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Biaryl and Aryl Ketone Synthesis via Pd-Catalyzed Decarboxylative Coupling of Carboxylate Salts with Aryl Triflates

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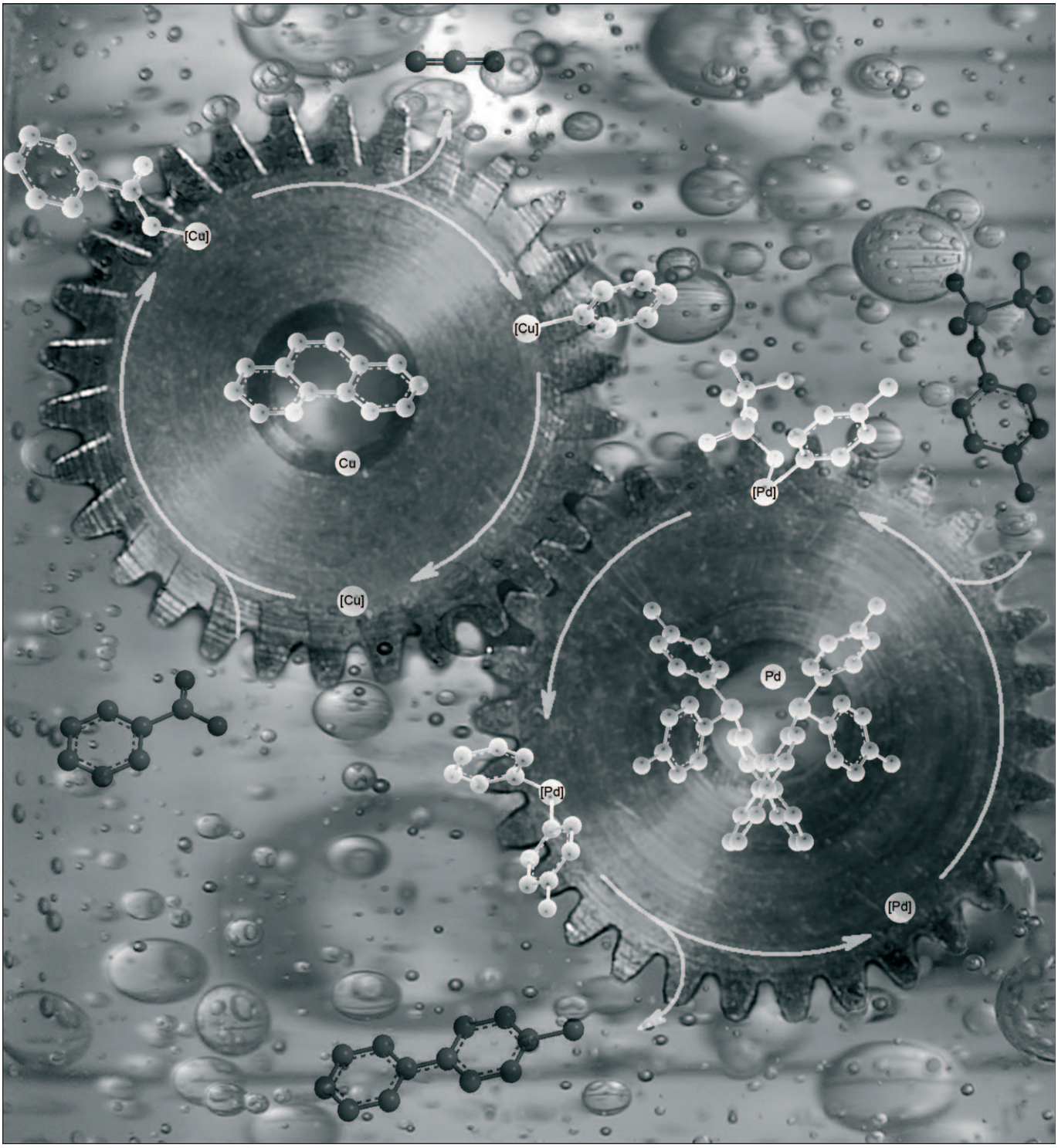


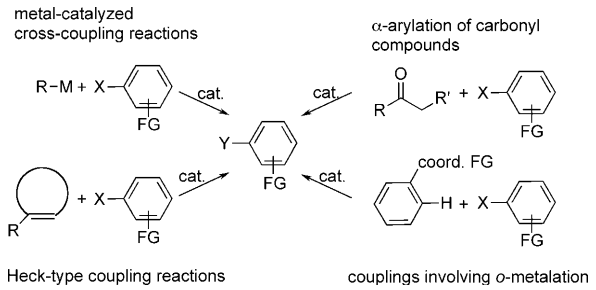
Abstract: A bimetallic catalyst system has been developed that for the first time allows the decarboxylative cross-coupling of aryl and acyl carboxylates with aryl triflates. In contrast to aryl halides, these electrophiles give rise to non-coordinating anions as byproducts, which do not interfere with the decarboxylation step that leads to the generation of the carbon nucleophilic cross-coupling partner. As a result, the scope of carboxylate substrates usable in this transformation was extended from *ortho*-substituted or otherwise activated derivatives to a broad range of *ortho*-, *meta*-, and *para*-substituted aromatic carboxylates. Two alternative protocols have been optimized, one involving heating the substrates in the presence of Cu^{I}/1,10-phenanthroline (10–15 mol%) and PdI_2/phosphine (2–3 mol%) in NMP for 1–24 h, the other involving Cu^{I}/1,10-phenanthroline (6–15 mol%) and $PdBr_2$/Tol-BINAP (2 mol%) in NMP using microwave heating for 5–10 min. While most products are accessible using standard heating, the use of microwave irradiation was found to be beneficial especially for the conversion of non-activated carboxylates with functionalized aryl triflates. The synthetic utility of the transformation is demonstrated with 48 examples showing the scope and limitations of both protocols. In mechanistic studies, the special role of microwave irradiation is elucidated, and further perspectives of decarboxylative cross-couplings are discussed.

Keywords: aryl triflates · carboxylic acids · cross-coupling · homogeneous catalysis · palladium

Introduction

The development of new synthetic methods has always been a key area of organic chemistry. The principal aim is to refine and extend the existing network of synthetic transformations by adding new paths to access valuable products from diverse starting points, by integrating renewable raw materials, and by improving the performance and sustainability of available synthetic steps. As a result, an increasing number of target molecules are becoming accessible in fewer and safer steps, higher yields and with less waste, starting from inexhaustible base chemicals. In the area of carbon–carbon bond formation, the regiospecificity, tolerance of functional groups and reduction of byproducts and waste has steadily been improved by the discovery of and constant progress in metal-catalyzed cross-coupling technology,[1] and the ongoing development of better reaction variants and catalysts. In these transformations, organometallic reagents, for example, organoboron,[2] -tin,[3] -zinc,[4] -copper,[5] -silicon[6] or -magnesium[7] compounds, are coupled with organohalides or pseudohalides at positions predefined by the two complementary leaving groups. Modern protocols reach impressive performance levels in terms of selectivity, functional group tolerance, and yield. However, their inherent weakness lies in the necessity to generate stoichiometric organometallic reagents in a separate step that are to be used as the carbon nucleophiles.

This drawback can be overcome with alternative methods for carbon–carbon bond formation in which the carbon nucleophile is generated under formal C–H activation at a metal catalyst.[8] Examples include Heck reactions,[9] Sonogashira couplings,[10] α-arylations of carbonyl compounds,[11] and couplings initiated by catalytic *ortho*-metallation steps (Scheme 1).[12] Unfortunately, most of these transformations proceed regiospecifically only for a limited range of substrate types.



Scheme 1. Strategies for aromatic carbon–carbon bond formation. M = B, Mg, Si, Zn, Cu, Sn, etc.; X = halogen, OSO_2R'', OMe, $OC(O)R''$, etc.; Y = carbon residue.

In the context of our work on the use of carboxylic acids as substrates in homogeneous catalysis,[13] we developed decarboxylative cross-couplings as an alternative strategy for C–C bond formation. In this reaction type, the carbon nucleophiles are generated in situ by a catalytic decarboxylation of carboxylate salts and cross-coupled with carbon electrophiles.[14] It maintains the advantage presented by traditional cross-couplings of being able to predefine the position of carbon–carbon bond formation by leaving groups, while obviating the need for stoichiometric organometallic reagents. Based on elemental steps also found in the pioneering work on decarboxylation reactions by Cohen,[15] Nilsson,[16] and Myers,[17] we propose a reaction principle as illustrated in Scheme 2.

The reaction starts with the extrusion of CO_2 from a copper carboxylate **II** generated by salt exchange between a

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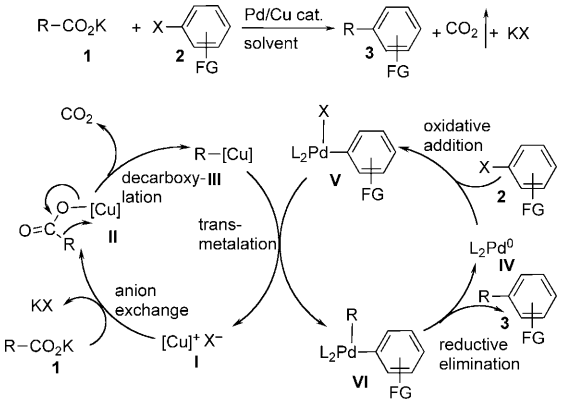


Scheme 2. Decarboxylative cross-coupling reactions; R = aryl, heteroaryl, vinyl, acyl; X = I, Br, Cl, OTf.

potassium carboxylate **1** and a copper(I)/1,10-phenanthroline catalyst **I**. The resulting organocopper species **III** transfers its carbon residue to an arylpalladium(II) complex **V** generated by oxidative addition of an aryl electrophile **2** to a palladium co-catalyst **IV**, giving rise to an organopalladium species **VI**, and liberating the copper(I)–phenanthroline salt **I**. The catalytic cycle for the palladium is closed by reductive elimination of the cross-coupled product **3** and regeneration of the initial palladium(0) species **IV**. The rate of the decarboxylation step strongly depends on the electronic nature of the carboxylate substrate, and a good balance of the rates of decarboxylation and cross-coupling is critical for minimizing side reactions and achieving good yields of the desired product.

