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Synthesis of Biaryls and Aryl Ketones *via* Microwave-Assisted Decarboxylative Cross-Couplings

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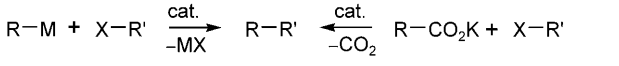
Abstract: A protocol for the microwave-assisted decarboxylative cross-couplings of carboxylic acid salts with aryl halides has been developed that allows the synthesis of various biaryls and aryl ketones in high yields. After careful adaptation of the bimetallic catalyst system and reaction conditions, these mechanistically complex transformations can now be performed within only five minutes in concentrated solution in a sealed vessel. This greatly simplified reaction protocol is ideally suited for applications in parallel synthesis and drug discovery.

Keywords: biaryls; copper; cross-coupling; microwave heating; palladium

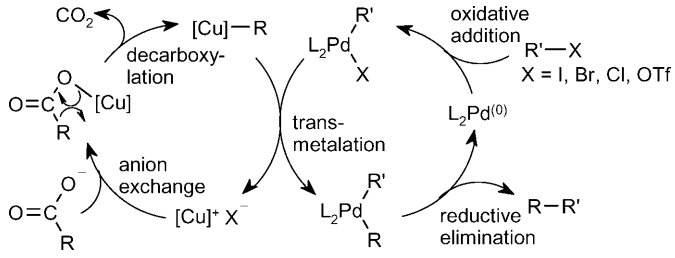
Introduction

Cross-coupling reactions under formation of C–C bonds are indispensable tools in organic synthesis.[1] In this context, decarboxylative cross-couplings have recently emerged as an advantageous alternative to the transition metal-catalyzed cross-coupling of preformed organometallic reagents (Scheme 1).[2]

We have shown that organometallic species can be generated *in situ* by extrusion of CO_2 from a simple carboxylate salt in the coordination sphere of a copper catalyst. The resulting organocopper species is then transmetallated to a palladium co-catalyst and cross-coupled with a carbon electrophile, following the general mechanism outlined in Scheme 2.



Scheme 1. Transition metal-catalyzed cross-coupling reactions.



Scheme 2. Mechanism of the decarboxylative cross-coupling.

This approach has successfully been employed in the synthesis of biaryls from aromatic carboxylates and aryl bromides,[3] chlorides,[4] and triflates,[5] as well as of aryl ketones from potassium α-oxocarboxylates.[6] Optimized reaction protocols have been developed for both small- and large-scale applications,[7] and the preparative value of this reaction type has been demonstrated in the synthesis of pharmaceutically relevant substances.[8]

Similar decarboxylative coupling reactions have also been reported by other groups. Myers et al.[9] have introduced the concept of decarboxylative couplings in their oxidative decarboxylative Heck reaction. Steglich et al.[10] as well as Forgione and Bilodeou et al.[11] have disclosed oxidative decarboxylative arylations of five-ring heteroarenecarboxylic acids. Becht et al.[12] showed that particularly electron-rich arenecarboxylates can be smoothly converted using Pd catalysts along with silver-based mediators. Crabtree has recently combined the concepts of oxidative decarboxylative couplings with C–H activation,[13] an approach that was further elaborated by Glorius et al.[14] Decarboxylative reaction variants have also been disclosed for Sonogashira couplings,[15] C–S couplings[16] and allylation reactions.[17]

Whereas, in principle, carboxylic acids are an appealing source of carbon nucleophiles, synthetic organic chemists may still hesitate to switch from traditional to decarboxylative cross-couplings, reluctant to

submit their valuable starting materials to the prolonged thermal stress involved in current protocols, that is, 160 °C over many hours. We saw the efficient heating provided by microwave irradiation as a promising approach to minimize reaction times in decarboxylative cross-couplings and enhance their practicality.

Single-mode laboratory microwave reactors have become established as standard equipment in many chemistry labs throughout academia and industry. They were found to be advantageous for many traditional transition metal-catalyzed reactions,[18] e.g., Suzuki cross-couplings,[19] Heck reactions,[20] Buchwald–Hartwig amination reactions,[21] and decarboxylative reactions of the Heck-type,[11] which can thus be carried out within short reaction times and in high yields. In this context, Forgione and Bilodeau used microwave radiation to promote their monometallic Pd-catalyzed decarboxylative arylation of five-membered heteroarene-2-carboxylic acids (Scheme 3).[11]

Crabtree et al.[13] reported microwaves to be beneficial in his Pd-catalyzed decarboxylative coupling of *in situ*-formed silver carboxylates, where Ag(I) is used in large excess as it also functions as a stoichiometric oxidant.

