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Low-Temperature Ag/Pd-Catalyzed Decarboxylative Cross-Coupling of Aryl Triflates with Aromatic Carboxylate Salts

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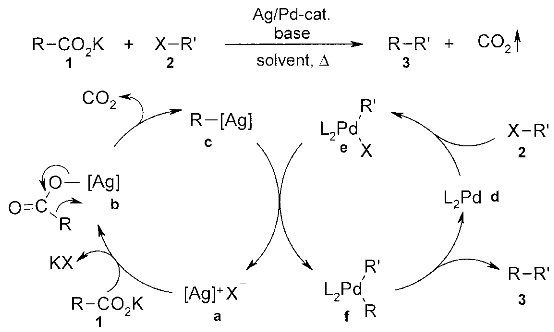
Metal-catalyzed decarboxylative couplings are evolving into powerful synthetic tools for the regioselective formation of C–C bonds. New protocols for Heck-type reactions,[1] oxidative arylations,[2] redox-neutral couplings,[3] and allylations[4] have provided innovative atom-economic and waste-minimized pathways among others to biaryls, vinyl arenes, and aryl ketones starting from readily available carboxylic acids.[5] These transformations have reached impressive performance levels in terms of selectivity, functional group tolerance, and yield.[6] However, their practical applicability is still somewhat limited by the high reaction temperatures currently required in the decarboxylation step.[7]

The redox-neutral decarboxylative cross-couplings developed in our group allow a regioselective C–C bond formation between aryl, heteroaryl, or acyl carboxylates and aryl halides to give biaryls or aryl ketones without resorting to stoichiometric amounts of organometallic reagents.[8] Instead, the carbon nucleophiles are generated in situ via extrusion of CO_2 at a copper- or silver-based decarboxylation catalyst.[9,3a] They are then transmetalated to the palladium catalyst, where their coupling with the aryl electrophile takes place (Scheme 1). The decarboxylation cocatalyst is vital for the conversion of most carboxylic acids. Only a few particularly reactive derivatives such as certain heteroarene-2-carboxylic acids[1] or monoalkyl oxalates[3d] can be coupled by palladium alone, presumably by a different mechanism. So far, silver-based systems have not presented advantages over copper ones in terms of reaction temperature or scope of decarboxylative cross-couplings. In contrast to copper(I), silver(I) had to be employed in overstoichiometric amounts, because a salt metathesis between the potassium carboxylates **1** and silver halides **a** formed within the catalytic cycle is impossible, precluding further turnover of the silver catalyst.[2a,3a,10]



Scheme 1. Ag/Pd-catalyzed decarboxylative cross-coupling. R = (hetero)aryl; R′ = (hetero)aryl; X = OTf, OTs.

However, when reevaluating the potential of silver catalysts for protodecarboxylation reactions, we discovered conditions under which silver salts mediate the extrusion of CO_2 from certain arenecarboxylates with higher efficiency than copper complexes.[11] The new silver-based protodecarboxylation proceeds at only 120 °C—a temperature more than 50 °C below that of the best known copper catalysts.[11] Larrosa et al. independently discovered a similar protocol.[12] In addition, we were able to show that decarboxylative cross-couplings can be performed using aryl electrophiles with non-coordinating leaving groups such as triflates[13] or tosylates.[14] We reasoned that the low affinity of these ions to silver(I) might enable the crucial salt metathesis between silver sulfonate salts **a** and potassium carboxylates **1** (Scheme 1). This prompted us to embark on the search for a new, low-temperature protocol for the decarboxylative cross-coupling of aryl sulfonates with potassium carboxylates using a Ag/Pd catalyst system.