In initial publications, the viability of this concept was demonstrated with the successful coupling of various aromatic carboxylates with aryl halides using a catalyst system consisting of 10 mol% of a $Cu^{I}Br$/1,10-phenanthroline catalyst along with 3 mol% palladium bromide.[14,18] Subsequently, the catalyst system has undergone continuous improvement, resulting, for example, in an extension of the substrate scope from aryl bromides to aryl chlorides.[19] Moreover, a novel aryl ketone synthesis was discovered based on an analogous decarboxylative coupling of α-oxocarboxylates with aryl halides.[20] In such decarboxylative cross-couplings, copper and silver can be employed as mediators for the decarboxylation step.[18,21] Becht et al. showed that the use of silver in overstoichiometric amounts is advantageous especially for methoxy-substituted arenecarboxylates.[22] Steglich,[23] Forgione and Bilodeau[24] discovered a different catalytic pathway for palladium-catalyzed decarboxylative cross-couplings, which is applicable specifically to five-ring heteroarenes bearing a carboxylate group in the 2-position. In their protocol, the carbopalladation presumably precedes the decarboxylation, so that the position of the carboxylate group is not the primary factor that defines the position of carbon–carbon bond formation.

Based on the proposed mechanism (Scheme 2), one would not expect to see such an inherent limitation regarding the substitution pattern at the arenecarboxylate salt for our decarboxylative cross-coupling protocol. Still, the initial procedures allowed the conversion only of *ortho*-substituted benzoates, heteroaromatic or otherwise activated derivatives. Subsequent mechanistic studies have indicated that this restriction is not intrinsic but a consequence of the strong affinity of the copper catalyst to the halide ions released in the cross-coupling step.[18,25]

Thus, the exchange of a halide ion for an arenecarboxylate at the copper center—required for catalytic turnover—is unfavorable unless aided by coordinating substituents in the vicinity of the carboxylate group. It will be a great challenge in future developments of the decarboxylation catalyst to overcome this limitation by designing ligand systems that induce a stronger preference for carboxylates over halide ions at the copper(I) center. An analogous strategy appears to be almost hopeless for silver-based decarboxylation systems considering the tremendous stability of silver halides.

We herein present a second strategy to surmount the above restriction for both copper- and silver-based systems. With newly designed palladium catalysts, we succeeded in activating and cross-coupling aryl triflates as carbon electrophiles with non-coordinating leaving groups. Because the triflate ions released in the process are unable to block the carboxylates out of the coordination sphere of the decarboxylation catalyst regardless of their substitution patterns, a much broader range of carboxylate substrates can be coupled with aryl triflates compared to aryl bromides. In a preliminary communication, we disclosed a first protocol with pertinent examples to demonstrate the viability of this approach.[26] In this full paper we give a detailed report of the catalyst development and the exploration of scope and limitations of the new transformation. Moreover, we present further studies leading to an improved protocol that proceeds within several minutes rather than hours, gives better yields compared to those reported with the initial procedure and allows the synthesis of many new examples.

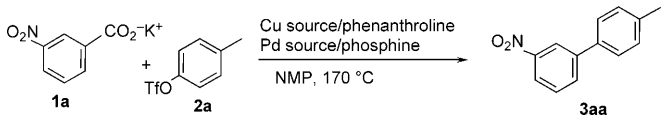
Results and Discussion

Aryl triflates have successfully been used as coupling partners in various transition metal-catalyzed reactions, for example, cross-couplings,[27] aminations,[28] cyanations,[29] and Heck-type couplings.[30] Their propensity to undergo oxidative addition is high, at a level comparable to that of aryl bromides.[31] As aryl triflates are generated from phenols, which in turn are usually accessed via different synthetic routes than aryl halides, they ideally complement the spectrum of substitution patterns available for the electrophilic coupling partner. Unfortunately, aryl triflates are prone to side reactions that are not observed for aryl halides, the most important being a cleavage of the triflate ester by water or nucleophiles under liberation of the corresponding phenol or phenyl ester. To ensure that the results obtained in the test reactions reflect only the catalyst performance and are not overlaid by such uncatalyzed background reactions, both model substrates for the desired decarboxylative

cross-coupling had to be chosen with great care. We decided to use 4-tolyl triflate (**2a**) as the electrophilic coupling partner, as this compound can be expected to be more hydrolytically stable than esters of more electron-deficient phenols. Nitro-substituted benzoates appeared to be an advantageous source of the nucleophilic coupling partner, because prior to decarboxylation the nucleophilicity of these electron-deficient carboxylates is relatively low, making them less likely to attack the aryl triflates via nucleophilic addition–elimination reactions.

Thus, we based our search for an effective catalyst system for the desired decarboxylative cross-coupling on the model reaction of potassium 3-nitrobenzoate (**1a**) with 4-tolyl triflate (**2a**), and evaluated various palladium cross-coupling catalysts in combination with Cu^{I}/1,10-phenanthroline decarboxylation co-catalysts. The key findings are summarized in Table 1, additional results having been disclosed in the preliminary communication.[26]

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



1a 2a 3aa

Entry	Cu source	Pd source	Phosphine	Yield [%]
1	CuI	$Pd(acac)_2$	$P(i\text{Pr})Ph_2$	15
2	CuI	$Pd(acac)_2$	$P(p\text{-Tol})_3$	39
3	CuI	$Pd(acac)_2$	BINAP	38
4	CuI	$Pd(acac)_2$	Tol-BINAP	47
5	Cu_2O	$Pd(acac)_2$	Tol-BINAP	52
6	Cu_2O	$Pd(dba)_2$	Tol-BINAP	31
7	Cu_2O	PdI_2	Tol-BINAP	58
8[b]	Cu_2O	PdI_2	Tol-BINAP	70
9[c]	Cu_2O	PdI_2	Tol-BINAP	59

[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 phosphines), 4 mL *N*-methylpyrrolidone (NMP), 170°C, 16 h. Yields determined by GC analysis using *n*-tetradecane as the internal standard. [b] 24 h reaction time. [c] Microwave heating: 190°C, 10 min (see Supporting Information).

The results illustrate that the choice of phosphine was the decisive factor for the successful development of this reaction (entries 1–4). This is not surprising as no coordinating anions are present to stabilize the palladium, so that it can only be held in solution if effectively stabilized by appropriate ligands.[32] In contrast to other cross-coupling reactions of triflates, in which the addition of excess halide salts is often beneficial, this was not an option here as the halides would have interfered with the decarboxylation step by coordinating to the copper, as discussed above. The best results were achieved using the electron-rich, chelating phosphine Tol-BINAP (entry 4), and the less expensive monodentate tri(*p*-tolyl)phosphine was also reasonably effective (entry 2). The copper and palladium precursors employed were less critical for the reaction outcome (entries 5–7): Copper(I) iodide and oxide were found to be almost equally suitable copper precursors, and while palladium(II) iodide was the most effective palladium source, other palladium(II) salts or palladium(0) precatalysts can also be used. With the best protocol resulting from these investigations, 3-nitro-4′-methylbiphenyl (**3aa**) was synthesized in 70% yield from potassium 3-nitrobenzoate (**1a**) and excess 4-tolyl triflate (**2a**) using 15 mol% Cu/1,10-phenanthroline and 3 mol% PdI_2/Tol-BINAP catalysts in the polar aprotic solvent NMP (entry 8). Our hypothesis that there is no intrinsic limitation of decarboxylative cross-couplings to 2-substituted carboxylate substrates is unambiguously validated by this result, proving that the substrate restrictions originally observed can be overcome when using aryl electrophiles with weakly coordinating leaving groups instead of aryl halides. However, the relatively harsh reaction conditions somewhat limit the preparative utility of this initial protocol.

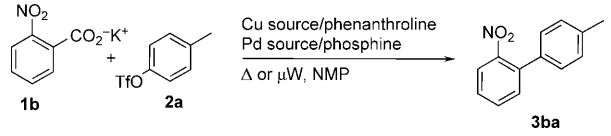
Inspired by reports on other transition-metal-catalyzed reactions[33] in which the reaction times could dramatically be shortened using microwave irradiation instead of conventional heating, for example, cross-couplings,[34] Buchwald–Hartwig aminations,[35] Heck reactions,[36] and decarboxylative couplings of five-ring heteroarenes,[24] we sought for a protocol that would allow decarboxylative cross-couplings to similarly benefit from the efficient heating that microwave irradiation provides. However, this proved to be a more complex modification than expected. We attribute this to the fact that in our decarboxylative coupling, two active metal catalysts need to concurrently be formed in situ, and their two interconnected catalytic cycles need to be microwave-accelerated to a similar extent in order to remain synchronized. Indeed, a closer inspection of relevant literature examples revealed that none of them involved two metals present only in catalytic amounts. For example, the seemingly related decarboxylative couplings that Forgione and Bilodeau successfully performed in a microwave reactor[24] proceed via a different mechanism that involves only a palladium catalyst without a co-catalyst. Crabtree et al. very recently disclosed a microwave-assisted protocol for an Ag/Pd-mediated decarboxylative coupling, but they had to use the decarboxylation catalyst in overstoichiometric amounts to achieve reasonable turnover.[37]

After intricate development of the reaction procedure, that is, limiting the microwave power to 150 W and preforming the catalyst before submitting it to microwave irradiation, we finally found a microwave-assisted protocol that allowed us performing our model reaction within only minutes at 190°C, rather than 16 h using conventional heating (Table 1, entry 9). Still, the yield remained lower than that achieved in the comparative experiment using conventional heating (see entry 8).

While evaluating the scope of the initial reaction protocol, we found that several substrate combinations gave unsatisfactory yields, presumably caused by thermal decomposition of the products. This prompted us to take another look at the alternative microwave-assisted protocol. To exclude that the limited success of our initial efforts was caused by an unfortunate choice of model substrates, we turned to potassi-

um 2-nitrobenzoate (**1b**) as the nucleophilic coupling partner this time, instead of the less reactive 3-nitrobenzoate (**1a**). The results of these screening reactions are summarized in Table 2.

