Synthetic Methods

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Palladium/Copper-Catalyzed Decarboxylative Cross-Coupling of Aryl Chlorides with Potassium Carboxylates[**]

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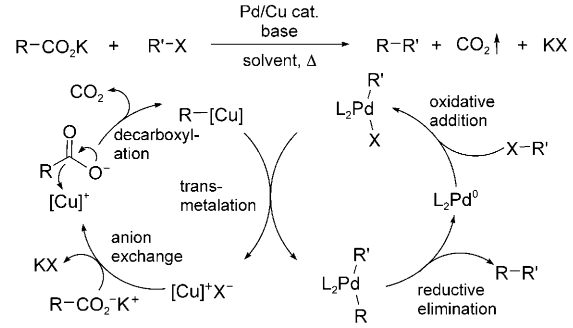
Over the last few decades, the formation of carbon–carbon bonds by the transition-metal-catalyzed cross-coupling of carbon nucleophiles with carbon electrophiles has evolved into a key synthetic approach for the construction of complex organic molecules.[1] The main reason for the success of this reaction type is that it enables the selective connection of even highly functionalized substrates at positions defined by two leaving groups of opposite polarity. Numerous cross-coupling procedures have been developed, for example, the Suzuki, Negishi, and Kumada reactions. A coupling reaction is therefore chosen for a given application on the basis of the availability, stability, and price of the required substrates and catalyst, as well as the efficiency, selectivity, and convenience of the reaction protocol.[2]

In this respect, organic chloride compounds are among the most attractive carbon electrophiles, particularly on industrial scale, because they are readily available in great structural diversity and at low cost.[3] Intensive research has resulted in the development of effective catalyst systems for the activation of the carbon–chlorine bond to enable efficient coupling with various organometallic compounds. Bulky, electron-rich ligands are usually used in these procedures for C–Cl bond activation, for example, phosphanes of the type described by the research groups of Buchwald,[4] Fu,[5] and Beller,[6] N-heterocyclic carbenes,[7] phosphites,[6] ferrocenyl phosphanes[8] or phosphine oxides,[9] or palladacycles.[10]

Although there are significant differences in the functional-group tolerance and reactivity of nucleophilic cross-coupling partners (e.g. organometallic compounds of the elements boron,[11] tin,[12] zinc,[13] copper,[14] or magnesium[15]), their availability and price are often comparable, as they are accessible by only a limited range of synthetic methods, which usually involve sensitive organometallic reagents.

In contrast to the above-mentioned cross-coupling reactions of preformed organometallic reagents, Pd/Cu-catalyzed decarboxylative cross-coupling reactions draw on widely available, stable, and inexpensive carboxylic acid salts as sources of the carbon nucleophile.[16,17] The extrusion of CO_2 from these substrates takes place within the coordination sphere of a copper/phenanthroline catalyst[18] to give organocopper intermediates, which are coupled directly with a carbon electrophile by a palladium cocatalyst. The proposed mechanism of this catalytic C–C bond formation is depicted in Scheme 1.



Scheme 1. Pd/Cu-catalyzed decarboxylative cross-coupling.

With such decarboxylative cross-coupling reactions, it should be possible to overcome some key limitations of traditional approaches. Their synthetic potential has been demonstrated for commercially important biaryl compounds, for example, valsartan and boscalid.[16,19] However, they have been developed to a far lesser extent than traditional C–C bond forming reactions, and improvements in substrate scope and reaction conditions are vital for them to become established as true synthetic alternatives. We report herein an important step in this direction, namely, the development of a second-generation catalyst that enables the use of non-activated aryl chlorides for the first time as substrates in decarboxylative cross-coupling reactions.

To identify an effective catalyst system for the decarboxylative cross-coupling of aryl chlorides, we chose the particularly demanding cross-coupling of electron-rich and therefore poorly reactive 4-chloroanisole with potassium 2-nitrobenzoate as a model reaction. We tested various combinations of copper and palladium salts, ligands, solvents, and reaction conditions (Table 1). As expected, our first-generation catalyst system consisting of copper iodide, 1,10-phenanthroline, and palladium(II) acetylacetonate, a system that was very effective in the analogous transformation of aryl bromides, displayed no activity in this test reaction (Table 1, entry 1).

