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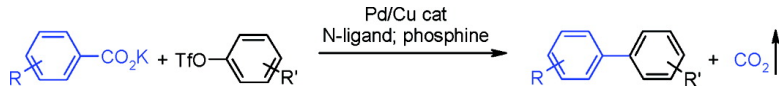

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Decarboxylative Biaryl Synthesis from Aromatic Carboxylates and Aryl Triflates

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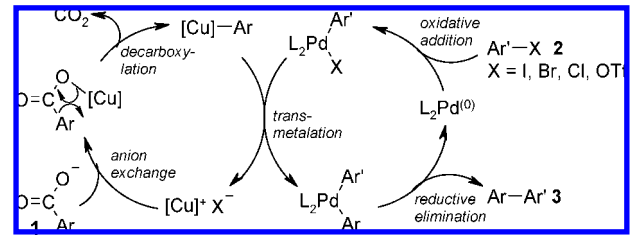
Metal-catalyzed cross-coupling reactions have become established as universal tools for C−C bond formation, in particular for the synthesis of unsymmetrical biaryls.[1] Typically, stoichiometric amounts of sensitive and costly organometallic reagents such as organoboron,[2] -tin,[3] -zinc,[4] -copper,[5] -silicon,[6] or -magnesium[7] compounds are coupled with organohalides or -pseudohalides under anaerobic conditions. As an alternative, we have introduced decarboxylative cross-couplings, in which carboxylic acid salts are converted into carbon nucleophiles by extrusion of CO_2 and directly coupled with carbon electrophiles.

The validity of this concept was demonstrated with a biaryl synthesis from aromatic carboxylates and aryl bromides or chlorides[8] and an analogous synthesis of aryl ketones from α-oxocarboxylates.[9] This approach combines the key benefit of regiospecificity with the broad availability, low cost, and easy handling of carboxylate substrates. These advantageous properties of carboxylic acid derivatives have triggered intense investigations of their uses as substrates in catalysis,[10] and over the past decade, a diverse set of reaction modes was discovered by Yamamoto,[11] Myers,[12] Forgione,[13] Dixneuf,[14] and us.[15]

Our decarboxylative biaryl synthesis is mediated by a bimetallic catalyst: A palladium complex inserts into the C−X bond of the aryl halide, while the extrusion of CO_2 from the carboxylate takes place within the coordination sphere of a copper-phenanthroline system, giving rise to an arylcopper species. In a transmetalation step, a diaryl-Pd species is formed that liberates the biaryl product via reductive elimination, thus regenerating the original Pd(0) species and closing the catalytic cycle for palladium. The copper halide formed alongside has to undergo salt metathesis with the potassium carboxylate to permit further turnover also of the decarboxylation catalyst (Scheme 1).

Mechanistic investigations revealed that the major limitation observed in the first-generation catalytic decarboxylative biaryl synthesis, namely its restriction to complexing substrates such as heterocyclic or ortho-substituted benzoic acids, is due to this thermodynamically unfavorable exchange of a halide for a nonortho-substituted benzoate derivative at the copper center.[16] A possible way to make catalytic decarboxylative couplings generally applicable to aromatic carboxylates regardless of their substitution pattern would be to find new ligands that increase the preference of the decarboxylation metal for carboxylate ions. While this is certainly imaginable for copper-based systems, such an approach is not likely to allow related Ag/Pd-mediated decarboxylative cross-coupling reactions to become catalytic in silver due to the stability of silver halides.[8b,17] We herein present an alternative solution to this problem: A new catalyst system was developed that allows the use of aryl triflates instead of aryl halides in decarboxylative cross-couplings. As the carboxylates will be able to successfully compete against the weakly coordinating triflate ions for coordination sites at the copper, the reaction is generally applicable to aromatic carboxylic acid salts regardless of their substitution pattern.

Scheme 1. Mechanism of the Decarboxylative Biaryl Synthesis



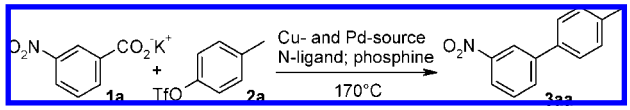
The challenge was to identify a ligand environment for the Pd that allows the activation of aryl triflates[18] and at the same time does not interfere with the Cu-mediated decarboxylation.[8b,16] We approached the search for an effective catalyst system using as a model reaction, the cross-coupling of 4-tolyl triflate (**2a**) with potassium 3-nitrobenzoate (**1a**), that we had been unable to couple with aryl halides using catalytic amounts of Cu and Pd.