Table 2. Development of a microwave-assisted reaction protocol.[a]



1b 2a 3ba

Entry	Cu Source	Pd Source	Phosphine	Yield [%]
1	Cu_2O	PdI_2	P(*p*-Tol)$_3$	83
2	Cu_2O	PdI_2	Tol-BINAP	74
3	Cu_2O	$PdBr_2$	P(*p*-Tol)$_3$	77
4	Cu_2O	$Pd(acac)_2$	P(*p*-Tol)$_3$	64
5[b]	Ag_2CO_3	$PdCl_2(PPh_3)_2$	PPh_3	52
6[c]	Cu_2O	PdI_2	P(*p*-Tol)$_3$	62
7[c]	Cu_2O	PdI_2	–	9
8[c]	Cu_2O	PdI_2	PPh_3	44
9[c]	Cu_2O	PdI_2	BINAP	52
10[c]	Cu_2O	PdI_2	Tol-BINAP	61
11[c]	Cu_2O	$PdBr_2$	Tol-BINAP	78
12[c]	Cu_2O	$PdCl_2$	Tol-BINAP	63
13[c]	Cu_2O	$Pd(acac)_2$	Tol-BINAP	80
14[c]	CuI	$Pd(acac)_2$	Tol-BINAP	79
15[c]	Cu_2O	$Pd(acac)_2$	P(*p*-Tol)$_3$	51
16[c,d]	Cu_2O	$Pd(acac)_2$	Tol-BINAP	81
17[e]	Cu_2O	$PdBr_2$	Tol-BINAP	80

[a] Reaction conditions: thermal conditions: 1 mmol of potassium 2-nitrobenzoate, 2 mmol of 4-tolyl triflate, 5 mol% Cu_2O, 10 mol% 1,10-phenanthroline, 2 mol% Pd source, 6 mol% phosphine (3 mol% for bidentate phosphines), 4.0 mL NMP, 170°C, 1 h. Yields determined by GC analysis using *n*-tetradecane as the internal standard. [b] 5 mol% Ag_2CO_3, 3 mol% $PdCl_2(PPh_3)_2$, 10 mol% PPh_3, 4 mL NMP 120°C, 16 h. [c] Microwave conditions: 3 mol% Cu source (1.5 mol% Cu_2O), 3 mol% 1,10-phenanthroline, 2 mol% Pd source, 6 mol% phosphine (3 mol% for bidentate phosphines), 1 mL NMP, 190°C/150 W/5 min. [d] 2.5 min reaction time. [e] 0.5 mmol potassium 3-nitrobenzoate, 1 mmol 4-tolyl triflate, 7.5 mol% Cu_2O, 15 mol% 1,10-phenanthroline, 2 mol% $PdBr_2$, 3 mol% Tol-BINAP, 3 mL NMP, 190°C/150 W/15 min.

Under thermal conditions (170°C), the best yields are obtained using Cu_2O/1,10-phenanthroline as the decarboxylation catalyst, and PdI_2/P(*p*-Tol)$_3$ as cross-coupling catalyst (entry 1). Remarkably, Tol-BINAP is slightly less effective for this substrate combination (entry 2). All other palladium and copper sources tested, including $Pd(acac)_2$, led to a decrease in yields (entries 3 and 4).

In the absence of halide ions, not only copper(I)- but also silver(I)-based decarboxylation mediators were found to be effective in catalytic amounts: After minimal optimization, a reasonable 52% yield was achieved using 5 mol% silver carbonate as a co-catalyst (entry 5). This is the first example of overstoichiometric turnover in a decarboxylative cross-coupling with a silver/palladium system based on the Ag^I employed, and, thus, an important milestone in the development of such alternative catalyst systems.

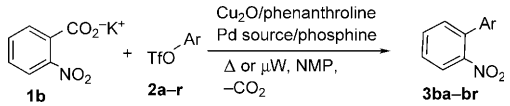
We then performed the reaction in the microwave with the optimized copper-based catalyst system, using the instrument settings and solvent amounts previously optimized for the coupling of potassium 3-nitrobenzoate (**1a**) with 4-tolyl triflate (**2a**) (see Table 1): In comparison to the thermal conditions, the concentration was increased by a factor of four to 1 mmol mL^{-1} to minimize the pressure buildup and still ensure homogeneity of the mixture. Moreover, the temperature was raised to 190°C using at most 150 W of microwave power, and the reaction time was reduced to 5 min. In order to keep the rate of decarboxylation in balance with the rate of cross-coupling, it was necessary to adjust the ratio of copper to palladium from 5:1 to 1.5:1. In doing so, we were able to reduce the amount of copper catalyst from 10 to 3 mol%, and still achieve an encouraging 62% yield of the biaryl **3ba** (entry 6). Careful reevaluation of the catalyst system revealed that Tol-BINAP and P(*p*-Tol)$_3$ were similarly effective in conjunction with PdI_2, and were superior to all other phosphines (entries 6–10). Variation of the palladium source led to the surprising discovery that under microwave conditions and with Tol-BINAP as the ligand, PdI_2 was no longer the optimal precursor, but that $PdBr_2$ and in particular $Pd(acac)_2$ gave better yields (entries 11–13). The copper source had a very limited influence on the reaction outcome (entry 14). Interestingly, P(*p*-Tol)$_3$, the most effective ligand under thermal conditions (entry 1), was now clearly inferior to Tol-BINAP (entries 13, 15). Under the best conditions, the reaction time could be reduced even further to 2.5 min, and a yield of 81% was achieved (entry 16). After this second round of catalyst optimization, the yields obtained were almost identical to those for thermal conditions despite the drastic reduction in both reaction time and loading of the decarboxylation catalyst.

Based on these findings, we also reevaluated the coupling of potassium 3-nitrobenzoate (**1a**) under microwave conditions. Replacing $Pd(acac)_2$ by $PdBr_2$ and slightly increasing the catalyst loading resulted in a very effective protocol for this non-activated carboxylate. Yields substantially higher than obtained with conventional heating were thus achieved (entry 17).

After having identified such effective protocols, we investigated the scope of the cross-coupling of potassium 2-nitrobenzoate (**1b**), an example representative of an activated carboxylate substrate, with various aryl triflates (Table 3). Under thermal conditions and using 10 mol% of copper and 2 mol% of palladium catalysts, all reactions were complete within one hour, and most products were obtained in good yields. A range of diversely functionalized substituents were tolerated, including ether, ester, formyl, keto, and pyridyl groups, fluorides, and chlorides. The yields were usually in the same range as for the corresponding aryl bromide substrates.[18]

In direct comparison, the microwave-assisted protocol was more effective for most substrates, as higher yields can often be obtained within only 5 min and using a lower loading of the copper catalyst (3 mol%). The current performance limit of both protocols is reached with ester, acyl, and nitro groups in the 2- and 4-positions of the aryl triflate. For such electron-deficient substrates, the thermal stability increasingly became a problem, so that triflate esters of even more

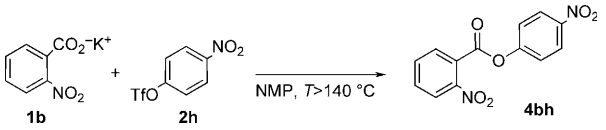
Table 3. Scope for the coupling of 2-nitrobenzoate with electrophiles.[a]



Product	Yield [%]	Product	Yield [%]
3ba	Δ: 91 μW: 84	**3bb**	Δ: 98 μW: 99
3bc	Δ: 83 μW: 87	**3bd**	Δ: 79 μW: 93
3be	Δ: 45 μW: 54	**3bf**	Δ: 30 μW: 23
3bg	Δ: 37 μW: 23	**3bh**	Δ: traces μW: 31
3bi	Δ: 99	**3bj**	Δ: 91
3bk	Δ: 91	**3bl**	Δ: 80
3bm	Δ: 79	**3bn**	Δ: 76
3bo	Δ: 75	**3bp**	Δ: 74
3bq	Δ: 64	**3br**	Δ: 63

[a] Reaction conditions: thermal (Δ): 1 mmol potassium 2-nitrobenzoate, 2 mmol triflate, 5 mol% Cu_2O, 10 mol% 1,10-phenanthroline, 2 mol% PdI_2, 6 mol% P(*p*-Tol)$_3$, 4 mL NMP, 170°C, 1 h, isolated yields; microwave (μW): 1.5 mol% Cu_2O, 3 mol% 1,10-phenanthroline, 2 mol% Pd(acac)$_2$, 3 mol% Tol-BINAP, 1 mL NMP, 190°C/150 W/5 min.

electron-deficient phenols were too unstable to even survive a few minutes of microwave heating. A control experiment confirmed that indeed, it is this thermal instability that accounts for the decreased yields, rather than the lack of catalyst performance. Thus, when heating 4-nitrophenyl triflate (**2h**) with potassium 2-nitrobenzoate (**1b**) above 140°C in the absence of a catalyst, the formation of 2-nitrobenzoic acid 4-nitrophenyl ester (**4bh**) is observed, which during workup partially hydrolyzes under formation of 4-nitrophenol (Scheme 3).



Scheme 3. Side reaction observed for electron-poor aryl triflates.

In order to further extend the scope to such electron-deficient carbon electrophiles, more active catalysts need to be developed that allow a conversion either at lower temperatures or of more stable sulfonates (see Scheme 5).

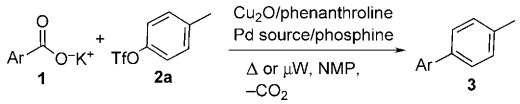
The scope of the reaction with regard to the carboxylate coupling partner was investigated next, using 4-tolyl triflate (**2a**) as the carbon electrophilic substrate (Table 4).

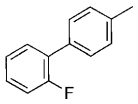
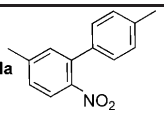
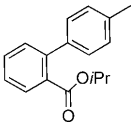
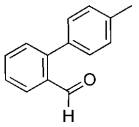
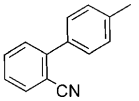
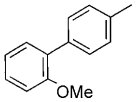
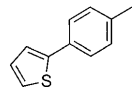
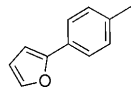
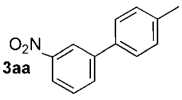
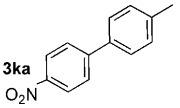
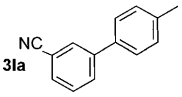
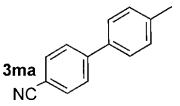
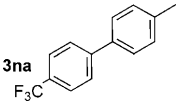
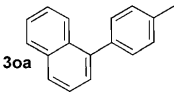
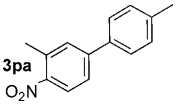
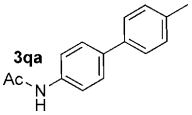
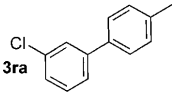
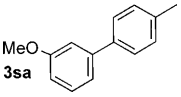
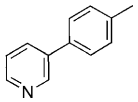
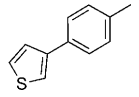
ortho-Substituted benzoates and five-ring heteroarene-2-carboxylates were cleanly coupled using both conventional heating (16 h, 170°C) with 10 mol% copper and 2 mol% palladium catalysts, and microwave irradiation (5 min, 190°C) with 5 mol% copper and 2 mol% palladium catalyst (entries 1–8). Both electron-donating and electron-withdrawing functional groups can be used as substituents in the *ortho*-position, including methoxy, acyl, formyl, and cyano groups. While the scope is reasonable for both protocols, it became increasingly evident that the microwave protocol is more effective: Even for particularly sensitive substrates such as **3ea** or **3sa**, moderate yields were obtained with this new protocol, whereas almost no conversion was observed with the thermal conditions. Moreover, the use of modern microwave technology, which involves the use of small, contained vessels, certified for pressure reactions, that are easy to degas and dry, is advantageous also from a practical standpoint as it makes delicate-to-perform decarboxylative cross-coupling reactions much simpler to carry out.

