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Biaryl Synthesis via Pd-Catalyzed Decarboxylative Coupling of Aromatic Carboxylates with Aryl Halides

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Abstract: A new strategy for the regiospecific construction of unsymmetrical biaryls is presented, in which easily available salts of carboxylic acids are decarboxylated *in situ* to give arylmetal species that serve as the nucleophilic component in a catalytic cross-coupling reaction with aryl halides. The catalyst system consists of a copper phenanthroline complex that mediates the extrusion of CO_2 from aromatic carboxylates to generate arylcopper species, and a palladium complex that catalyzes the cross-coupling of these intermediates with aryl halides. This bimetallic system allows the direct coupling of various aryl, heteroaryl, or vinyl carboxylic acids with aryl or heteroaryl iodides, bromides, or chlorides at 160 °C in the presence of a mild base such as potassium carbonate. The present scope and potential economic impact of the reaction are demonstrated by the synthesis of 42 biaryls, some of which are of substantial industrial relevance. Remaining challenges and future perspectives of the new transformation are discussed.

Introduction

The biaryl moiety is an important structural motif in a great number of biologically active compounds and functional molecules.[1] In Figure 1, the natural product Biphenomycin,[2] the pharmaceuticals Valsartan[3] and Telmisartan,[4] the agrochemical Boscalid,[5] and liquid crystals for LCD screens[6] are depicted as examples of immensely economically valuable biaryls.

Traditional syntheses of biphenyl derivatives[7] such as the Scholl reaction,[8] the Gomberg−Bachmann[9] reaction, or Ullmann-type couplings[10] require rather harsh conditions and often suffer from low yields for the unsymmetrically substituted biaryls while recent strategies, including processes that involve directed ortho-metalation, are limited to a narrow range of substrates.[11] Catalytic cross-coupling reactions, e.g., of organotin,[12] -zinc,[13] -copper,[14] -boron,[15] or -magnesium compounds[16] constitute the most generally applicable strategy for synthesis of biaryls (Scheme 1). Among them, the Suzuki−Miyaura

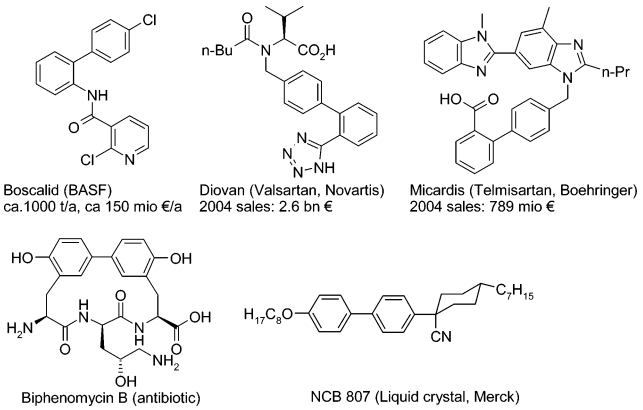

Figure 1. Examples illustrating the significance of the biaryl structural motif.

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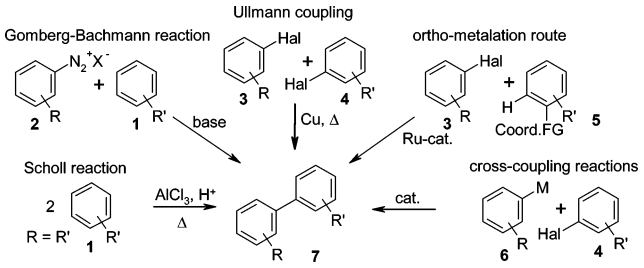
Scheme 1. Traditional Biaryl Syntheses



coupling of arylboronic acids is probably most widely used, both in laboratory and industrial biaryl syntheses.[17] Over the last decades, it has continuously been improved and reached an impressive level of performance.[18]

However, even the Suzuki−Miyaura reaction suffers from a fundamental drawback common to all related catalytic cross-couplings of aryl nucleophiles and electrophiles: It requires the use of stoichiometric amounts of an expensive organometallic compound, in this case a boronic acid. Like most other organometallic carbon nucleophiles applied in cross-coupling reactions, this must be prepared from sensitive precursors under elaborate anaerobic conditions.[19] For this reason, the formation of the organometallic coupling partner is often more difficult than the actual cross-coupling, especially when performed on an industrial scale. This issue is illustrated below for the synthesis of a Boscalid intermediate at BASF (Scheme 2, top), currently one of the largest industrial applications of the Suzuki−Miyaura reaction (ca. 1000 t/a).