The addition of bulky, electron-rich phosphanes to increase the electron-density at the palladium center appeared to be a promising strategy for creating a more active catalyst system and thereby facilitating an insertion into the stable carbon–chlorine bond.[20] However, our previous experiments with aryl bromides had revealed that

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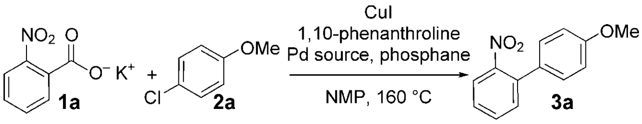
Table 1: Development of the catalyst system.[a]



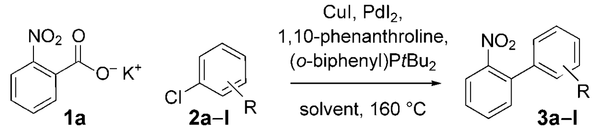
Entry	Pd source	Phosphane	Yield [%][b]
1	[Pd(acac)$_2$]	–	0
2	[Pd(acac)$_2$]	PPh$_3$	0
3	[Pd(acac)$_2$]	binap	13
4	[Pd(acac)$_2$]	P(*i*Pr)Ph$_2$	5
5	[Pd(acac)$_2$]	P*n*Bu$_3$	4
6	[Pd(acac)$_2$]	P*n*Oct$_3$	10
7	[Pd(acac)$_2$]	P*i*Pr$_3$	39
8	[Pd(acac)$_2$]	PCy$_3$	4
9	[Pd(acac)$_2$]	PCyp$_3$	30
10	[Pd(acac)$_2$]	P*t*Bu$_3$	21
11	[Pd(acac)$_2$]	(*o*-biphenyl)PCy$_2$	6
12	[Pd(acac)$_2$]	davephos	7
13	[Pd(acac)$_2$]	(*o*-biphenyl)P*t*Bu$_2$	60
14[c]	[Pd(acac)$_2$]	(*o*-biphenyl)P*t*Bu$_2$	38
15[d]	[Pd(acac)$_2$]	(*o*-biphenyl)P*t*Bu$_2$	48
16	[Pd(dba)$_2$]	(*o*-biphenyl)P*t*Bu$_2$	17
17	Pd(OAc)$_2$	(*o*-biphenyl)P*t*Bu$_2$	35
18	PdCl$_2$	(*o*-biphenyl)P*t*Bu$_2$	50
19	[Pd(F$_6$-acac)$_2$]	(*o*-biphenyl)P*t*Bu$_2$	53
20	PdBr$_2$	(*o*-biphenyl)P*t*Bu$_2$	62
21	PdI$_2$	(*o*-biphenyl)P*t*Bu$_2$	65

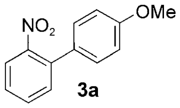
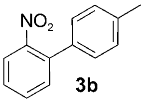
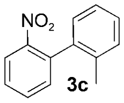
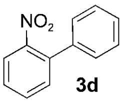
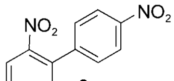
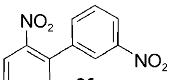
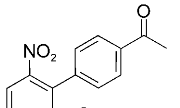
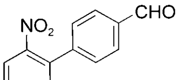
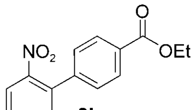
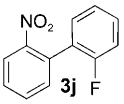
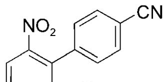
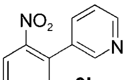
[a] Reaction conditions: CuI (2 mol%), Pd source (2 mol%), ligand (2 mol%; 1 mol% for bidentate ligands), 1,10-phenanthroline (2 mol%), NMP (1.5 mL), 160°C, 24 h. [b] Yields were determined by GC analysis with *n*-tetradecane as an internal standard. [c] Cu$_2$O (2 mol%) was used as the copper source. [d] The reaction was carried out in NMP/quinoline (3:1). acac = acetylacetonate, binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, Cy = cyclohexyl, Cyp = cyclopentyl, davephos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, dba = *trans*,*trans*-dibenzylideneacetone, NMP = 1-methyl-2-pyrrolidinone.