For the cross-coupling of the less reactive *meta*- and *para*-substituted carboxylates, we applied the conditions previously optimized for potassium 3-nitrobenzoate (**1a**), that is, conventional heating (24 h, 170°C) with 15 mol% copper and 3 mol% palladium catalysts, and microwave irradiation (15 min, 190°C) with 15 mol% copper and 2 mol% palladium catalysts (entries 9–20). Both protocols proved to be effective for the coupling of a broad range of benzoates bearing methyl, cyano, nitro, methoxy, and amide substituents, and even for potassium nicotinate as an example of a six-membered heterocycle. The successful coupling of potassium 3-thiophenecarboxylate illustrates that for this type of decarboxylative cross-coupling and in contrast to that of Bilodeau, five-membered heterocycles can be arylated not only in the 2- but also in the 3-position, underlining once again the mechanistic differences of both protocols.[24]

With the new microwave-based protocol, higher yields were achieved than with that involving conventional heating, and only few limitations remain: For particularly electron-rich *para*-substituted benzoates, for example, potassium 4-anisate, the desired biaryl product was observed only in trace quantities. Instead, the strong nucleophilicity of this electron-rich benzoate derivative facilitates the transesterification to such an extent that the resulting formation of 4-

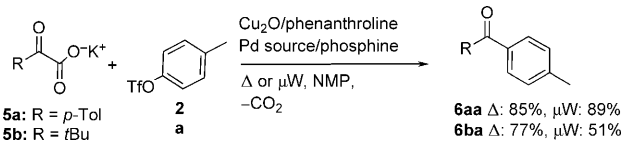
Table 4. Scope with regard to the carboxylate.[a]



Product	Yield [%]	Product	Yield [%]
3ca 	Δ: 76 μW: 73[b,c]	**3da** 	Δ: 72 μW: 73[b]
3ea 	Δ: 30 μW: 58[b]	**3fa** 	Δ: 45 μW: 54[b]
3ga 	Δ: 44 μW: 50[b]	**3ha** 	Δ: 40 μW: 40[b]
3ia 	Δ:75 μW: 82[b,c]	**3ja** 	Δ: 75 μW: 75[b,c]
3aa 	Δ: 72[d] μW: 84[e]	**3ka** 	Δ: 68[d] μW: 81[e]
3la 	Δ: 52[d] μW: 83[e]	**3ma** 	Δ: 58[d] μW: 76[e]
3na 	Δ: 44[d] μW: 74[e]	**3oa** 	Δ: 49[d] μW: 71[e]
3pa 	Δ: 62[d] μW: 69[e]	**3qa** 	Δ: 53[d] μW: 59[e]
3ra 	Δ: 40[d] μW: 59[e]	**3sa** 	Δ: 5[d,f] μW: 54[e]
3ta 	Δ: 41[d] μW: 50[e]	**3ua** 	Δ: 54[d] μW: 65[e]

[a] Reaction conditions: 1 mmol of potassium carboxylate, 2 mmol of 4-tolyl triflate, 5 mol% Cu_2O, 10 mol% 1,10-phenanthroline, 2 mol% PdI_2, 6 mol% P(*p*-Tol)$_3$, 4 mL NMP, 170°C, 16 h, isolated yields. [b] 2.5 mol% Cu_2O, 5 mol% 1,10-phenanthroline, 2 mol% Pd(acac)$_2$, 3 mol% Tol-BINAP, 1 mL NMP, 190°C/150 W/5 min. [c] 1 mmol of 4-tolyl triflate. [d] 7.5 mol% Cu_2O, 15 mol% 1,10-phenanthroline, 3 mol% PdI_2, 4.5 mol% Tol-BINAP, 24 h. [e] 0.5 mmol of potassium carboxylate, 1 mmol of 4-tolyl triflate, 7.5 mol% Cu_2O, 15 mol% 1,10-phenanthroline, 2 mol% $PdBr_2$, 3 mol% Tol-BINAP, 3 mL NMP, 190°C/150 W/10 min. [f] Yield determined by GC analysis using *n*-tetradecane as the internal standard.

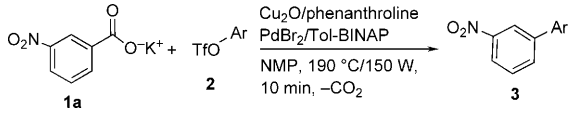
anisic acid 4-tolyl ester successfully competes with the desired cross-coupling. For such strongly nucleophilic carboxylates, this uncatalyzed background reaction becomes significant starting at temperatures above 140°C (see Scheme 3). Such remaining restrictions can probably be overcome with new catalyst generations operating at lower temperatures or, alternatively, by employing more robust aryl sulfonates (see Scheme 5).

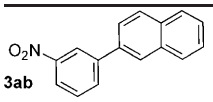
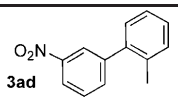
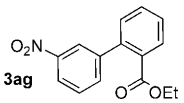
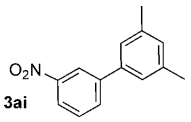
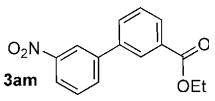
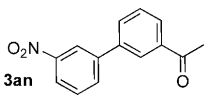
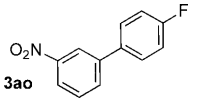
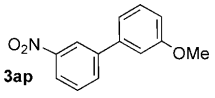


Scheme 4. Decarboxylative cross-coupling of α-oxocarboxylates with aryl triflates.

The above investigations revealed that whereas the coupling of non-*ortho*-substituted benzoates is certainly feasible, it is substantially more difficult than that of activated carboxylates. Beyond demonstrating future perspectives of the concept of decarboxylative couplings, it was our goal to probe the immediate synthetic value of the new transformation. Therefore, we decided to investigate to what extent non-activated carboxylates, as exemplified by potassium 3-nitrobenzoate (**1a**), can be coupled with triflate electrophiles (Table 5). We were pleased to find that this test substrate was successfully coupled with a sizeable number of variously substituted aryl triflates.

Table 5. Scope for the coupling of 3-nitrobenzoate with electrophiles.[a]

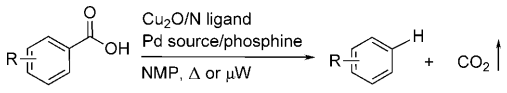


Product	Yield [%]	Product	Yield [%]
3ab 	74	**3ad** 	61
3ag 	34	**3ai** 	69
3am 	40	**3an** 	49
3ao 	64	**3ap** 	40

[a] Reaction conditions: 0.5 mmol of potassium 3-nitrobenzoate, 1 mmol of aryl triflate, 7.5 mol% Cu_2O, 15 mol% 1,10-phenanthroline, 2 mol% $PdBr_2$, 3 mol% Tol-BINAP, 3 mL NMP, 190°C/150 W/10 min, isolated yields.

Longer reaction times are required for such non-activated carboxylates, leading to increased thermal stress of the functionalized triflates. Expectedly, the undesired transesterification of the triflates was thus more strongly limiting, and several triflates did not tolerate the high reaction temperatures

Table 6. Effects of additives on the Cu-catalyzed protodecarboxylation.[a]



7a: R = 3-NO_2
7b: R = 4-CN
7c: R = 4-MeO

8

Entry	N Ligand	Pd Source	Pd Source	3-NO_2- (8a)	4-CN- (8b)	4-MeO (8c)
				Yield [%]		
1	–	–	–	28	10	0
2	1,10-Phen	–	–	50	89	39 (51)[b]
3	1,10-Phen	PdI_2	–	49	51	14
4	1,10-Phen	$Pd(dba)_2$	–	54	86	30
5	1,10-Phen	–	Tol-BINAP	35	13	0
6	1,10-Phen	PdI_2	Tol-BINAP	59	19	0
7	1,10-Phen	$Pd(dba)_2$	Tol-BINAP	49	40	11
8[c]	1,10-Phen	–	–	70	99	99
9[c]	1,10-Phen	PdI_2	Tol-BINAP	59	42	25

[a] Reaction conditions: 1 mmol of benzoic acid derivative, 7.5 mol% Cu_2O, 15 mol% N-ligand, 3 mol% Pd source, 4.5 mol% Tol-BINAP, 2 mL NMP, 170°C, 16 h. Yields were determined by GC analysis using *n*-tetradecane as the internal standard. [b] 15 mol% 4,7-diphenyl-1,10-phenanthroline instead of 1,10-phenanthroline. [c] 1 mL NMP, 190°C/150 W/5 min.

of the protocol involving conventional heating long enough to give satisfactory yields of the desired biaryl products. Fortunately, the newly developed microwave-assisted protocol was visibly more effective here, and a range of 3-nitro-substituted biaryls could be synthesized in moderate to good yields, allowing the conversion even of sensitive triflates bearing esters, fluoride, or keto groups.

The beneficial effect of microwave-induced heating was so profound in these last examples that we decided to perform a series of photodecarboxylation experiments to elucidate the reason for the strong acceleration of the decarboxylation step (Table 6).