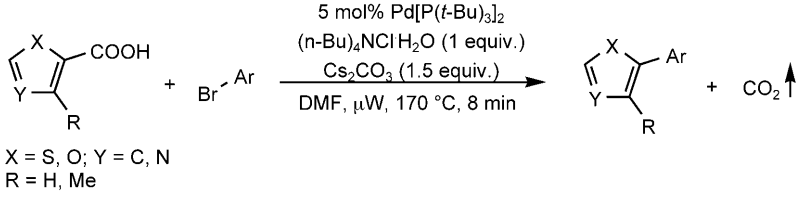
In contrast to these processes, our decarboxylative cross-coupling protocol is based on the synchronized catalytic cycles of two different metals, and will only work well if the delicate balance between them is not disturbed. Achieving such a balance in the microwave is not an easy task, knowing from previous investigations that microwave irradiation accelerates the Cu-catalyzed decarboxylation step to a much larger extent than the cross-coupling step.[22]

We were thus not surprised that initial attempts at simply transferring the existing procedures for the cross-coupling, for example, of potassium 2-nitrobenzoate with 4-tolyl bromide, to the microwave failed (see below). Still, we were motivated to continue this effort because, in theory, microwave technology perfectly meets the requirements of decarboxylative couplings on the laboratory scale, combining efficient heating with the possibility to use small, contained vessels certified for pressure reactions. It would thus be comparatively simple to provide the dry and inert conditions needed for the reactions. Moreover, their progress would easily be followed by monitoring the build-up of carbon dioxide gas on the pressure sensor. Finally, the CO_2 by-product would not be able to escape and carry with it any volatile starting materials as is often the case at high temperatures in open standard glassware.

Results and Discussion

In search for a suitable microwave protocol, we chose the reaction of potassium 2-nitrobenzoate (**1a**) with 4-tolyl bromide (**2a**) as a model, knowing from previous investigations that this substrate combination reacts very reliably under appropriate conditions. The reaction proceeds smoothly using conventional heating at 160 °C for 24 h and a catalyst system consisting of copper iodide, 1,10-phenanthroline, and palladium acetylacetonate in NMP.[2b] However, transferring the reaction to a microwave under otherwise unchanged conditions led to varying and mostly unsatisfactory results. The reaction mixture strongly absorbs microwave radiation, causing a rapid increase in temperature and pressure during the first few seconds, while the suspension is still inhomogeneous and catalyst preformation incomplete. From the pressure graphs, we concluded that the catalyst often lost its activity within a minute, presumably due to local overheating, and that the reactions thus stalled at incomplete conversions, most of the starting material was recovered unchanged. The palladium catalyst proved to be particularly sensitive, as appreciable amounts of Pd black were usually formed.

The decisive measures towards reproducibility were to reduce the amount of solvent to 1 mL on a 1 mmol scale, to limit the microwave power to 50 W, and to homogenize the reaction mixture prior to microwave irradiation by stirring it for 10 min at 50 °C in the sealed vial. This way, an encouraging yield of 29% was achieved after a reaction time of 10 min, at a maximum temperature set to 160 °C (Table 1, entry 1). Alternatively, the catalyst can be pre-formed directly in the microwave when limiting the power to 5 W and 100 °C for the catalyst preformation (1 min), and then raising it to 15 W and 160 °C until the pressure buildup levels out, usually 4 min (Table 1, entry 2). When performing the reaction on a 1 mmol scale, the pressure never reached 6 bar, which we con-



Scheme 3. Biaryl synthesis according to Bilodeau and Forgione.

sidered to be safe taking into account that the vessels used are certified for up to 20 bars.