In contrast to organometallic compounds, metal salts of aromatic carboxylic acids are stable against air and water and easily available at low cost. As the extrusion of CO_2 from such compounds should lead to the formation of organometallic species, we imagined that a combination of this step with a catalytic cross-coupling with an aryl halide could give a particularly attractive biaryl synthesis (Scheme 2, bottom). The main challenge in the design of such a process was that metal salts of aromatic carboxylates require extreme temperatures to lose CO_2, and that under such conditions, the resulting aryl-metal species are likely to undergo a fast protonation by the surrounding medium to give the corresponding arenes before they can be successfully coupled with aryl electrophiles.[20]

In order to reach our goal of a decarboxylative cross-coupling, we needed to design an efficient catalyst system with the dual ability to facilitate the strongly endothermic extrusion of carbon dioxide from aryl carboxylates to form stable aryl-metal compounds, and to mediate the selective cross-coupling of these species with aryl electrophiles. Copper appeared to be the metal of choice for the decarboxylation step, as it is widely used in protodecarboxylation procedures.[21] However, anticipating the known complications of Ullmann-type couplings such as low selectivities for the heterocoupling and low catalyst productivity, we saw little opportunity to also use this metal as the catalyst for the cross-coupling step.[22] Here, palladium seemed to be a more promising candidate, being known to efficiently mediate a large number of two-electron cross-coupling reactions.

A possible reaction pathway for the desired transformation is outlined in Scheme 3. The reaction of the aryl carboxylic acid with the copper catalyst would initially follow the proposed pathway for protodecarboxylation reactions, wherein the copper derivative is believed to coordinate to the carboxylate oxygen, shift to the aryl π-system, and insert into the C−C(O) bond under extrusion of CO_2 to form a stable aryl-copper intermediate.[20b] In parallel, the aryl halide should oxidatively add to the palladium catalyst. The arylcopper species would then transfer its aryl group to the palladium under formation of a copper halide, and finally, the desired biaryl would be released, regenerating the initial palladium species and resuming the catalytic cycle. In principle, the copper halide should be able to react with alkali metal carboxylates under ligand exchange, so that a stoichiometric amount of copper is not required.

We recently disclosed the viability of this concept along with a few examples in a preliminary communication.[23] In this full paper we give a detailed report of the catalyst development and the exploration of scope and limitations of the new transformation, as well as providing many new examples that reflect further progress in this field. Two alternative protocols for the biaryl formation are disclosed, one of which proceeds at 160 °C and is catalytic in palladium and for a steadily increasing number of substrates also in copper, whereas the other involves a stoichiometric amount of copper(II) carbonate as the base but operates at a lower temperature (120 °C).

Results and Discussion

Development of the Decarboxylative Cross-Coupling Methodology. As the model reaction for our screening experiments, we selected the cross-coupling of 2-nitrobenzoic acid (**10a**) with 4-bromochlorobenzene to form 2-nitro-4′-chlorobiphenyl; not only is this reaction of particular commercial interest as a key intermediate in the synthesis of Boscalid (see Figure 1),[5] but it also allows an easy detection of all reactants, products, and byproducts by gas chromatography (Scheme 4).