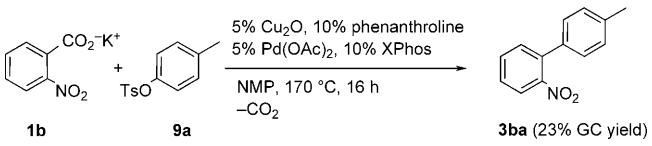
All these protodecarboxylation reactions were performed in parallel for three representative benzoic acids, 3-nitrobenzoic acid (**7a**) as an electron-poor, non-activated example, 4-cyanobenzoic acid (**7b**) as an electron-poor derivative substituted with a problematic coordinating group, and 4-methoxybenzoic acid (**7c**) as an electron-rich substrate. Upon heating the benzoic acids to 170°C over 16 h with Cu^I oxide in the absence of a nitrogen ligand, only low conversions were achieved for the decarboxylation of electron-deficient derivatives **7a** and **7b**, and the electron-rich compound **7c** showed no reaction at all (entry 1). When 1,10-phenanthroline was present in the mixture as a copper ligand, reasonable turnovers were obtained for all three derivatives, although the performance of especially developed protodecarboxylation catalysts was not quite reached (entry 2).[25] An addition of palladium(II) iodide did not significantly affect the turnover of 3-nitrobenzoic acid (**7a**), but had a strong influence on the decarboxylation of the less reactive derivatives **7b** and **7c** (entry 3). We attribute this to palladium(II) competing with copper(I) for the phenanthroline ligands, leading to a partial loss in activity of the copper decarboxylation catalyst. In contrast, no such effect was observed when instead of PdI_2, the palladium(0) precursor $Pd(dba)_2$ was added, which has a lower preference for amine ligands (entry 4). Tol-BINAP, the ligand used to stabilize the palladium cross-coupling catalyst, also has an adverse effect on the reaction turnover, presumably due to its coordination to the copper catalyst in competition with 1,10-phenanthroline (entry 5). The presence of a combination of PdI_2 and Tol-BINAP leaves the rate of decarboxylation unaffected for the 3-nitro derivative (**7a**), but depletes the yield for **7b** and shuts down the reaction altogether for **7c** (entry 6). This adverse effect of the palladium co-catalyst on the decarboxylation is less pronounced when a Pd^0 precursor is employed, and can most likely again be attributed to ligand-exchange reactions between Cu^I and Pd^{II} (entry 7). When performing a similar series of experiments for the microwave-assisted protodecarboxylation, such clear trends were no longer observed. In the control experiments (entry 8), all three carboxylic acids were quantitatively converted, and the respective arenes were detected in high yields. The presence of a Pd precursor and/or a phosphine ligand affected the decarboxylations, but to a much smaller extent than under thermal conditions, so that even for the least reactive derivative **7c**, the product, anisole (**8c**), was still detected in 25% yield (entry 9). This may indicate that the protodecarboxylation is strongly accelerated by microwave irradiation, whereas ligand exchange is not. Another interpretation of these findings is that under microwave irradiation, the palladium(II) catalyst is almost instantaneously reduced to palladium(0), which binds strongly to the Tol-BINAP ligand, so that much less of either species is available to interfere with the copper decarboxylation catalyst. Moreover, a decomposition of the palladium catalyst under liberation of phosphine should be less likely to occur in the short reaction time in the microwave, which would offer an additional explanation for the better yields achieved with the latter protocol.

We were especially pleased to find that the new catalyst not only allows the use of aryl triflates in the cross-coupling of aromatic carboxylates but also in our recently disclosed decarboxylative aryl ketone synthesis. In this transformation, α-oxocarboxylate salts are decarboxylated under formation of acyl nucleophiles,[20] which are then directly coupled with the aryl triflates to give the corresponding aryl ketones (Scheme 4). The representative examples illustrate that both aromatic and an aliphatic α-oxocarboxylate salts can be coupled in reasonable yields both using conventional heating and microwave irradiation.

Conclusions

Overall, the new protocol for the decarboxylative cross-coupling of potassium carboxylates with aryl triflates presents a powerful strategy for overcoming remaining substrate restrictions that had so far limited the practical applicability of decarboxylative couplings. It allows performing decarboxylative cross-couplings with a much broader range of aromatic carboxylates regardless of their substitution pattern, and thus gives additional evidence that previously observed restrictions of the substrate scope were due largely to the presence of coordinating halide anions in the reaction mixture. Moreover, it extends the scope of utilizable aryl electrophiles to phenol-derived compounds, which themselves are often accessed via fundamentally different synthetic routes than aryl halides. Many biaryls were shown to be accessible using standard heating, and with the use of microwave irradiation in combination with a specially adapted catalyst system, an even broader range of non-activated carboxylates was successfully coupled with various functionalized aryl triflates. The new catalyst systems also allow the coupling of α-oxocarboxylate salts with aryl triflates to give the corresponding ketones, which represents a substantial extension of this decarboxylative ketone synthesis.

As a next milestone towards establishing decarboxylative cross-couplings as true alternatives to traditional carbon–carbon bond forming methods based on preformed organometallic reagents, we see the development of improved catalysts that will allow using more robust and less expensive sulfonates, for example, mesylates or tosylates. These compounds can be expected to possess an enhanced stability against thermal decomposition and to be resistant against nucleophilic attack by electron-rich carboxylates, and their use could thus allow accessing the few product structures still outside of the protocols disclosed herein. Although we are a long way from having discovered a practical protocol for the conversion of these derivatives, first experiments have provided very encouraging results. For example, 23% of 4-methyl-2′-nitrobiphenyl (**3ba**) was formed when coupling potassium 2-nitrobenzoate (**1b**) with 4-tolyl tosylate (**9a**) using 10 mol% Cu^{I}/1,10-phenanthroline and 5 mol% $Pd(OAc)_2$/XPhos catalysts in NMP at 170 °C.



Scheme 5. First example of a successful coupling of an aryl tosylate.

Finally, the temperatures required by current catalyst systems for decarboxylative cross-couplings remain high. Having now established that such transformations have a much broader scope than originally perceived, the development of decarboxylation catalysts capable of operating at lower temperatures will be in the focus of our interest. This represents a greater challenge, but substantial progress was made over the last months. Since we have already succeeded in performing protodecarboxylations at temperatures of only 120 °C with a silver-based catalyst (Table 2), we are optimistic that with future catalyst generations, decarboxylative cross-couplings can soon routinely be performed in refluxing toluene.

Experimental Section

General methods: Reactions were performed in oven-dried glassware under a nitrogen atmosphere containing a Teflon-coated stirring bar and dry septum. All microwave irradiation experiments were carried out in oven-dried appropriate microwave process tubes (10 mL) equipped with Teflon-coated stirring bars and septum caps under an argon atmosphere. For the exclusion of atmospheric oxygen from the reaction media, three freeze-pump thaw cycles were preformed before the reagents were mixed. Solvents were purified by standard procedures prior to use. All reactions were monitored by GC using *n*-tetradecane as an internal standard. Response factors of the products with regard to *n*-tetradecane were obtained experimentally by analyzing known quantities of the substances. GC analyses were carried out using an HP-5 capillary column (phenyl methyl siloxane 30 m × 320 × 0.25, 100/2.3–30–300/3) and a time program beginning with 2 min at 60 °C followed by 30 °C min^{-1} ramp to 300 °C, then 3 min at this temperature. Column chromatography was performed using a Combi Flash Companion-Chromatography-System (Isco-Systems) and RediSep packed columns (12 g). NMR spectra were obtained on Bruker AMX 400 or on Bruker Avance 600 systems using $CDCl_3$, $[D_4]$MeOH and D_2O as solvents, with proton and carbon resonances at 400/600 MHz and 101/151 MHz, respectively. Mass spectral data were acquired on a GC-MS Saturn 2100 T (Varian). Microwave assisted reactions were performed using the Discover LabMate with CEM′s ChemDriver reaction monitoring software.

1-Methyl-2-pyrrolidone (NMP) was dried by removing water as a toluene azeotrope. Copper salts and palladium(II) iodide were dried in vacuo at 60 and 80 °C, respectively, prior to use. All potassium salts were dried for 2 h in vacuo at room temperature prior to use. All other compounds are commercially available and were used without further purification.

General procedure for the synthesis of potassium salts of the carboxylic acids (1a–u): A 250 mL, two-necked, round-bottomed flask was charged with the carboxylic acid (20.0 mmol) and ethanol (20.0 mL). To this, a solution of potassium *tert*-butoxide (2.24 g, 20.0 mmol) in ethanol (20.0 mL) was added dropwise over 2 h. After complete addition, the reaction mixture was stirred for another 1 h at room temperature. A gradual formation of a white precipitate was observed. The resulting solid was collected by filtration through a 7 cm Büchner funnel, washed sequentially with ethanol (2 × 10.0 mL) and cold (0 °C) diethyl ether (10.0 mL), transferred to a round-bottomed flask, and dried at 2×10^{-3} mmHg to provide the corresponding potassium salts of the carboxylic acids **1a–u** in 81–98% yield.

General procedure for the synthesis of aryl trifluoromethanesulfonates (2a–r): A solution of trifluoromethanesulfonic anhydride (4.00 mL, 24.0 mmol) in CH_2Cl_2 (10.0 mL) was added dropwise to a solution of the corresponding phenol (20.0 mmol) and pyridine (3.23 mL, 40.0 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C. After complete addition, the mixture was warmed to room temperature and allowed to stir for 1 h. The mixture was then diluted with Et_2O (30 mL), quenched with 10% aq. HCl and washed successively with sat. $NaHCO_3$ and brine. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the residue was purified by Kugelrohr distillation to give the trifluoromethanesulfonates **2a–r** in 79–99% yield.

General procedure for the biaryl synthesis under thermal conditions

Method A (activated carboxylates in Tables 3 and 4): An oven-dried, nitrogen-flushed 20 mL vessel was charged with the potassium carboxylate **1b–j** (1.00 mmol), copper(I) oxide (7.2 mg, 0.05 mmol), palladium(II)

iodide (7.2 mg, 0.02 mmol), 1,10-phenanthroline (18.0 mg, 0.10 mmol) and P(*p*-Tol)$_3$ (18.0 mg, 0.06 mmol). Under an atmosphere of nitrogen, a degassed solution of the aryl triflate (**2a**–**r**) (2.00 mmol) and the internal standard *n*-tetradecane (50 μL) in NMP (4 mL) was added via syringe. The resulting mixture was stirred at 170 °C for 1–16 h depending on the reactivity of the substrate. After the reaction was complete, the mixture was cooled to room temperature, diluted with aqueous HCl (1N, 10 mL) and extracted with ethyl acetate (3×20.0 mL). The combined organic layers were washed with water 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 gradient) yielding the corresponding biaryl.