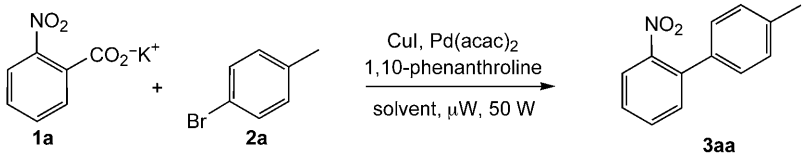
Systematic investigations revealed that the yields increased at higher temperatures (Table 1, entries 1, 3–6), causing the internal pressure to rise to a moderate value of 6 bar at 190 °C. At this temperature, the reaction time could be reduced to 5 min (Table 1, entry 7). The combination of palladium acetylacetonate, copper iodide, and 1,10-phenanthroline remained the catalyst of choice (Table 1, entries 8–11). Whereas the amount of palladium could be reduced to 1 mol%, 3 mol% of copper were required for full conversion (Table 1, entries 9, 12).

The best solvent system consisted of a mixture of NMP and quinoline (Table 1, entry 8); either solvent individually was less effective (Table 1, entries 13, 14). Non-polar solvents such as mesitylene did not allow for effective heating, while lower boiling polar solvents such as THF caused pressures too close to, or even in excess of, 20 bar, which was the limit for the vessels used.

In order to probe whether the reduction of the reaction time was indeed caused by the microwave irradiation, we conducted a control experiment in which an identical reaction vessel was completely submerged into a tightly fitting cavity of an aluminium block preheated to 200 °C (Table 1 entries 19, 20). Even when heated in this efficient way, the reaction took 6 h to complete, demonstrating that a comparable rate enhancement cannot be achieved when increasing the temperature in the conventional heating protocol.

Under optimized conditions, the biaryl product **3aa** was formed in high yields starting from preformed potassium 2-nitrobenzoate (Table 1, entry 8). It is also possible to deprotonate 2-nitrobenzoic acid *in situ* with potassium carbonate, while trapping the reaction water with molecular sieves. However, we found this

Table 1. Investigation of the conditions.[a]



1a **2a** **3aa**

#	*T* [°C]	*t* [min]	Catalyst	Solvent	Yield [%][b]
1	160	10	2% $Pd(acac)_2$, 3% CuI	NMP/quin.	29
2[c]	160	10	2% $Pd(acac)_2$, 3% CuI	NMP/quin.	20
3	170	10	2% $Pd(acac)_2$, 3% CuI	NMP/quin.	49
4	180	10	2% $Pd(acac)_2$, 3% CuI	NMP/quin.	75
5	190	10	2% $Pd(acac)_2$, 3% CuI	NMP/quin.	88
6	200	10	2% $Pd(acac)_2$, 3% CuI	NMP/quin.	86
7	190	5	2% $Pd(acac)_2$, 3% CuI	NMP/quin.	87
8	190	5	1% $Pd(acac)_2$, 3% CuI	NMP/quin.	87
9	190	5	1% $Pd(OAc)_2$, 3% CuI	NMP/quin.	71
10	190	5	1% $PdBr_2$, 3% CuI	NMP/quin.	72
11	190	5	1% $Pd(dba)_2$, 3% CuI	NMP/quin.	26
12[d]	190	5	1% $Pd(acac)_2$, 1.5% CuI	NMP/quin.	48
13[e]	190	5	1% $Pd(acac)_2$, 3% CuI	NMP	57
14[e]	190	5	1% $Pd(acac)_2$, 3% CuI	quin.	50
15[e]	190	5	1% $Pd(acac)_2$, 3% CuI	mes.	0
16[e]	190	5	1% $Pd(acac)_2$, 3% CuI	DMF	49
17[f]	190	5	1% $Pd(acac)_2$, 3% CuI	NMP/mes.	55
18[g]	190	5	1% $Pd(acac)_2$, 3% CuI	NMP/quin.	55
19[h]	200	1 h	1% $Pd(acac)_2$, 3% CuI	NMP/quin.	48
20[h]	200	6 h	1% $Pd(acac)_2$, 3% CuI	NMP/quin.	87

[a] *Reaction conditions*: 1.2 mmol potassium 2-nitrobenzoate, 1.0 mmol 4-bromotoluene, 0.03 mmol CuI, 0.05 mmol 1,10-phenanthroline, 0.02 mmol Pd source, 1.0 mL of a 1:1 mixture of NMP and quinoline. All reactions were performed at a maximum of 50 W; quin. = quinoline, mes. = mesitylene.

[b] Conversions were determined by GC analysis using *n*-tetradecane as internal standard.

[c] Catalyst pre-formed directly in the microwave.

[d] 0.025 mmol 1,10-phenanthroline.

[e] 1.0 mL solvent.