many phosphanes, particularly electron-rich phosphanes, also coordinate to the copper cocatalyst and retard the decarboxylation step. Therefore, the results of varying the phosphane do not follow a clear trend (Table 1, entries 2–13): Triaryl phosphanes and linear trialkyl phosphanes were almost ineffective, a somewhat higher yield was observed with moderately electron rich, sterically demanding triisopropylphosphane, and tricyclohexylphosphane and extremely bulky tri-*tert*-butylphosphane were again less effective. Particularly high yields were observed with the bulky monodentate ligand di(*tert*-butyl)biphenylphosphane, whereas some structurally related biphenylphosphanes were almost completely ineffective. We next varied the copper and palladium sources and found that the presence of halide counterions facilitates the reaction.[21] A catalyst system generated in situ from CuI and PdI$_2$ in combination with the ligands 1,10-phenanthroline and di(*tert*-butyl)biphenylphosphane was found to be optimal and mediated the desired transformation in good yields at a low catalyst loading of 2 mol% each of the copper and palladium precatalysts.

Having identified an efficient reaction protocol that enables the smooth cross-coupling even of particularly electron-rich 4-chloroanisole, we next investigated its scope with regard to the aryl chloride coupling partner. Both electron-rich and electron-poor aryl chlorides underwent smooth conversion when common functionalities, such as ester, ether, cyano, and formyl groups, were present as substituents on the aromatic ring, with the formation of compounds **3a–k** (Table 2). Moreover, the coupling of 3-chloropyridine with **1a** to give **3l** demonstrates that even basic nitrogen heterocycles are compatible with this transformation.

Table 2: Scope of the cross-coupling reaction with regard to the aryl chloride.[a]

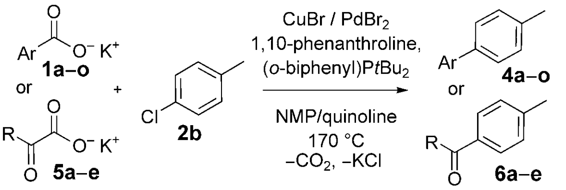


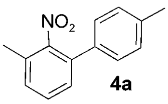
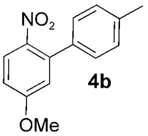
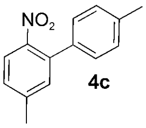
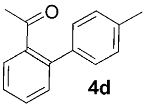
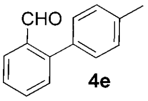
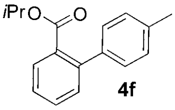
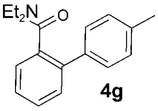
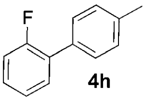
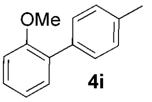
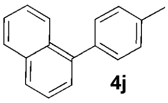
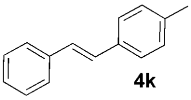
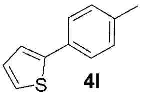
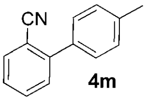
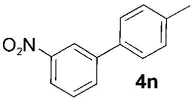
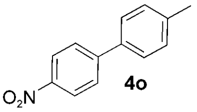
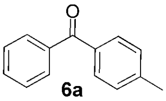
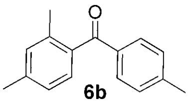
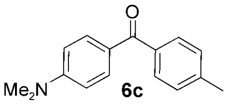
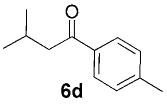
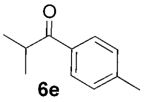
Product	Yield [%]	Product	Yield [%]
 **3a**	61	 **3b**	71
 **3c**	66	 **3d**	88[b,c]
 **3e**	71[b,c]	 **3f**	75[b]
 **3g**	55[b,c]	 **3h**	68[b]
 **3i**	66	 **3j**	81
 **3k**	83[b]	 **3l**	75

[a] Reaction conditions: CuI (2 mol%), PdI$_2$ (2 mol%), (*o*-biphenyl)P*t*Bu$_2$ (2 mol%), 1,10-phenanthroline (2 mol%), NMP (1.5 mL), 160°C, 24 h. [b] The reaction was carried out in a mixture of NMP (1.5 mL) and quinoline (0.5 mL). [c] [Pd(acac)$_2$] (2 mol%) was used as the Pd source.