We based the catalyst development on the model reaction of potassium 2-nitrobenzoate (**1a**) with 4-chlorophenyl triflate (**2a**) (see Table 1). Using a catalyst analogous to the copper-based version but employing Ag_2CO_3 (5 mol %) instead of Cu_2O/1,10-phenanthroline, modest turnover was ob-

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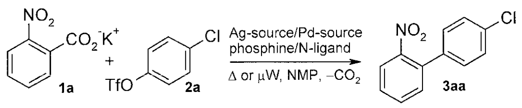
Table 1. Development of the catalyst system.[a]



Entry	Ag source	Pd source	Phosphine	N ligand	T [°C]	Yield [%]
1	Ag_2CO_3	PdI_2	P(*p*-Tol)$_3$	–	130	17
2	Ag_2CO_3	[Pd(acac)$_2$]	P(*p*-Tol)$_3$	–	130	6
3	Ag_2CO_3	[Pd(dba)$_2$]	P(*p*-Tol)$_3$	–	130	54
4	Ag_2CO_3	$PdBr_2$	P(*p*-Tol)$_3$	–	130	77
5	Ag_2CO_3	$PdCl_2$	P(*p*-Tol)$_3$	–	130	85
6	Ag_2CO_3	$PdCl_2$	–	–	130	0
7	Ag_2CO_3	$PdCl_2$	P(*p*-MeOC$_6$H$_5$)$_3$	–	130	73
8	Ag_2CO_3	$PdCl_2$	P(*o*-Tol)$_3$	–	130	0
9	Ag_2CO_3	$PdCl_2$	*i*PrPPh$_2$	–	130	55
10	Ag_2CO_3	$PdCl_2$	Tol-BINAP	–	130	75
11	Ag_2CO_3	$PdCl_2$	PPh_3	–	130	86
12	AgOAc	$PdCl_2$	PPh_3	–	130	67
13	AgOTf	$PdCl_2$	PPh_3	–	130	68
14	Ag_2O	$PdCl_2$	PPh_3	–	130	29
15	Ag_2CO_3	$PdCl_2$	PPh_3	phen	130	29
16	Ag_2CO_3	$PdCl_2$	PPh_3	pyridine	130	82
17	Ag_2CO_3	$PdCl_2$	PPh_3	DMAP	130	47
18	Ag_2CO_3	$PdCl_2$	PPh_3	2,6-lutidine	130	96
19[b]	Ag_2CO_3	$PdCl_2$	PPh_3	2,6-lutidine	130	74
20[b]	Ag_2CO_3	$PdCl_2$	PPh_3	2,6-lutidine	120	58
21[c]	Ag_2CO_3	$PdCl_2$	PPh_3	2,6-lutidine	130	80

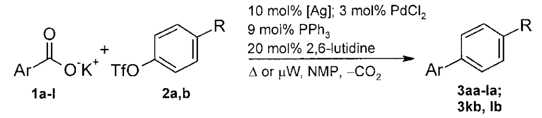
[a] Conditions: 1 mmol of potassium 2-nitrobenzoate (**1a**), 2 mmol of 4-chlorophenyl triflate (**2a**), 10 mol% of Ag source (5 mol% of Ag_2CO_3, Ag_2O), 3 mol% of Pd source, 9 mol% of phosphine (4.5 mol% for bidentate phosphines), 20 mol% of N ligand, 4.0 mL of NMP, 16 h. Yields determined by GC analysis using *n*-tetradecane as the internal standard. phen = 1,10-phenanthroline. [b] 4 h. [c] µW: 0.5 mmol of potassium carboxylate, 1 mmol of **2a**, 3 mL NMP, 130 °C/150 Watt/5 min.

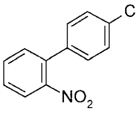
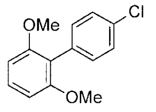
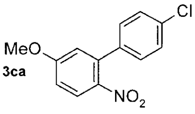
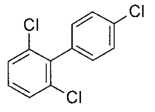
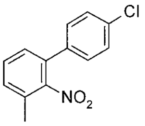
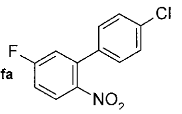
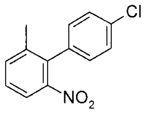
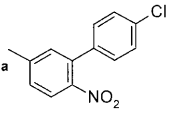
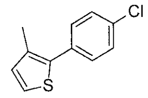
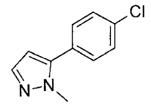
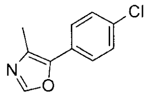
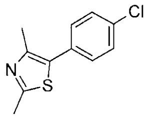
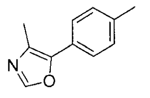
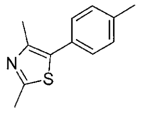
served already at a temperature of 130 °C (Table 1, entry 1). At such a low temperature, the corresponding Cu/Pd system had displayed almost no activity.