Method B (non-activated carboxylates in Table 4): Method B is analogous to Method A, but with a higher loading of a modified catalyst and a reaction time of 24 h. The following amounts were used: potassium carboxylate (**1a**, **1k**–**u**) (1.00 mmol), copper(I) oxide (10.7 mg, 0.075 mmol), palladium(II) iodide (10.8 mg, 0.03 mmol), 1,10-phenanthroline (27.0 mg, 0.15 mmol), Tol-BINAP (30.5 mg, 0.045 mmol), 4-tolyl triflate (**2a**) (480 mg, 2.00 mmol), *n*-tetradecane (50 μL), and NMP (4 mL).

General procedure for the biaryl synthesis under microwave-assisted conditions

Method C (activated carboxylates in Table 3): An oven-dried, argon flushed 10 mL microwave vessel was charged with potassium 2-nitrobenzoate (**1b**) (1.00 mmol), copper(I) oxide (1.10 mg, 0.015 mmol), palladium(II) acetylacetonate (6.10 mg, 0.02 mmol), 1,10-phenanthroline (5.40 mg, 0.03 mmol) and Tol-BINAP (20.4 mg, 0.03 mmol). A degassed solution of the aryl trifluoromethanesulfonate (**2a**–**h**) (2.00 mmol) and the internal standard *n*-tetradecane (50 μL) in NMP (1 mL) was added via syringe. The resulting solution was then stirred for 5 min at 50 °C followed by microwave irradiation at 190 °C for 5 min at a maximum power of 150 W and cooled afterwards with air jet cooling. The maximal pressure noted was 4.5 bar. The mixture was then diluted with aqueous HCl (1 N, 10 mL) and extracted with ethyl acetate (3×20.0 mL). The combined organic layers were washed with water 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 gradient), yielding the corresponding biaryl.

Method C′ (Table 4): Method C′ is based on Method C, but with a higher loading of the copper(I)/phenanthroline catalyst. The following amounts were used: potassium carboxylate (**1c**–**j**) (1.00 mmol), copper(I) oxide (3.6 mg, 0.025 mmol), palladium(II) acetylacetonate (6.10 mg, 0.02 mmol), 1,10-phenanthroline (9.0 mg, 0.05 mmol), Tol-BINAP (20.4 mg, 0.03 mmol), 4-tolyl triflate (**2a**) (480 mg, 2.00 mmol), *n*-tetradecane (50 μL), and NMP (1 mL).

Method D (non-activated carboxylates in Tables 4 and 5): Method D is based on Method C, but using higher loading of copper catalyst, a higher volume of NMP and a longer reaction time. The following amounts were used: potassium salt of the carboxylic acid (**1a**, **1k**–**u**) (0.50 mmol), copper(I) oxide (5.37 mg, 0.0375 mmol), palladium(II) bromide (2.66 mg, 0.01 mmol), 1,10-phenanthroline (13.5 mg, 0.075 mmol), Tol-BINAP (10.2 mg, 0.015 mmol) and a solution of the trifluoromethanesulfonate (**2a**, **d**, **g**, **i**, **m**–**p**) (1.00 mmol) and the internal standard *n*-tetradecane (50 μL) in NMP (3 mL). The resulting solution was then stirred for 5 min at 50 °C followed by microwave irradiation at 190 °C for 10 min at a maximum power of 150 W and cooled afterwards with air jet cooling. The isolated yield was determined by combining two identical 0.5 mmol-scale reactions. The resulting mixture was then diluted with aqueous HCl (1 N, 10 mL) and extracted with ethyl acetate (3×20.0 mL). The combined organic layers were washed with water 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 gradient), yielding the corresponding biaryl.

4′-Methyl-3-nitrobiphenyl (3aa): Compound **3aa** was prepared following Method B from potassium 3-nitrobenzoate (**1a**) (205 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol) in NMP (8 mL), yielding **3aa** as a pale yellow solid (153 mg, 72 %). M.p. 65–67 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′-methyl-3-nitrobiphenyl [CAS: 53812-68-3]. Compound **3aa** was also prepared in 84 % yield (179 mg) using the same amounts of starting materials via two 0.5 mmol batches following Method D.

4′-Methyl-2-nitrobiphenyl (3ba): Compound **3ba** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3ba** after 1 h reaction time as a yellow oil (193 mg, 91 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′-methyl-2-nitrobiphenyl [CAS: 70680-21-6]. Using the same amounts, compound **3ba** was also prepared following Method C in 84 % yield (178 mg).

2-(2-Nitrophenyl)naphthalene (3bb): Compound **3bb** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and 2-naphthyl trifluoromethanesulfonate (**2b**) (552 mg, 2.00 mmol), yielding **3bb** after 1 h reaction time as a yellow solid (243 mg, 98 %). M.p. 98–100 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-(2-nitrophenyl)naphthalene [CAS: 94064-83-2]. Using the same amounts, compound **3bb** was also prepared following Method C in 99 % yield (245 mg).

4′-Methoxy-2-nitrobiphenyl (3bc): Compound **3bc** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and 4-methoxyphenyl trifluoromethanesulfonate (**2c**) (512 mg, 2.00 mmol), yielding **3bc** after 1 h reaction time as a yellow solid (189 mg, 83 %). M.p. 60–61 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′-methoxy-2-nitrobiphenyl [CAS: 20013-55-2]. Using the same amounts, compound **3bc** was also prepared following Method C in 87 % yield (198 mg).

2′-Methyl-2-nitrobiphenyl (3bd): Compound **3bd** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and 2-methylphenyl trifluoromethanesulfonate (**2d**) (480 mg, 2.00 mmol), yielding **3bd** after 1 h reaction time as a yellow oil (166 mg, 79 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2′-methyl-2-nitrobiphenyl [CAS: 67992-12-5]. Using the same amounts, compound **3bd** was also prepared following Method C in 93 % yield (198 mg).

1-(2′-Nitrobiphenyl-4-yl)-propan-1-one (3be): Compound **3be** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and 4-propionylphenyl trifluoromethanesulfonate (**2e**) (564 mg, 2.00 mmol), yielding **3be** after 1 h reaction time as a yellow solid (116 mg, 45 %). M.p. 83–84 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.4 Hz, 2H), 7.92 (dd, J = 8.1, 0.9 Hz, 1H), 7.65 (td, J = 7.6, 1.0 Hz, 1H), 7.53 (td, J = 7.8, 1.3 Hz, 1H), 7.43 (dd, J = 7.7, 1.0 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 3.03 ppm (q, J = 7.2 Hz, 2H), 1.24 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 200.1, 148.9, 142.0, 136.4, 135.5, 132.6, 131.7, 128.8, 128.3, 128.2, 124.4, 31.9, 8.2 ppm; elemental analysis calcd (%) for $C_{15}H_{13}NO_3$: C 70.6, H 5.13, N 5.49; found: C 70.7, H 5.3, N, 5.49; MS (ion trap, EI, 70 eV): m/z (%): 255 (3) [M^+], 227 (19), 226 (100), 180 (11), 152 (12); using the same amounts, compound **3be** was also prepared following Method C in 54 % yield (139 mg).

4-Acyl-2′-nitrobiphenyl (3bf): Compound **3bf** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (206 mg, 1.00 mmol) and 4-acylphenyl trifluoromethanesulfonate (**2f**) (536 mg, 2.00 mmol) yielding **3bf** after 1 h reaction time as a yellow solid (72 mg, 30 %). M.p. 100–102 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-acyl-2′-nitrobiphenyl [CAS: 5730-96-1]. Using the same amounts, compound **3bf** was also prepared following Method C in 23 % yield (56 mg).

Ethyl 2′-nitrobiphenyl-2-carboxylate (3bg): Compound **3bg** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and ethyl 2-(trifluoromethylsulfonyloxy)benzoate (**2g**) (596 mg, 2.00 mmol), yielding **3bg** after 1 h reaction time as a yellow oil (100 mg, 37 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for ethyl 2′-nitrobiphenyl-2-carboxylate [CAS: 72256-33-8]. Using the same amounts, compound **3bg** was also prepared following Method C in 23 % yield (63 mg).

4-Nitro-2′-nitrobiphenyl (3bh): Compound **3bh** was prepared following Method C from potassium 2-nitrobenzoate (**1b**) (206 mg, 1.00 mmol) and

4-nitrophenyl trifluoromethanesulfonate (**2h**) (546 mg, 2.00 mmol) yielding **3bh** as an orange solid (76 mg, 31%). M.p. 87–89°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-nitro-2′-nitrobiphenyl [CAS: 606-81-5].

3′,5′-Dimethyl-2-nitrobiphenyl (3bi): Compound **3bi** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and 3,5-dimethylphenyl trifluoromethanesulfonate (**2i**) (508 mg, 2.00 mmol), yielding **3bi** after 1 h reaction time as a yellow oil (225 mg, 99%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3′,5′-dimethyl-2-nitrobiphenyl [CAS: 51839-09-9].

2-Nitrobiphenyl (3bj): Compound **3bj** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and phenyl trifluoromethanesulfonate (**2j**) (452 mg, 2.00 mmol), yielding **3bj** after 1 h reaction time as a yellow oil (181 mg, 91%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-nitrobiphenyl [CAS: 86-00-0].

4-Chloro-2′-nitrobiphenyl (3bk): Compound **3bk** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and 4-chlorophenyl trifluoromethanesulfonate (**2k**) (521 mg, 2.00 mmol), yielding **3bk** after 1 h reaction time as a yellow solid (211.5 mg, 91%). M.p. 60–62°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-chloro-2′-nitrobiphenyl [CAS: 6271-80-3].

8-(2′-Nitrophenyl)quinoline (3bl): Compound **3bl** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and 8-quinolinyl trifluoromethanesulfonate (**2l**) (554 mg, 2.00 mmol), yielding **3bl** after 1 h reaction time as a yellow solid (200 mg, 80%). M.p. 129–131°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 8-(2′-nitrophenyl)quinoline [CAS: 108530-08-1].

Ethyl 2′-nitrobiphenyl-3-carboxylate (3bm): Compound **3bm** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and ethyl 3-(trifluoromethylsulfonyloxy)benzoate (**2m**) (596 mg, 2.00 mmol), yielding **3bm** after 1 h reaction time as a yellow oil (214 mg, 79%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for ethyl 2′-nitrobiphenyl-3-carboxylate [CAS: 236102-71-9].