Selected results from our screening experiments are summarized in Table 1. With a monometallic palladium catalyst, all attempts failed to achieve any reaction turnover (Entry 1). This was not particularly surprising, as known palladium(II)-mediated decarboxylations, e.g., in Heck-type reactions of aryl carboxylic acids with olefins or of aryl halides with pyrrolecarboxylic acids, involve completely different mechanisms that cannot come into play in our model reaction.[24] Without palladium but using a stoichiometric amount of copper, the desired product could not be detected under various conditions at temperatures below 200 °C (Entry 2). However, when the carboxylic acid was deprotonated with a stoichiometric amount of $CuCO_3$ and reacted with the aryl bromide in the presence of

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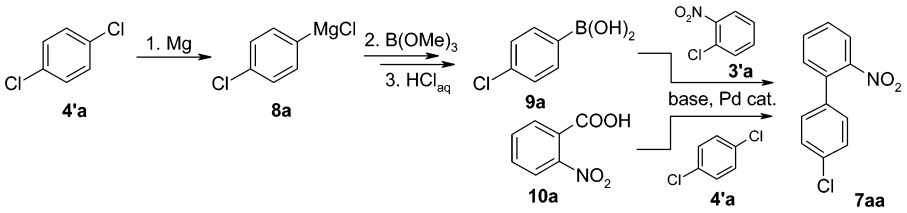
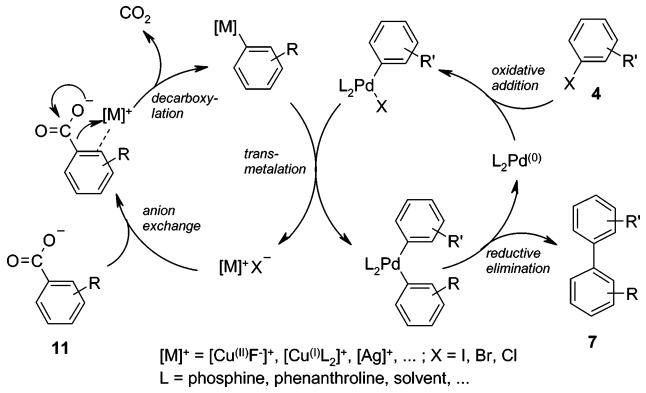
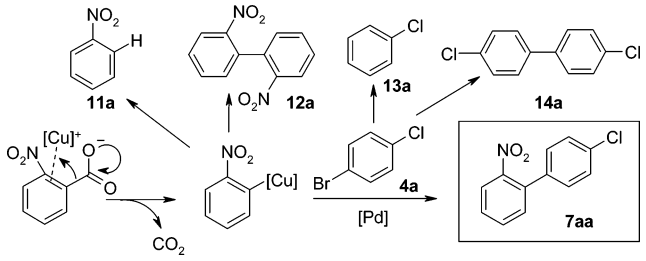
Scheme 2. Biaryl Synthesis from Aryl Halides *via* Boronic Acids and from Carboxylic Acids



Scheme 3. Proposed Mechanism for a Decarboxylative Biaryl Synthesis



Scheme 4. Products and Observed Byproducts for the Model Reaction



a catalytic amount of palladium at a temperature as low as 120 °C, small amounts of the desired biaryl **7aa** were detected along with some arene **11a** and the homocoupling products **12a** and **14a** (Entry 3). While modifications of the palladium source had only little influence on the reaction outcome (Entry 4), the addition of metal salts, particularly of alkali metal fluorides, significantly facilitated the reaction turnover, presumably due to an intermediate formation of ArC(O)OCuF, which seems to lower the decarboxylation barrier (Entries 5−7). This is in good agreement with the previously described finding that in the pyrolysis of Cu(II) benzoate, only one of the two carboxyl groups coordinated to the copper extrudes CO_2, leading to the formation of phenyl benzoate as an important byproduct.[25]

At this stage of our reaction development, protodecarboxylation to nitrobenzene (**11a**) became the main side reaction, so that we sought ways to efficiently remove water from the reaction mixture. Since the reaction temperature exceeded 100 °C, the water formed in the decarboxylation step mostly evaporated from the reaction medium and condensed in a cooler part of the vessel. Drying was clearly more effective when fitting the reaction vessel with a Soxhlet apparatus filled with molecular sieves, leading to a significant enhancement of the yields. For small-scale applications, suspending an excess of powdered 3 Å molecular sieves directly in the reaction mixture was more practical and suppressed the protodecarboxylation just as effectively, so that satisfactory yields were achieved with either method (Entry 8). The decarboxylation step could also be mediated by silver carbonate as an alternative to copper carbonate (Entry 9), but due to the high price of this metal, we did not further investigate this option and instead focused on optimizing the cross-coupling catalyst. A beneficial effect was observed for the addition of phosphines as ligands for the palladium; among them, diphenyl isopropylphosphine proved to have the ideal steric and electronic properties (Entries 10−13). *N*-Methylpyrrolidine (NMP) was the best solvent, but the reaction could also be performed in other polar aprotic media (Entries 14−17). We were pleased to find that the model reaction proceeded in excellent selectivity and almost quantitative conversion under optimized conditions, consisting of stoichiometric amounts of $CuCO_3$ and KF, an excess of powdered molecular sieves, and 2 mol % of a $Pd(acac)_2$/P(*i*-Pr)Ph_2 catalyst in an NMP solution at 120 °C.