[f] 1.0 mL of a 1:1 mixture of NMP and mesitylene.

[g] 1.2 mmol 2-nitrobenzoic acid, 1.2 mmol K_2CO_3, 250 mg of 3 Å molecular sieves.

[h] Reaction was carried out in an oil bath.

procedure to be less convenient as the additional amount of CO_2 and water formed in the deprotonation step led to a further pressure increase in the reaction vessel, which we considered to be an unnecessary potential risk to take. We also found that for most substrates, the conversion was slightly lower using the *in-situ* protocol, and that deposition of Pd black was observed. We attributed this to local overheating at the molecular sieves (Table 1, entry 18).

Having established a reliable protocol, we next tested its generality by applying it to the synthesis of biaryls from various carboxylates **1** and aryl halides **2**. As can be seen from Table 2, both electron-rich and electron-poor aryl bromides were smoothly coupled with potassium 2-nitrobenzoate (**1a**) within just five minutes at an average power of 10–15 W, in yields that are comparable with those achieved after 24 h of conventional heating. Common functionalities are tolerated, and even a basic nitrogen heterocycle was coupled in high yields (compound **2g**).

An analogous adaptation to the microwave of the recently reported catalyst system for decarboxylative cross-couplings of aryl chlorides was also successful, as demonstrated in the coupling of potassium 2-nitrobenzoate (**1a**) with 4-chlorotoluene (**2h**) in the presence of CuI/1,10-phenanthroline and $Pd(acac)_2$/di(*tert*-butyl)biphenylphosphine (Table 2, entry 8).

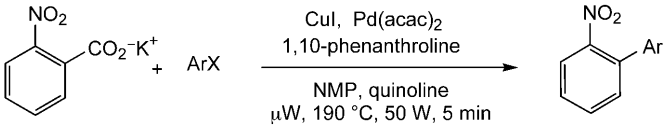
The scope of the protocol with regard to the carboxylate substrates was tested in their coupling with 4-bromotoluene (**2a**). We were pleased to find that the full range of arenecarboxylic acid salts that can presently be decarboxylated with a copper/phenanthroline system was successfully converted (Table 3): *ortho*-substituted arenecarboxylates and heterocyclic derivatives such as 2-thiophenecarboxylate reacted smoothly in good to moderate yields.

Examples **5aa** and **5ba** show that the decarboxylative cross-coupling of α-oxocarboxylates with aryl bromides under formation of aryl ketones can also be carried out under microwave conditions with substantial rate acceleration (Scheme 4).

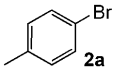
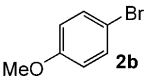
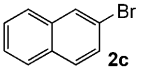
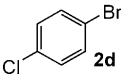
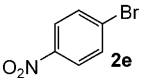
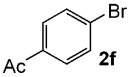
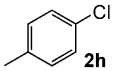
As previously observed in the thermal reaction protocol, the catalyst system is widely applicable to 2-substituted or hetereocyclic deriviatives. It is less suitable for electron-rich arene carboxylates such as 2-methoxybenzoate. Even after substantial modifications to the Pd/Cu catalyst system, only modest yields were obtained. For the conversion of electron-rich substrates, we therefore recommend the use of Pd/Ag-based systems, which show the best activity for precisely this substrate class and thus ideally complement the substrate scope of the present protocol.

Potassium 3-nitrobenzoate (**1j**) represents the performance limit of the current catalyst system under microwave conditions just as with thermal heating. With this copper/phenanthroline-based decarboxylation catalyst, halide salt byproducts impede the decarboxylation step of arenecarboxylates other than 2-substituted or heterocyclic derivatives. This limitation can presently only be overcome under halide-free conditions by the use of aryl triflates as carbon electrophiles.[5]

Table 2. Substrate scope with regard to the aryl halides.[a]



1a **2a – g** **3aa – ag**

#	ArX	Product	Yield [%][b]
1		**3aa**	93
2		**3ab**	78
3		**3ac**	84
4		**3ad**	92
5		**3ae**	87
6		**3af**	64
7		**3ag**	83
8[c]		**3aa**	57

[a] *Reaction conditions*: 1.2 mmol potassium 2-nitrobenzoate, 1.0 mmol aryl bromide, 0.03 mmol CuI, 0.05 mmol 1,10-phenanthroline, 0.01 mmol $Pd(acac)_2$, 0.5 mL NMP, 0.5 mL quinoline, 190 °C, 50 W, 5 min.