The scope of the procedure with regard to the carboxylate coupling partner was explored with 4-chlorotoluene as the carbon electrophile. The new catalyst system is effective in the coupling of all aromatic carboxylic acids that can currently be decarboxylated with a copper/phenanthroline system (Table 3): Besides potassium 2-nitrobenzoates, other *ortho*-substituted aromatic carboxylates, the heterocyclic derivative 2-thiophenecarboxylate, and potassium cinnamate were coupled smoothly with 4-chlorotoluene. The products were formed in the presence of the palladium (2 mol%) and copper catalysts (10 mol%) in yields that generally matched

Table 3: Synthesis of biaryl compounds and ketones with a range of carboxylic acids.[a]



Product	Yield [%]	Product	Yield [%]
 **4a**	80	 **4b**	76
 **4c**	75[b]	 **4d**	90[c]
 **4e**	70	 **4f**	65[d]
 **4g**	40	 **4h**	82[b]
 **4i**	65	 **4j**	53
 **4k**	82[b]	 **4l**	65[b]
 **4m**	47[d]	 **4n**	13[d]
 **4o**	traces	 **6a**	58[d]
 **6b**	28[d]	 **6c**	66[d]
 **6d**	73[d]	 **6e**	73[d]

[a] The part of the molecule that originates from the carboxylate is drawn on the left-hand side. Reaction conditions: CuBr (10 mol%), $PdBr_2$ (2 mol%), (*o*-biphenyl)P*t*Bu_2 (2 mol%), 1,10-phenanthroline (10 mol%), NMP (1.5 mL), quinoline (0.5 mL), 170°C, 24 h. [b] CuF_2 (10 mol%) was used as the copper source. [c] $[Pd(acac)_2]$ (2 mol%) was used as the Pd source. [d] The reaction was carried out by a modified method (see the Supporting Information).

or even exceeded those reported previously for the coupling of the corresponding aryl bromides. However, the reaction of non-*ortho*-substituted benzoic acids furnished the corresponding biaryl compounds **4n**,**o** in low yields, which never exceeded the amount of the copper catalyst used.[22]

We were pleased to find that the new catalyst system is effective without modification in our recently disclosed decarboxylative synthesis of aryl ketones.[23] In this transformation, acyl nucleophiles are generated from α-oxocarboxylates by extrusion of CO_2 at a copper catalyst and coupled directly with aryl halides by a palladium cocatalyst (Table 3, products **6a**–**e**). The selected examples show that the aryl bromide substrates used in the original procedure can be substituted for aryl chlorides with the new catalyst system without significant decreases in yield.

In summary, we have developed a new catalyst system for decarboxylative cross-coupling reactions that enables the use of non-activated aryl chloride substrates for the first time. The system is generated in situ from CuI, 1,10-phenanthroline, PdI_2, and di(*tert*-butyl)biphenylphosphane and is generally applicable to the synthesis of biaryl compounds from the salts of aromatic carboxylic acids, as well as to the synthesis of aryl ketones from α-ketocarboxylates. Current studies are directed towards the development of a new generation of copper cocatalysts, with which we hope to overcome the remaining limitations of our decarboxylative coupling reactions, particularly with respect to the range of carboxylic acid substrates that can be used.

Experimental Section

General procedure for the synthesis of **3a–l**: Compound **1a** (1.50 mmol), copper(I) iodide (0.02 mmol), 1,10-phenanthroline (0.02 mmol), palladium iodide (0.02 mmol), and di(*tert*-butyl)biphenylphosphane (0.02 mmol) were placed in an oven-dried 20 mL crimp-top vial equipped with a septum cap, and the reaction vessel was evacuated and filled with nitrogen three times. A stock solution of the aryl chloride **2a–l** (1.00 mmol) and the internal GC standard *n*-tetradecane (50 μL) in NMP (1.5 mL) was added with a syringe, and the resulting mixture was stirred at 160°C for 24 h, then poured into aqueous HCl (1N, 20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with a saturated solution of sodium hydrogen carbonate and then with brine, dried over $MgSO_4$, and filtered, and the solvents were removed in vacuo. Purification of the residue by column chromatography (SiO_2, ethyl acetate/hexane gradient) yielded the corresponding biaryl compound.

For detailed experimental procedures and spectroscopic data, see the Supporting Information.

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Keywords: aryl chlorides · carboxylic acids · cross-coupling · decarboxylation · palladium

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