Following the proposed mechanism (Scheme 3), the copper salt should be regenerated after each transmetalation step, so that a catalytic amount should theoretically suffice. However, when we tried to replace some of the $CuCO_3$ by K_2CO_3, the yields dropped to below the amount of copper employed (Entry 18). Raising the temperature from 120 °C or prolonging the reaction time did not change this, and in either case we observed a color shift from green to brown, indicative of a partial reduction of Cu(II) to Cu(I). A control experiment revealed that at 160 °C, the reduction of the copper by the NMP solvent was complete within less than 1 h. This led us to conclude that a reaction protocol catalytic in both metals would only be possible with more stable but less effective Cu(I) complexes, at the expense of an increased reaction temperature. However, even at 160 °C, stoichiometric amounts of simple copper(I) salts gave only very low conversions (Entries 19, 20). A reaction catalytic in copper appeared to be out of reach until we discovered that chelating bipyridine derivatives dramatically enhanced the decarboxylation activity of the copper catalyst (Entries 21−23). In the presence of bipyridine as the ligand for both copper and palladium, turnover was accomplished for the first time using substoichiometric amounts of copper, and with 3% phenanthroline as the ligand, 1% CuI and 0.5% $Pd(acac)_2$ sufficed for near-quantitative coupling in small-scale experiments (Entries 22, 23).

This optimized protocol could be easily scaled up from millimolar to molar quantities without a decrease in yields. On the contrary, when performed on preparative scale, its efficiency could be further enhanced using a more elaborate reaction setup consisting of a round-bottom flask equipped with a Soxhlet apparatus filled with molecular sieves. The flask was charged with purified potassium 2-nitrobenzoate and 4-bromotoluene in a 1:1 ratio as a concentrated solution in a toluene/quinoline

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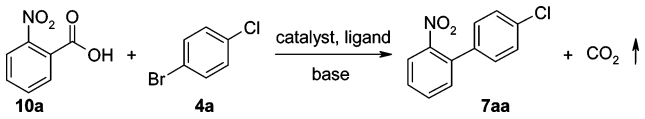
Table 1. Development of Decarboxylative Cross-Coupling Reaction Conditions[a]