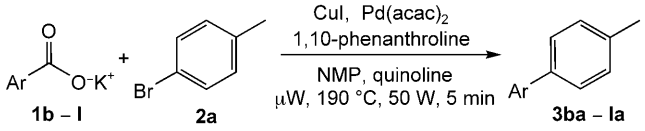
[b] Isolated yields.

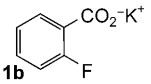
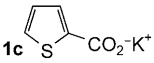
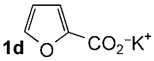
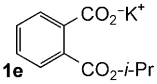
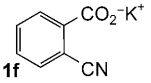
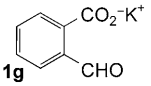
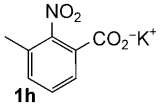
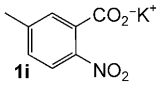
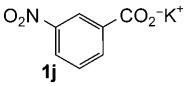
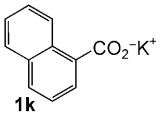
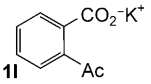
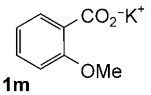
[c] 0.5 mmol 4-chlorotoluene, 0.01 mmol di(*tert*-butyl)biphenylphosphine as ligand.

Conclusions

A convenient microwave-assisted decarboxylative cross-coupling of aryl and acyl carboxylates with aryl bromides has been developed. Benefitting from the efficient heating and possibility to use small, contained vessels certified for pressure reactions, the protocol allows a fast and convenient synthesis of a broad variety of biaryls and aryl ketones. Electron-rich and -poor aryl bromides are coupled in high yields within 5 min, thus making this protocol attrac-

Table 3. Substrate scope with regard to the aryl carboxylates.[a]



#	Carboxylate	Product	Yield [%][b]
1		**3ba**	81
2		**3ca**	75
3		**3da**	38
4[c]		**3ea**	54
5[d]		**3fa**	67
6		**3ga**	35
7		**3ha**	87
8		**3ia**	81
9		**3ja**	5[e]
10		**3ka**	31
11		**3la**	38
12		**3ma**	0

[a] *Reaction conditions*: 1.2 mmol potassium carboxylate, 1.0 mmol 4-bromotoluene, 0.10 mmol CuI, 0.17 mmol 1,10-phenanthroline, 0.01 mmol $Pd(acac)_2$, 0.5 mL NMP, 0.5 mL quinoline, 190 °C, 50 W, 5 min.

[b] Isolated yields.

[c] 0.10 mmol Cu_2O.

[d] 1.2 mmol 2-cyanobenzoic acid, 0.15 mmol CuO, 0.15 mmol 1,10-phenanthroline, 0.02 mmol $PdBr_2$, 0.50 mmol KF, 1.0 mmol K_2CO_3, 250 mg 3 Å molecular sieves, 1.00 mL quinoline, 250 °C, max. 150 W, 5 min.

[e] GC yield.

tive for organic synthesis and parallel reactions in drug discovery.

Experimental Section

General Methods

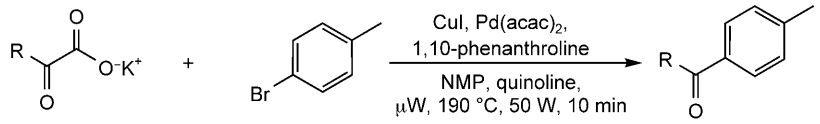
All reactions were performed in oven-dried microwave vials (10 mL) containing a Teflon-coated stir bar and a septum under an argon atmosphere. Three freeze-pump-thaw cycles were preformed before the reagents were mixed. All microwave irradiation experiments were carried out in a monomode microwave apparatus equipped with a pressure control system and a vertically-focused IR temperature sensor. After the irradiation period, the reaction vessel was cooled rapidly (60–120 sec) to ambient temperature by air jet cooling. The maximum pressure detected during the reaction was 5.5 bar. GC analyses were carried out using a 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 on silica gel (12 g). NMR spectra were recorded at 200, 400 or 600 MHz using $CDCl_3$, MeOH-d_4, DMSO-d_6 and D_2O as solvents, with proton and carbon resonances at 200/400/600 MHz and 50/101/151 MHz, respectively. Mass spectral data were acquired on a GC-MS instrument. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. 1-Methyl-2-pyrrolidone (NMP) was dried by removing water as a toluene azeotrope prior to use. Quinoline was distilled over 3 Å molecular sieves prior to use. Copper salts and potassium fluoride were dried under vacuum at 60 °C; potassium carbonate was dried under vacuum at 120 °C prior to use. All potassium salts of the carboxylic acids were dried under vacuum at room temperature for 2 h prior to use.