3′-Acetyl-2-nitrobiphenyl (3bn): Compound **3bn** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and 3-acetylphenyl trifluoromethanesulfonate (**2n**) (536 mg, 2.00 mmol), yielding **3bn** after 1 h reaction time as a yellow solid (183 mg, 76%). M.p. 95–98°C; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.95$ (dt, $J = 7.1$, 1.8 Hz, 1H), 7.89–7.90 (m, 1H), 7.88 (dd, $J = 8.1$, 0.9 Hz, 1H), 7.61 (td, $J = 7.6$, 1.0 Hz, 1H), 7.44–7.51 (m, 3H), 7.41 (dd, $J = 7.7$, 1.3 Hz, 1H), 2.58 ppm (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) $\delta = 197.5$, 148.7, 138.0, 137.2, 135.3, 132.5, 132.4, 131.8, 128.8, 128.6, 128.0, 127.6, 124.2, 26.5 ppm; elemental analysis calcd (%) for $C_{14}H_{11}NO_3$: C 69.7, H 4.6, N 5.8; found: C 69.5, H 4.5, N 5.5; MS (ion trap, EI, 70 eV): m/z (%): 241 (15) [M^+], 226 (100), 199 (12), 182 (16), 153 (15), 152 (13), 115 (12).

4′-Fluoro-2-nitrobiphenyl (3bo): Compound **3bo** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and 4-fluorophenyl trifluoromethanesulfonate (**2o**) (488 mg, 2.00 mmol), yielding **3bo** after 1 h reaction time as a yellow oil (163 mg, 75%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′-fluoro-2-nitrobiphenyl [CAS: 390-38-5].

3′-Methoxy-2-nitrobiphenyl (3bp): Compound **3bp** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and 3-methoxyphenyl trifluoromethanesulfonate (**2p**) (512 mg, 2.00 mmol), yielding **3bp** after 1 h reaction time as a yellow oil (170 mg, 74%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3′-methoxy-2-nitrobiphenyl [CAS: 92017-95-3].

2′-Nitrobiphenyl-3-carbaldehyde (3bq): Compound **3bq** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and 3-formylphenyl trifluoromethanesulfonate (**2q**) (508 mg, 2.00 mmol), yielding **3bq** after 1 h reaction time as a colorless oil (145 mg, 64%). ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 10.03$ (s, 1H), 7.94 (dd, $J = 8.2$, 1.2 Hz, 1H), 7.91 (dt, $J = 7.2$, 1.6 Hz, 1H), 7.83 (t, $J = 1.7$ Hz, 1H), 7.66 (td, $J = 7.6$, 1.3 Hz, 1H), 7.59 (t, $J = 7.4$ Hz, 1H), 7.52–7.57 (m, 2H), 7.44 ppm (dd, $J = 7.6$, 1.4 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) $\delta =$ 191.7, 148.7, 138.6, 136.6, 135.0, 133.7, 132.7, 131.9, 129.4, 129.2, 128.9, 128.9, 124.4 ppm; elemental analysis calcd (%) for $C_{13}H_9NO_3$: C 68.7, H 4.0, N 6.2; found: C 68.3, H 3.7, N 6.1; MS (ion trap, EI, 70 eV): m/z (%): 226 (13) [M^+], 210 (55), 199 (85), 182 (100), 154 (100), 152 (90), 115 (100).

2-Methyl-8-(2′-nitrophenyl)quinoline (3br): Compound **3br** was prepared following Method A from potassium 2-nitrobenzoate (**1b**) (205 mg, 1.00 mmol) and 8-quinolinyl trifluoromethanesulfonate (**2r**) (554 mg, 2.00 mmol), yielding **3br** after 1 h reaction time as a yellow solid (200 mg, 80%). M.p. 129–131°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 8-(2′-nitrophenyl)quinoline [CAS: 108530-08-1].

2-Fluoro-4′-methylbiphenyl (3ca): Compound **3ca** was prepared following Method A from potassium 2-fluorobenzoate (**1c**) (178 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3ca** after 16 h reaction time as a colorless oil (141 mg, 76%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-fluoro-4′-methylbiphenyl [CAS: 72093-41-5]. Compound **3ca** was also prepared following Method C′, only using 1.00 mmol of 4-methylphenyl trifluoromethanesulfonate (**2a**) (240 mg), in 73% yield (135 mg).

4′,5-Dimethyl-2-nitrobiphenyl (3da): Compound **3da** was prepared following Method A from potassium 5-methyl-2-nitrobenzoate (**1d**) (219 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3da** after 16 h reaction time as a pale yellow solid (164 mg, 72%). M.p. 60–62°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′,5-dimethyl-2-nitrobiphenyl [CAS: 70689-98-4]. Using the same amounts, compound **3da** was also prepared following Method C′ in 73% yield (166 mg).

Isopropyl 4′-methylbiphenyl-2-carboxylate (3ea): Compound **3ea** was prepared following Method A from potassium 2-(isopropoxycarbonyl)-benzoate (**1e**) (246 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3ea** after 16 h reaction time as a white solid (76 mg, 30%). M.p. 130–131°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for isopropyl 4′-methylbiphenyl-2-carboxylate [CAS: 937166-54-6]. Using the same amounts, compound **3ea** was also prepared following Method C′ in 58% yield (147 mg).

4′-Methylbiphenyl-2-carbaldehyde (3fa): Compound **3fa** was prepared following Method A from potassium 2-formylbenzoate (**1f**) (188 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3fa** after 16 h reaction time as a yellow oil (88.3 mg, 45%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′-methylbiphenyl-2-carbaldehyde [CAS: 16191-28-9]. Using the same amounts, compound **3fa** was also prepared following Method C′ in 54% yield (106 mg).

4′-Methylbiphenyl-2-carbonitrile (3ga): Compound **3ga** was prepared following Method A from potassium 2-cyanobenzoate (**1g**) (185 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3ga** after 16 h reaction time as a white solid (85.4 mg, 44%). M.p. 43–48°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′-methylbiphenyl-2-carbonitrile [CAS: 114772-53-1]. Using the same amounts, compound **3ga** was also prepared following Method C′ in 50% yield (97.0 mg).

2-Methoxy-4′-methylbiphenyl (3ha): Compound **3ha** was prepared following Method A from potassium 2-methoxybenzoate (**1h**) (190 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3ha** after 16 h reaction time as a pale yellow solid (80.5 mg, 40%). M.p. 81–83°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-methoxy-4′-methylbiphenyl [CAS: 92495-53-9]. Using the same amounts, compound **3ha** was also prepared following Method C′ in 40% yield (80.5 mg).

2-(4-Methylphenyl)thiophene (3ia): Compound **3ia** was prepared following Method A from potassium thiophene-2-carboxylate (**1i**) (166 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg,

2.00 mmol), yielding **3ia** after 16 h reaction time as a white solid (131 mg, 75%). M.p. 60–62°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-(4-methylphenyl)thiophene [CAS: 16939-04-1]. Compound **3ia** was also prepared following Method C′, only using 1.00 mmol of 4-methylphenyl trifluoromethanesulfonate (**2a**) (240 mg), in 82% yield (143 mg).

2-(4-Methylphenyl)furan (3ja): Compound **3ja** was prepared following Method A from potassium furan-2-carboxylate (**1j**) (150 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3ja** after 16 h reaction time as a yellow oil (119 mg, 75%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-(4-methylphenyl)furan [CAS: 17113-32-5]. Using the same amounts, compound **3ja** was also prepared following Method C′, only using 1.00 mmol of 4-methylphenyl trifluoromethanesulfonate (**2a**) (240 mg), in 75% yield (119 mg).

4-Methyl-4′-nitrobiphenyl (3ka): Compound **3ka** was prepared following Method B from potassium 4-nitrobenzoate (**1k**) (205 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3ka** as a white solid (146 mg, 68%). M.p. 116–117°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methyl-4′-nitrobiphenyl [CAS: 2143-88-6]. Using the same amounts, compound **3ka** was also prepared following Method D in 81% yield (174 mg).

4′-Methylbiphenyl-3-carbonitrile (3la): Compound **3la** was prepared following Method B from potassium 3-cyanobenzoate (**1l**) (185 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3la** as a pale yellow solid (100 mg, 52%). M.p. 50–51°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methylbiphenyl-3′-carbonitrile [CAS: 133909-96-3]. Compound **3la** was also prepared following Method D in 83% yield (160 mg).

4′-Methylbiphenyl-4-carbonitrile (3ma): Compound **3ma** was prepared following Method B from potassium 4-cyanobenzoate (**1m**) (185 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3ma** as a pale yellow solid (112 mg, 58%). M.p. 89–91°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methylbiphenyl-4′-carbonitrile [CAS: 50670-50-3]. Compound **3ma** was also prepared following Method D in 76% yield (147 mg).

4′-Methyl-4-(trifluoromethyl)biphenyl (3na): Compound **3na** was prepared following Method B from potassium 4-(trifluoromethyl)benzoate (**1n**) (228 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3na** as a white solid (80 mg, 44%). M.p. 122–124°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′-methyl-4-(trifluoromethyl)biphenyl [CAS: 97067-18-0]. Compound **3na** was also prepared following Method D in 74% yield (135 mg).

1-(4-Methylphenyl)naphthalene (3oa): Compound **3oa** was prepared following Method B from potassium 1-naphthoate (**1o**) (210 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3oa** as a colorless oil (107 mg, 49%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 1-(4-methylphenyl)naphthalene [CAS: 24423-07-2]. Compound **3oa** was also prepared following Method D in 71% yield (155 mg).

3,4′-Dimethyl-4-nitrobiphenyl (3pa): Compound **3pa** was prepared following Method B from potassium 3-methyl-4-nitrobenzoate (**1p**) (197 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3pa** as a yellow solid (142 mg, 62%. M.p. 56–57°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.05–8.08 (m, 1H), 7.50–7.52 (m, 2H), 7.49–7.50 (m, 2H), 7.28 (d, J = 7.9 Hz, 2H), 2.67 (s, 3H), 2.41 ppm (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 147.6, 145.9, 138.7, 135.8, 134.3, 131.0, 129.7, 127.1, 125.4, 125.1, 21.1, 21.0 ppm; elemental analysis calcd (%) for $C_{14}H_{13}NO_2$: C 74.0, H 5.8, N 6.16; found: C 73.8, H 5.8, N 6.00; MS (ion trap, EI, 70 eV): m/z (%): 227 (100) [M^+], 210 (92), 182 (35), 167 (38), 166 (22), 165 (49), 155 (25). Compound **3pa** was also prepared following Method D in 69% yield (158 mg).