The nature of the palladium precursor had a profound influence on the catalyst performance. A switch to $PdCl_2$ resulted in an 85 % yield of the desired biaryl (Table 1, entries 2–5). The choice of phosphine also influenced the reaction outcome. Best results were obtained with P(*p*-Tol)$_3$ or the inexpensive PPh_3. The use of sterically demanding ligands such as P(*o*-Tol)$_3$ had an adverse effect on the decarboxylation step (Table 1, entries 6–11). Among the silver sources tested, silver carbonate gave the best results, but other silver salts may be used as well (Table 1, entries 12–14). The reaction works best in aprotic solvents such as *N*-methylpyrrolidone (NMP) or dimethylacetamide (DMAc). We also probed whether the activity of the silver catalyst could be enhanced by the addition of nitrogen ligands. Phenanthroline, which was the most effective ligand for copper, hampered the activity of silver. Better results were obtained with pyridine-type ligands, and near-quantitative yields were achieved with the sterically encumbered 2,6-lutidine (20 mol%) (Table 1, entries 15–18). The reaction is almost complete within 4 h (Table 1, entry 19), and moderate yields are achieved even at 120 °C (Table 1, entry 20). On small scales, it is advantageous to perform the reaction in a laboratory microwave. Only five minutes of microwave irradiation (130 °C, max 150 W) are sufficient to achieve 80 % yield of the biaryl **3aa** (Table 1, entry 21). In comparison, previous copper-based catalyst systems require 190 °C to reach such short reaction times.[13]

Under these optimized conditions (5 mol% Ag_2CO_3, 3 mol% $PdCl_2$, 9 mol% PPh_3, 20 mol% 2,6-lutidine, 130 °C), we investigated the scope of the new protocol with regard to the potassium carboxylate in its coupling with 4-chlorophenyl triflate (**2a**) (Table 2).

Table 2. Scope with regard to the carboxylate.[a]



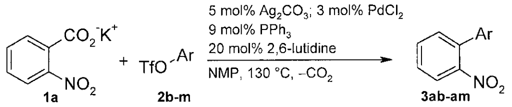
Product		Yield [%]	Product		Yield [%]
3aa		87	**3ba**		74
3ca		74	**3da**		76[b]
3ea		65[b]	**3fa**		92
3ga		84[c]	**3ha**		80[c]
3ia		56[c]	**3ja**		60
3ka		87	**3la**		80
3kb		89	**3lb**		75

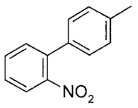
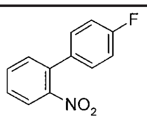
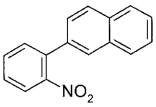
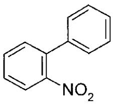
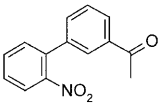
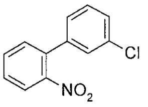
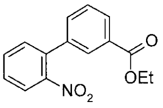
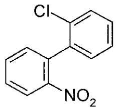
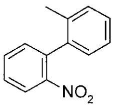
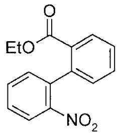
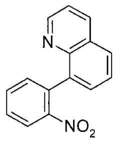
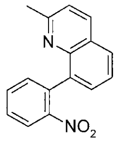
[a] Conditions: 1 mmol of potassium carboxylate, 2 mmol of aryl triflate, 5 mol% of Ag_2CO_3, 3 mol% of $PdCl_2$, 9 mol% of PPh_3, 20 mol% of 2,6-lutidine, 4 mL of NMP, 130 °C, 16 h, isolated yields. [b] 10 mol% of AgOTf. [c] µW: 0.5 mmol of potassium carboxylate, 1 mmol of triflate, 3 mL of NMP, 130 °C/150 Watt/5 min.