Procedure for the Synthesis of the Potassium Carboxylates 1a–l and the Potassium α-Oxocarboxylates 4a and b

A 250-mL, two-neck, round-bottom flask was charged with the carboxylic acid (20.0 mmol) and ethanol (20 mL). To this, a solution of potassium *tert*-butoxide (2.24 g, 20.0 mmol) in ethanol (20 mL) was added dropwise over 2 h. After complete addition, the reaction mixture was stirred for another 1 h at room temperature. The 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 mL) and cold (0 °C) diethyl ether (10 mL), transferred to a round-bottomed flask, and dried at 2×10^{-3} mmHg to provide the corresponding potassium carboxylates **1a–l**/α-oxocarboxylates **4a, b** in 81–98% yield.

General Procedure for the Biaryl Synthesis (Table 2/ Table 3)

Method A (Table 2): An oven-dried 10-mL microwave vial was charged with potassium 2-nitrobenzoate (**1a**) (246 mg, 1.20 mmol), copper(I) iodide (5.70 mg, 0.03 mmol), palladi-



4a: R = Ph
4b: R = PhMe

2a

5aa: 83%
5ba: 66%

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

um(II) acetylacetonate (3.00 mg, 0.01 mmol) and 1,10-phenanthroline (9.00 mg, 0.05 mmol). The reaction vessel was sealed, evacuated and flushed with argon three times. Subsequently, a solution of the aryl bromide (**2a–g**) (1.00 mmol) in NMP (0.5 mL) and quinoline (0.5 mL) was added *via* syringe. The resulting mixture was first stirred in a water bath at 50 °C for 10 min, then irradiated in the microwave at 190 °C for 5 min at a maximum power of 50 W causing the pressure to rise to 5.5 bar, then air-jet cooled. The reaction mixture was diluted with aqueous HCl (1 N, 10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the volatiles were removed under vacuum. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient), yielding the corresponding biaryl.

We found that this reaction can be conducted safely on 1 mmol scales using unscratched 10-mL vessels certified for pressures of up to 20 bar, because under these conditions, the pressure remains well below 6 bar. However, care has to be taken when performing the reaction on scales of 3 mmol or more. One has to remember that one equivalent of gaseous carbon dioxide is released within the process. The pressure must be monitored carefully, as in rare cases, a palladium mirror forms which may cause strong local overheating and ultimately a bursting of the vessel.

4-Methyl-2′-nitrobiphenyl (3aa): Compound **3aa** [CAS: 70680–21–6] was prepared following Method A from potassium 2-nitrobenzoate (**1a**) (246 mg, 1.20 mmol) and 4-bromotoluene (**2a**) (171 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **3aa** as an orange oil; yield: 198 mg (93%).

Compound **3aa** was also prepared following Method A but on 0.50 mmol scale from potassium 2-nitrobenzoate (**1a**) (123 mg, 0.60 mmol) and 4-chlorotoluene (**2h**) (63.3 mg, 0.50 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **3aa** as an orange oil; yield: 61.0 mg (57%).

4-Methoxy-2′-nitrobiphenyl (3ab): Compound **3ab** [CAS: 20013–55–2] was prepared following Method A from potassium 2-nitrobenzoate (**1a**) (246 mg, 1.20 mmol) and 4-bromoanisole (**2b**) (191 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **3ab** as a yellow solid; yield: 192 mg (78%).

1-(2-Nitrophenyl)naphthalene (3ac): Compound **3ac** [CAS: 5415–59–8] was prepared following Method A from potassium 2-nitrobenzoate (**1a**) (246 mg, 1.20 mmol) and 1-bromonaphthalene (**2c**) (222 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **3ac** as an orange solid; yield: 222 mg (84%).

4-Chloro-2′-nitrobiphenyl (3ad): Compound **3ad** [CAS: 6271–80–3] was prepared following Method A from potassium 2-nitrobenzoate (**1a**) (246 mg, 1.20 mmol) and 1-bromo-4-chlorobenzene (**2d**) (195 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **3ad** as a yellow solid; yield: 220 mg (92%).