***N*-(4′-Methylbiphenyl-4-yl)acetamide (3qa)**: Compound **3qa** was prepared following Method B from potassium 4-acetamidobenzoate (**1q**) (217 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3qa** as a white solid (119 mg, 53%). M.p. 165–168°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for *N*-(4′-methylbiphenyl-4-yl)acetamide [CAS: 1215-21-0]. Compound **3qa** was also prepared following Method D in 59% yield (132 mg).

3-Chloro-4′-methylbiphenyl (3ra): Compound **3ra** was prepared following Method B from potassium 3-chlorobenzoate (**1r**) (228 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3ra** as colorless oil (80.0 mg, 40%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3-chloro-4′-methylbiphenyl [CAS: 19482-19-0]. Compound **3ra** was also prepared following Method D in 59% yield (118 mg).

3-Methoxy-4′-methylbiphenyl (3sa): Compound **3sa** was prepared following Method D from potassium 3-methoxybenzoate (**1s**) (95 mg, 0.50 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (240 mg, 1.00 mmol). After combining two identical 0.5 mmol scale-reactions compound **3sa** was isolated as a pale yellow solid (107 mg, 54%). M.p. 74–76°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3-methoxy-4′-methylbiphenyl [CAS: 24423-07-2].

3-(4-Methylphenyl)pyridine (3ta): Compound **3ta** was prepared following Method B from potassium nicotinate (**1t**) (161 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3ta** as a colorless oil (69.1 mg, 41%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3-(4-methylphenyl)-pyridine [CAS: 4423-09-0]. Compound **3ta** was also prepared following Method D in 50% yield (84 mg).

3-(4-Methylphenyl)thiophene (3ua): Compound **3ua** was prepared following Method B from potassium thiophene-3-carboxylate (**1u**) (166 mg, 1.00 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **3ua** as a white solid (94 mg, 54%). M.p. 70–72°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3-(4-methylphenyl)thiophene [CAS: 16939-05-2]. Compound **3ua** was also prepared following Method D in 65% yield (113 mg).

2-(3-Nitrophenyl)naphthalene (3ab): Compound **3ab** was prepared following Method B from potassium 3-nitrobenzoate (**1a**) (205 mg, 0.50 mmol) and 2-naphthyl trifluoromethanesulfonate (**2b**) (552 mg, 2.00 mmol) in NMP (8 mL), yielding **3ab** as a yellow solid (154 mg, 62%). M.p. 110–112°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-(3-nitrophenyl)-naphthalene [CAS: 94064-82-1]. Compound **3ab** was also prepared in 74% yield (184 mg) using the same amounts of starting materials via two 0.5 mmol batches following Method D.

2′-Methyl-3-nitrobiphenyl (3ad): Compound **3ad** was prepared following Method B from potassium 3-nitrobenzoate (**1a**) (205 mg, 1.00 mmol) and 2-methylphenyl trifluoromethanesulfonate (**2d**) (480 mg, 2.00 mmol) in NMP (8 mL), yielding **3ad** as an orange oil (87 mg, 41%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2′-methyl-3-nitrobiphenyl [CAS: 51264-60-9]. Compound **3ad** was also prepared in 61% yield (129 mg) using the same amounts of starting materials via two 0.5 mmol batches following Method D.

Ethyl 3′-nitrobiphenyl-2-carboxylate (3ag): Compound **3ag** was prepared following Method D from potassium 3-nitrobenzoate (**1a**) (103 mg, 0.50 mmol) and ethyl 2-(trifluoromethylsulfonyloxy)benzoate (**2g**) (298 mg, 1.00 mmol). After combining two identical 0.5 mmol-scale reactions, compound **3ag** was isolated as colorless oil (92 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (ddd, J = 8.0, 2.2, 1.0 Hz, 1H), 8.18 (t, J = 1.9 Hz, 1H), 7.96 (dd, J = 7.8, 1.4 Hz, 1H), 7.62 (ddd, J = 7.7, 1.4, 1.2 Hz, 1H), 7.53–7.60 (m, 2H), 7.49 (td, J = 7.6, 1.2 Hz, 1H), 7.34 (dd, J = 7.5, 1.0 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 1.07 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.4, 143.4, 140.4, 134.6, 131.7, 130.7, 130.5, 129.6, 128.7, 128.3, 123.5, 122.0, 121.4, 61.1, 13.8 ppm; elemental analysis calcd (%) for $C_{14}H_{13}NO_2$: C 66.4, H 4.8, N 5.2; found: C 66.6, H 4.7, N 5.0. MS (Ion trap, EI, 70 eV): m/z (%): 271 (45) [M^+], 226 (100), 225 (25), 210 (28), 196 (32), 180 (31), 151 (27).

3′,5′-Dimethyl-3-nitrobiphenyl (3ai): Compound **3ai** was prepared following Method D from potassium 3-nitrobenzoate (**1a**) (103 mg, 0.50 mmol) and 3,5-dimethylphenyl trifluoromethanesulfonate (**2i**) (254 mg, 1.00 mmol). After combining two identical 0.5 mmol-scale reactions, compound **3ai** was isolated as a yellow solid (157 mg, 69%). M.p. 65–66°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3′,5′-dimethyl-3-nitrobiphenyl [CAS: 337973-04-3].

Ethyl 3′-nitrobiphenyl-3-carboxylate (3an): Compound **3an** was prepared following Method D from potassium 3-nitrobenzoate (**1a**) (102.5 mg, 0.50 mmol) and ethyl 3-(trifluoromethylsulfonyloxy)benzoate (**2i**) (298 mg, 1.00 mmol). After combining two identical 0.5 mmol-scale reactions, compound **3an** was isolated as yellow oil (108 mg, 40%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for ethyl 3′-nitrobiphenyl-3-carboxylate [CAS: 942232-55-5].

3′-Acetyl-3-nitrobiphenyl (3am): Compound **3am** was prepared following Method B from potassium 3-nitrobenzoate (**1a**) (205 mg, 1.00 mmol) and 3-acetylphenyl trifluoromethanesulfonate (**2m**) (536 mg, 2.00 mmol) in NMP (8 mL), yielding **3am** as a white solid (135 mg, 58%). M.p. 85–86°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3′-acetyl-3-nitrobiphenyl [CAS: 371157-19-6]. Compound **3ad** was also prepared following Method D in 49% yield (114 mg).

4′-Fluoro-3-nitrobiphenyl (3ao): Compound **3ao** was prepared following Method D from potassium 3-nitrobenzoate (**1a**) (103 mg, 0.50 mmol) and 4-fluorophenyl trifluoromethanesulfonate (**2o**) (244 mg, 1.00 mmol). After combining two identical 0.5 mmol-scale reactions, compound **3ao** was isolated as a yellow solid (139 mg, 64%). M.p. 81–84°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′-fluoro-3-nitrobiphenyl [CAS: 10540-32-6].

3′-Methoxy-3-nitrobiphenyl (3ap): Compound **3ap** was prepared following Method D from potassium 3-nitrobenzoate (**1a**) (103 mg, 0.50 mmol) and 3-methoxyphenyl trifluoromethanesulfonate (**2p**) (256 mg, 1.00 mmol) yielding **3ap** as a yellow oil (91.6 mg, 40%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3′-methoxy-3-nitrobiphenyl [CAS: 128923-93-3].

4,4′-Dimethylbenzophenone (6aa) (see Scheme 4): Compound **6aa** was prepared following Method A heating 16 h, from potassium oxo-(4-methylphenyl)acetate (**5a**) (203 mg, 1.2 mmol) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **6aa** as a light yellow solid (179 mg, 85%). M.p. 67–68°C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4,4′-dimethylbenzophenone [CAS: 611-97-2]. Compound **6aa** was also prepared following Method C′ in 89% yield (187 mg).

4′,2,2-Trimethylpropiophenone (6ba) (see Scheme 4): Compound **6ba** was prepared following Method A heating 16 h, from potassium 3,3,3-trimethylpyruvate (168 mg, 1.0 mmol) (**5b**) and 4-methylphenyl trifluoromethanesulfonate (**2a**) (480 mg, 2.00 mmol), yielding **6ba** as a colorless oil (136 mg, 77%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′,2,2-trimethylpropiophenone [CAS: 30314-44-4]. Compound **6ba** was also prepared following Method C′ in 51% yield (88 mg).

General procedure for the decarboxylation study (Table 6)

Method A (thermal conditions): An oven-dried, nitrogen flushed vessel was charged with the carboxylic acid (**7a–c**) (1.00 mmol), Cu_2O (10.7 mg, 0.075 mmol) and the appropriate amount of phenanthroline (0 or 0.15 mmol), Tol-BINAP (0 or 0.045 mmol), PdI_2 (0 or 0.03 mmol), $Pd(dba)_2$ (0 or 0.03 mmol), KI (0 or 0.06 mmol), KOTf (0 or 1.00 mmol), see Table 6. A degassed solution of *n*-tetradecane in NMP (2.0 mL) was added via syringe and the resulting mixture was stirred at 170°C for 16 h. Then, the reaction mixture was allowed to cool to room temperature and was diluted with ethyl acetate (2 mL). An aliquot of the reaction mixture (0.25 mL) was dissolved in ethyl acetate (2 mL), washed with HCl (5 N, 2 mL), dried over $MgSO_4$/$NaHCO_3$ and analyzed by GC.

Method B (microwave-assisted conditions): An oven-dried, argon flushed 10 mL microwave vessel was charged with the carboxylic acid **7a–c** (1.00 mmol), Cu_2O (10.7 mg, 0.075 mmol) and the appropriate amount of phenanthroline (0 or 0.15 mmol), Tol-BINAP (0 or 0.045 mmol), PdI_2 (0 or 0.03 mmol), see Table 6. Subsequently, a solution of *n*-tetradecane (50 μL) in NMP (1 mL) was added via syringe. The resulting mixture was then stirred at 190°C for 15 min at a maximum power of 150 W and cooled afterwards with air jet cooling. The pressure noted at this temperature was 4.5 bar. Then, the reaction mixture was diluted with ethyl acetate (2 mL). An aliquot of the reaction mixture (0.25 mL) was dissolved in ethyl acetate (2 mL), washed with HCl (5 N, 2 mL), dried over $MgSO_4$/$NaHCO_3$ and analyzed by GC.

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