A few key experiments selected from our investigation of various Cu and Pd salts, ligands, and conditions are displayed in Table 1. We were pleased to find that the replacement of 4-tolyl bromide with the corresponding triflate directly increased the reaction turnover from less than one to more than two with our first-generation system, CuI/1,10-phenanthroline and $Pd(acac)_2$ (entries 1, 2), thus confirming the viability of our strategy. The decisive factor in making the transformation effective was the choice of phosphine, and we found the sterically demanding, moderately electron-rich chelating phosphine Tol-BINAP to ideally stabilize the Pd while maintaining the decarboxylation activity of the Cu at the highest possible level (entries 3−8). Among the palladium sources tested, PdI_2 gave the best results, but other Pd salts may be used as well (entries 11, 13−15). The Cu cocatalyst is best generated from Cu_2O and 1,10-phenanthroline, which remained the best commercially available ligand (entries 8−11). The potassium carboxylate could also be generated in situ, although this gave slightly inferior yields (entry 19). Other metal cations were less effective (entry 12). Notably, the reaction was complete within 10 min at 190 °C when conducted in the microwave (entry 18). With the best catalyst system, the desired 3-nitro-4′-methylbiphenyl (**3aa**) was obtained in yields of up to 70% using 15 mol% Cu and 3 mol% Pd catalysts in the polar aprotic solvent NMP when employing excess triflate (entry 16).

This catalyst allows the decarboxylative coupling of 4-tolyl triflate with various aromatic and heterocyclic carboxylates in reasonable yields, regardless of their substitution pattern (Table 2). Notably, even thiophene-3-carboxylate (**1i**), which had been unreactive in a mechanistically distinct decarboxylative coupling,[13] was smoothly converted. The main side reactions observed were

10.1021/ja8050926 CCC: $40.75

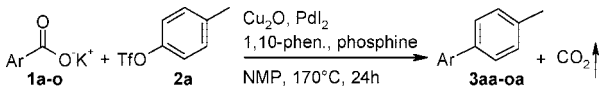
Table 1. Development of the Catalyst System[a]



entry	Cu source	Pd source	phosphine	yield/%
1[b]	CuI	$Pd(acac)_2$	–	11
2	”	”	–	34
3	”	”	$P(Ph)_3$	24
4	”	”	$P(p\text{-Tol})_3$	39
5	”	”	$P(Cy)_3$	28
6	”	”	BINAP	38
7	”	”	dppb	36
8	”	”	Tol-BINAP	47
9	CuBr	”	”	49
10	$CuCl_2$	”	”	14
11	Cu_2O	”	”	52
12[c]	”	”	”	11
13	”	$Pd(OAc)_2$	”	49
14	”	$Pd(dba)_2$	”	31
15	”	PdI_2	”	58
16[d]	”	”	”	70
17[d,e]	”	”	”	39
18[f]	”	”	”	59
19[f,g]	”	”	”	52

[a] *Reaction conditions*: 1 mmol of potassium 3-nitrobenzoate, 2 mmol of 4-tolyl triflate, 15 mol% Cu source (7.5 mol% for Cu_2O), 15 mol% 1,10-phenanthroline, 3 mol% Pd source, 9 mol% phosphine (4.5 mol% for bidentate), 4 mL of NMP, 170°C, 16 h. Yields determined by GC using *n*-tetradecane as internal standard. [b] 1 mmol of 4-bromotoluene instead of the triflate. [c] Sodium 3-nitrobenzoate instead of potassium 3-nitrobenzoate. [d] 24 h. [e] 1 mmol of 4-tolyl triflate. [f] Microwave, 190 °C, 10 min (see Supporting Information). [g] 3-Nitrobenzoic acid instead of potassium 3-nitrobenzoate, 0.55 mmol of K_2CO_3, 250 mg of 3 Å molecular sieves.