2,4′-Dinitrobiphenyl (3ae): Compound **3ae** [CAS: 606–81–5] was prepared following Method A from potassium 2-nitrobenzoate (**1a**) (246 mg, 1.20 mmol) and 1-bromo-4-nitrobenzene (**2e**) (202 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **3ae** as an orange solid; yield: 212 mg (87%).

4-Acetyl-2′-nitrobiphenyl (3af): Compound **3af** [CAS: 5730–96–1] was prepared following Method A from potassium 2-nitrobenzoate (**1a**) (246 mg, 1.20 mmol) and 4-bromoacetophenone (**2f**) (201 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **3af** as a light yellow solid; yield: 157 mg (64%).

3-(2-Nitrophenyl)pyridine (3ag): Compound **3ag** [CAS: 4253–80–9] was prepared following Method A from potassium 2-nitrobenzoate (**1a**) (246 mg, 1.20 mmol) and 3-bromopyridine (**2g**) (158 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 3:2) afforded **3ag** as an orange oil; yield: 167 mg (83%).

Method B (Table 3): An oven-dried 10-mL microwave vial was charged with the potassium carboxylate (**1b–l**) (1.20 mmol), copper(I) iodide (19.0 mg, 0.10 mmol), palladium(II) acetylacetonate (3.00 mg, 0.01 mmol) and 1,10-phenanthroline (29.9 mg, 0.16 mmol). The reaction vessel was sealed, evacuated and flushed with argon three times. Subsequently, a solution of 4-bromotoluene (**2a**) (171 mg, 1.00 mmol) in NMP (0.5 mL) and quinoline (0.5 mL) was added *via* syringe. The resulting mixture was first stirred in a water bath at 50 °C for 10 min, then irradiated in the microwave at 190 °C for 5 min at a maximum power of 50 W, then air-jet cooled. The reaction mixture was diluted with aqueous HCl (1 N, 10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the volatiles were removed under vacuum. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient), yielding the corresponding biaryl.

2-Fluoro-4′-methylbiphenyl (3ba): Compound **3ba** [CAS: 72093–41–5] was prepared following Method B from potassium 2-fluorobenzoate (**1b**) (214 mg, 1.20 mmol) and 4-bromotoluene (**2a**) (171 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane) afforded **3ba** as a colorless oil; yield: 151 mg (81%).

2-(4-Methylphenyl)thiophene (3ca): Compound **3ca** [CAS: 16939–04–1] was prepared following Method B from potassium thiophene-2-carboxylate (**1c**) (199 mg, 1.20 mmol) and 4-bromotoluene (**2a**) (171 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane) afforded **3ca** as a white solid; yield: 130 mg (75%).

2-(4-Methylphenyl)furan (3da): Compound **3da** [CAS: 17113–32–5] was prepared following Method B from potassi-

um furan-3-carboxylate (**1d**) (180 mg, 1.20 mmol) and 4-bromotoluene (**2a**) (171 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane) afforded **3da** as a colorless oil; yield: 102 mg (38%).

4′-Methylbiphenyl-2-carboxylic acid isopropyl ester (3ea): Compound **3ea** [CAS: 937166–54–6] was prepared following Method B from potassium 2-isopropyloxycarbonyl benzoate (**1e**) (296 mg, 1.20 mmol), copper(I) oxide (14.3 mg, 0.10 mmol) and 4-bromotoluene (**2a**) (171 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **3ea** as a white solid; yield: 138 mg (54%).

2-Cyano-4′-methylbiphenyl (3fa): Compound **3fa** [CAS: 114772–53–1] was prepared from 2-cyanobenzoic acid (**1f**) (177 mg, 1.20 mmol), copper(II) oxide (11.9 mg, 0.15 mmol), palladium(II) bromide (5.30 mg, 0.02 mmol), 1,10-phenanthroline (27.0 mg, 0.15 mmol), potassium carbonate (138 mg, 1.00 mmol), potassium fluoride (29.0 mg, 0.50 mmol) and 3 Å molecular sieves (250 mg, pulverized and dried in the microwave). The reaction vessel was evacuated and flushed with argon three times. Subsequently, a solution of 4-bromotoluene (**2a**) (171 mg, 1.00 mmol) in quinoline (1.0 mL) was added *via* syringe. The resulting mixture was stirred in the microwave at 250 °C for 5 min at 150 W, then diluted with aqueous HCl (1 N, 10 mL), and extracted repeatedly with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the volatiles were removed under vacuum. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate 4:1), affording **3fa** as a yellow solid; yield: 130 mg (68%).