Aromatic carboxylates functionalized in the *ortho* position, for example, with chloro, nitro, or ether groups, were smoothly converted even at this low reaction temperature. A particular strength of the new catalyst is that it is suitable for the coupling of polychlorinated carboxylates, which do not turn over with copper-based catalysts. However, for the coupling of *meta-* and *para-* substituted carboxylates, the silver-based system is less effective than the copper-based one. Heteroarenes with the carboxylate group directly adjacent to any ring heteroatom were also coupled in high yields. The coupling of such compounds with other catalyst systems requires much higher temperatures (170 °C).[1] A benefit of the lower reaction temperature is that transesterification between the aryl triflates and nucleophilic benzoates is suppressed, so that the protodecarboxylation of the carboxylates by traces of residual water is the only remaining side reaction. While the heterobiaryls are thus formed more cleanly by using silver rather than at copper catalysts, the scope of the copper protocol is wider, because it includes heteroarenes with the carboxylate group in the 3-position.

As illustrated by the examples in Table 3, there are very few restrictions with regard to the aryl triflate coupling partner. Sterically demanding substrates, and triflates with common functionalities such as halides, esters, ketones, and heterocycles were all converted in high yields with potassium 2-nitrobenzoate (**1a**). The current performance limit is reached with ester, acyl, and nitro groups in the 4-positions of the aryl triflate. For such triflates of very acidic phenols, it was impossible to avoid transesterification even at the low temperatures used in this protocol.

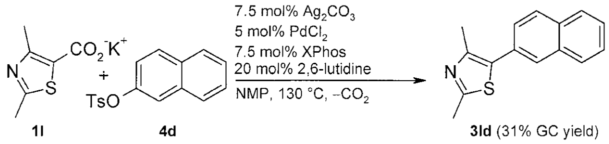
Table 3. Scope for the coupling of 2-nitrobenzoate with electrophiles.[a]



Product	Yield [%]	Product	Yield [%]
3ab 	73	3ac 	82
3ad 	72	3ae 	64
3af 	49	3ag 	72
3ah 	81	3ai 	36
3aj 	49	3ak 	76
3al 	64	3am 	25

[a] Reaction conditions: 1 mmol of potassium 2-nitrobenzoate (**1a**), 2 mmol of triflate, 5 mol % of Ag_2CO_3, 3 mol % of $PdCl_2$, 9 mol % of PPh_3, 20 mol % of 2,6-lutidine, 4 mL of NMP, 130 °C, 16 h, isolated yields.

We therefore probed whether more robust aryl tosylates could also be converted. With slight adaptations of the protocol, we were indeed able to obtain an encouraging 31 % yield of 5-(2-naphthyl)-2,4-dimethyl-1,3-thiazole (**3ld**) when coupling potassium 2,4-dimethyl-1,3-thiazole-5-carboxylate (**1l**) with 2-naphthyl tosylate (**4d**) (Scheme 2). Unfortunately, the currently most effective palladium ligand (XPhos) interferes with the decarboxylation step, so that further ligand design is required to bring this transformation to synthetic maturity.



Scheme 2. Successful coupling of an aryl tosylate.

Overall, we have developed a new Ag/Pd catalyst system that allows the decarboxylative biaryl synthesis of potassium arenecarboxylates and aryl triflates at only 120–130 °C. This low-temperature protocol, which is particularly suitable for halogenated and heterocyclic arenecarboxylate substrates, represents an important milestone in the evolution of decarboxylative cross-couplings into true synthetic alternatives to traditional couplings of preformed organometallic reagents.

Experimental Section

Preparative-scale synthesis of 4′-chloro-2-nitrobiphenyl (3aa) [CAS 6271-80-3]: An oven-dried, nitrogen-flushed 60 mL vessel was charged with potassium 2-nitrobenzoate (**1a**) (2.05 g, 10.0 mmol), silver carbonate (138 mg, 0.50 mmol), palladium(II) chloride (53.7 mg, 0.30 mmol), and triphenylphosphine (236 mg, 0.90 mmol). Under a nitrogen atmosphere, a degassed solution of 4-chlorophenyl triflate (**2a**) (5.21 g, 20.0 mmol) and 2,6-lutidine (214 mg, 2.0 mmol) in NMP (40 mL) was added by using a syringe. The resulting mixture was stirred at 130 °C for 8 h. After the reaction was complete, the mixture was cooled to room temperature, diluted with aqueous HCl ($1\,mol\,L^{-1}$, 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 (SiO_2, ethyl acetate/hexane 1:20) yielding the corresponding biaryl **3aa** (2.02 g, 87 %).

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Keywords: aryl triflates · carboxylic acids · cross-coupling · palladium · silver

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