cycles. This adjustment indeed resulted in reduced amounts of the protodecarboxylation by-product, until at a 1:1 ratio, only trace quantities of nitrobenzene (**4a**) were observed (entries 9 and 10). Shortening the reaction time to 4 hours led to a further increase in yield (compare entry 9 with entries 11 and 12). Further experiments confirmed Cu_2O and $[Pd(acac)_2]$ to be the most effective catalyst precursors, although other palladium(II) or palladium(0) compounds can be used as well (entries 13–16).

In contrast to the protocols involving aryl halides as electrophiles, the coupling of aryl tosylates is not limited to *ortho*-substituted benzoates. With a slightly modified protocol, that is, employing an increased copper/palladium ratio of 3:1 and microwave irradiation, satisfactory yields were also achieved in the coupling of 3-nitrobenzoate (**1b**) with 4-tolyl tosylate (entry 19).

Having thus identified two complementary protocols for the coupling of activated and non-activated carboxylic acid salts, respectively, we probed their scope with regard to the electrophilic coupling partner (Table 2). The reactions were performed with either 2-nitrobenzoate (**1a**) or with 3-nitrobenzoate (**1b**). Both reaction protocols are broadly applicable

Table 2: Scope with regard to the electrophilic partner.[a]



Product	Yield [%]	Product	Yield [%]
3aa	Δ: 73 μW: 59	**3ab**	Δ: 71 μW: 64
3ac	Δ: 91 μW: 70	**3ad**	Δ: 53 μW: 40
3ae	Δ: 39 μW: 85	**3af**	Δ: 75 μW: 69
3ag	Δ: 83 μW: 76	**3ah**	Δ: 76 μW: 59
3ai	Δ: 66 μW: 62	**3aj**	Δ: 49 μW: 49
3ak	Δ: 33 μW: 42	**3ba**	μW: 59[b]
3bc	μW: 52[a]	**3bf**	μW: 51[b]

[a] Reaction conditions: Δ: 170°C, 4 h; μW: 180°C/100 W/2 min. For details, see the Supporting Information. [b] 15 mol% of Cu, 190°C/150 W/5 min.

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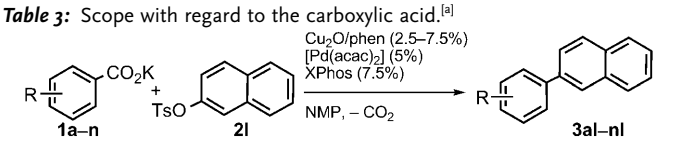
with regard to the aryl tosylate coupling partners. Electron-rich and electron-poor electrophiles were coupled in good yields, and various functionalities including aldehydes, ketones, esters, tertiary amino groups, and even nitrogen heterocycles were tolerated.

The scope of the new protocols, with regard to the carboxylate substrates, was tested using 2-naphthyl tosylate (**2l**), which is an easy-to-purify, crystalline solid. For activated carboxylates, the reaction conditions optimized for the conversion of 2-nitrobenzoate (**1a**) were employed, whereas the reaction conditions for 3-nitrobenzoate (**1b**) were used for all other carboxylates. As can be seen from Table 3, a broad range of arenecarboxylic acid salts including *ortho*-, *meta*-, and *para*-substituted benzoates as well as heterocyclic carboxylates was successfully converted. Decarboxylative coupling reactions of aryl tosylates are thus similarly broadly applicable as those of aryl triflates, but at substantially reduced cost.

Overall, an important milestone has been achieved in the field of decarboxylative cross-coupling chemistry by enabling the use of tosylates as carbon electrophiles. Ongoing work is directed towards incorporating recently discovered low-temperature decarboxylation catalysts[21] into such cross-coupling protocols with the goal of lowering the reaction temperatures below 120 °C.

Table 3: Scope with regard to the carboxylic acid.[a]



Product	Yield [%]	Product	Yield [%]
3al	Δ: 84 μW: 97	**3cl**	Δ: 76 μW: 79
3dl	Δ: 76 μW: 80	**3el**	Δ: 96 μW: 99
3fl	Δ: 62 μW: 78	**3gl**	μW: 78
3hl	Δ: 24 μW: 99	**3il**	μW: 53[b]
3bl	μW: 60[b]	**3jl**	μW: 53[b]
3kl	μW: 74[b]	**3ll**	μW: 89[b]
3ml	μW: 37[b]	**3nl**	μW: 46[b]

[a] Reaction conditions: Δ: 170 °C, 4 h; μW: 180 °C/100 W/2 min. For details, see the Supporting Information. [b] 15 mol% of Cu, 190 °C/150 W/5 min.

Experimental Section

Preparative-scale synthesis of 2-(2-nitrophenyl)naphthalene (**3al**): An oven-dried, nitrogen-flushed vessel was charged with potassium 2-nitrobenzoate (**1a**; 2.05 g, 10.0 mmol), copper(I) oxide (36.9 mg, 0.25 mmol), 1,10-phenanthroline (90.1 mg, 0.50 mmol) palladium(II) acetylacetonate (152 mg, 0.50 mmol), and XPhos (358 mg, 0.75 mmol). Under an atmosphere of nitrogen, a degassed solution of 2-naphthyl-*p*-toluenesulfonate (**2l**; 5.97 g, 20.0 mmol) in NMP (30 mL) was added by syringe. The resulting reaction mixture was stirred at 170 °C for 4 h. After the reaction was complete, the mixture was cooled to room temperature, diluted with aqueous HCl (1N, 100 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/hexanes 1:20) yielding the corresponding biaryl **3al** [CAS: 94064-83-2] (1.98 g, 80 %).

The reactions in Table 2 and Table 3 were performed accordingly on smaller scales, and the products were purified by column chromatography on silica gel (ethyl acetate/hexane gradient). For full experimental procedures, see the Supporting Information.

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