4-Methyl-2′-formylbiphenyl (3ga): Compound **3ga** [CAS: 16191–28–9] was prepared following Method B from potassium 2-formylbenzoate (**1g**) (226 mg, 1.20 mmol) and 4-bromotoluene (**2a**) (171 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **3ga** as a light yellow oil; yield: 68.0 mg (35%).

3,4′-Dimethyl-2-nitrobiphenyl (3ha): Compound **3ha** was prepared following Method B from potassium 3-methyl-2-nitrobenzoate (**1h**) (263 mg, 1.20 mmol) and 4-bromotoluene (**2a**) (171 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **3ha** as a yellow solid; yield: 198 mg (87%); mp 71–72 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.40 (t, J = 7.7 Hz, 1H), 7.25–7.28 (m, 4H), 7.21–7.24 (m, 2H), 2.39 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 150.8 (s), 138.2 (s), 134.2 (s), 133.7 (s), 132.9 (s), 132.7 (s), 129.9 (s), 129.9 (s), 129.5 (s), 129.4 (s), 128.5 (s), 127.7 (s), 124.5 (s), 21.1 (s), 17.3 (s); MS (EI): *m/z* (%) = 227 (85) [M^+], 210 (100), 199 (53), 182 (64), 165 (57), 156 (31); IR (KBr): $\tilde{\nu}$ = 2919 (m), 1526 (s), 1466 (s), 1369 (s), 851 (m), 782 (s), 517 (m) cm^{-1}; anal. calcd. for $C_{14}H_{13}NO_2$: C 74.0, H 5.8, N 6.2; found: C 74.0, H 5.8, N 6.1.

4′,5-Dimethyl-2-nitrobiphenyl (3ia): Compound **3ia** [CAS: 70689–98–4] was prepared following Method B from potassium 5-methyl-2-nitrobenzoate (**1i**) (263 mg, 1.20 mmol) and 4-bromotoluene (**2a**) (171 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **3ia** as a light yellow solid; yield: 183 mg (81%).

4-Methyl-3′-nitrobiphenyl (3ja): Compound **3ja** [CAS: 53812–68–3] was prepared following Method B from potassium 3-nitrobenzoate (**1j**) (246 mg, 1.20 mmol) and 4-bromotoluene (**2a**) (171 mg, 1.00 mmol), afforded **3ja** in 5% GC yield.

1-(4-Methylphenyl)naphthalene (3ka): Compound **3ka** [CAS: 27331–34–6] was prepared following Method B from potassium 1-naphthoate (**1k**) (252 mg, 1.20 mmol) and 4-bromotoluene (**2a**) (171 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane) afforded **3ka** as a colorless solid; yield: 65.9 mg (31%).

2-Acetyl-4′-methylbiphenyl (3la): Compound **3la** [CAS: 16927–79–0] was prepared following Method B from potassium 2-acetylbenzoate (**1l**) (243 mg, 1.20 mmol) and 4-bromotoluene (**2a**) (171 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **3la** as a yellow oil; yield: 80.5 mg (38%).

4-Methylbenzophenone (5aa): Compound **5aa** [CAS: 134–84–9] was prepared following Method B from potassium oxophenyl acetate (**4a**) (226 mg, 1.20 mmol) and 4-bromotoluene (**2a**) (171 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **5aa** as a yellow solid; yield: 162 mg (83%).

4,4′-Dimethylbenzophenone (5ba): Compound **5ba** [CAS: 611–97–2] was prepared following Method B from potassium oxo(4-methylphenyl) acetate (**4b**) (243 mg, 1.20 mmol) and 4-bromotoluene (**2a**) (171 mg, 1.00 mmol). Purification by column chromatography (SiO_2, hexane/ethyl acetate 4:1) afforded **5ba** as a light yellow solid; yield: 139 mg (66%).

The spectroscopic data (^{1}H, ^{13}C NMR, GC-MS) of all known compounds were found to be identical with those reported in the literature.

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