Table 2. Scope with Regard to the Carboxylate Substrates[a]



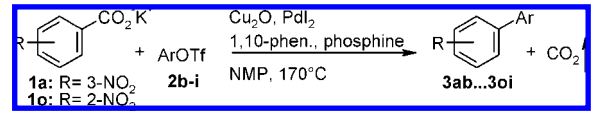
carboxylate	Ar	product	yield/%
1a	3-NO_2-C_6H_4-	**3aa**	72 (61)[b]
1b	4-NO_2-C_6H_4-	**3ba**	68
1c	3-CN-C_6H_4-	**3ca**	52
1d	4-CN-C_6H_4-	**3da**	58
1e	3-Me-4-NO_2-C_6H_3-	**3ea**	62
1f	3-Cl-C_6H_4-	**3fa**	40
1g	4-MeC(O)NH-C_6H_4-	**3ga**	53
1h	3-pyridinyl-	**3ha**	41
1i	3-thienyl-	**3ia**	54
1j	2-F-C_6H_4-	**3ja**	76
1k	2-MeC(O)-C_6H_4-	**3ka**	80
1l	2-MeO-C_6H_4-	**3la**	40
1m	2-thienyl-	**3ma**	75[c]
1n	2-furyl-	**3na**	75[c]
1o	2-NO_2-C_6H_4-	**3oa**	91[c]

[a] *Reaction conditions*: 1 mmol of potassium carboxylate, 2 mmol of 4-tolyl triflate, 7.5 mol% Cu_2O, 15 mol% 1,10-phenanthroline, 3 mol% PdI_2, 4.5 mol% Tol-BINAP, 4.0 mL of NMP, 170 °C, 24 h, isolated yields. [b] Microwave, 190 °C, 10 min (see Supporting Information). [c] 5 mol% Cu_2O, 10 mol% 1,10-phenanthroline, 2 mol% PdI_2, 6 mol% $P(p\text{-Tol})_3$.

protodecarboxylation of the carboxylates and, for particularly nucleophilic benzoates (e.g., **1l**), their transesterification with the aryl triflates. For particularly reactive carboxylates (**1m**−**o**), the catalyst loading and reaction time can significantly be reduced, even when using the inexpensive but less active $P(p\text{-Tol})_3$ ligand.

Selected examples in Table 3 demonstrate that steric bulk and common functionalities including ethers, amides, nitro, nitriles, and heterocycles are tolerated also in the triflate coupling partner.

Table 3. Scope with Regard to the Triflate Coupling Partner[a]



carboxylate	triflate	Ar	product	yield/%
1a	**2b**	2-naphthyl-	**3ab**	62[b]
”	**2c**	3-Ac-C_6H_4-	**3ac**	58[b]
1o	**2b**	2-naphthyl-	**3ob**	98
”	**2d**	Ph-	**3od**	91
”	**2e**	4-MeO-C_6H_4-	**3oe**	83
”	**2f**	2-Me-C_6H_4-	**3of**	79
”	**2g**	4-EtC(O)-C_6H_4-	**3og**	45
”	**2h**	4-Cl-C_6H_4-	**3oh**	91
”	**2i**	quinoline-8-yl-	**3oi**	80

[b] 7.5 mol% Cu_2O, 15 mol% 1,10-phenanthroline, 3 mol% PdI_2, 4.5 mol% Tol-BINAP, 8.0 mL of NMP, 24 h. [a] *Reaction conditions*: 1 mmol of potassium carboxylate, 2 mmol of triflate, 5 mol% Cu_2O, 10 mol% 1,10-phenanthroline, 2 mol% PdI_2, 6 mol% $P(p\text{-Tol})_3$, 4.0 mL of NMP, 170°C, 1 h, isolated yields.

Overall, by enabling the use of triflates as carbon electrophiles, a critical limitation of the original decarboxylative biaryl synthesis has been overcome, namely its restriction to ortho-substituted benzoates. Ongoing work is directed toward replacing 1,10-phenanthroline with a customized ligand with the goal of enhancing the decarboxylation activity of the copper, to allow for milder reaction conditions and further widen the substrate scope.

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Supporting Information Available: Experimental data and procedures for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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