10a **4a** **7aa**

entry	catalyst	ligand	base	additives	*T* (°C)	solvent	**7aa** (%)
1	2% $Pd(acac)_2$	6% PPh_3	K_2CO_3	−	120	NMP	0
2	−	6% PPh_3	$CuCO_3$	−	120	NMP	0
3	2% $Pd(acac)_2$	6% PPh_3	$CuCO_3$	−	120	NMP	5
4	2% $PdCl_2$	6% PPh_3	$CuCO_3$	−	120	NMP	3
5	2% $Pd(acac)_2$	6% PPh_3	$CuCO_3$	KBr	120	NMP	14
6	2% $Pd(acac)_2$	6% PPh_3	$CuCO_3$	NaF	120	NMP	16
7	2% $Pd(acac)_2$	6% PPh_3	$CuCO_3$	KF	120	NMP	32
8	2% $Pd(acac)_2$	6% PPh_3	$CuCO_3$	KF/3 Å MS	120	NMP	84
9	2% $Pd(acac)_2$	6% PPh_3	Ag_2CO_3	KF/3 Å MS	120	NMP	47
10	2% $Pd(acac)_2$	3% BINAP	$CuCO_3$	KF/3 Å MS	120	NMP	76
11	2% $Pd(acac)_2$	6% $P(Cy)_3$	$CuCO_3$	KF/3 Å MS	120	NMP	60
12	2% $Pd(acac)_2$	10% bipyridine	$CuCO_3$	KF/3 Å MS	120	NMP	35
13	2% $Pd(acac)_2$	6% P(*i*-Pr)Ph_2	$CuCO_3$	KF/3 Å MS	120	NMP	98
14	2% $Pd(acac)_2$	6% P(*i*-Pr)Ph_2	$CuCO_3$	KF/3 Å MS	120	DMSO	69
15	2% $Pd(acac)_2$	6% P(*i*-Pr)Ph_2	$CuCO_3$	KF/3 Å MS	120	DMPU	62
16	2% $Pd(acac)_2$	6% P(*i*-Pr)Ph_2	$CuCO_3$	KF/3 Å MS	120	mesitylene	0
17	2% $Pd(acac)_2$	6% P(*i*-Pr)Ph_2	$CuCO_3$	KF/3 Å MS	120	diglyme	40
18	2% $Pd(acac)_2$, 5% $CuCO_3$	6% P(*i*-Pr)Ph_2	K_2CO_3	KF/3 Å MS	120	NMP	4
19	2% $Pd(acac)_2$, 120% CuI	6% P(*i*-Pr)Ph_2	K_2CO_3	3 Å MS	120	NMP	5
20	2% $Pd(acac)_2$, 120% CuI	6% P(*i*-Pr)Ph_2	K_2CO_3	3 Å MS	160	NMP	22
21	2% $Pd(acac)_2$, 120% CuI	10% bipyridine	K_2CO_3	3 Å MS	160	NMP	72
22	2% $Pd(acac)_2$, 30% CuI	30% bipyridine	K_2CO_3	3 Å MS	160	NMP	78
23	0.5% $Pd(acac)_2$, 1% CuI	3% phenanthr	K_2CO_3	3 Å MS	160	NMP	98
24[b]	0.03% $Pd(acac)_2$, 0.3% Cu*	−	−	−	150	toluene/quinoline	**7ac** 92

[a] Conditions: 1.00 mmol 4-bromochlorobenzene, 1.50 mmol 2-nitrobenzoic acid, 1.50 mmol base (1.20 mmol for K_2CO_3), 1.50 mmol additive (500 mg for molecular sieves = MS), 24 h. Conversions were determined by GC analysis using *n*-tetradecane as the internal standard. [b] Conditions: 80.0 mmol 4-bromotoluene, 80.0 mmol potassium 2-nitrobenzoate, (1,10-phenanthroline)bis (triphenylphosphine)copper(I) nitrate (Cu*) as cocatalyst/azeotropic removal of water, isolated yield.

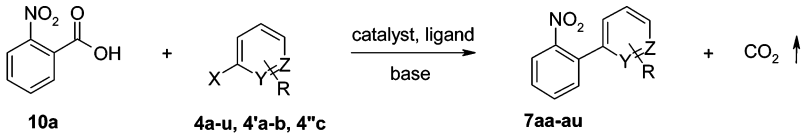
mixture. After addition of the catalyst, part of the solvent was distilled off while azeotroping off traces of water until a constant boiling temperature of 150 °C was reached. Under these conditions, the catalyst loading could be reduced to 0.03% Pd and 0.3% Cu in the form of commercially available (1,10-phenanthroline)bis(triphenylphosphine)copper(I) nitrate. The product was isolated in an impressive 92% yield and >99% purity after aqueous workup and Kugelrohr distillation (Entry 24).

Scope with Regard to the Halide Substrate. We next set out to explore the generality of the reaction with regard to the aryl halide coupling partner and were pleased to find that both reaction protocols are broadly applicable to the coupling of a wide array of aryl bromides with 2-nitrobenzoic acid (**10a**) (Table 2). Both electron-rich and electron-poor derivatives were successfully converted, and a broad range of functional groups including esters, ethers, aldehydes, ketones, nitriles, thioethers, and even nitrogen-containing heterocycles were tolerated. Sterically demanding substrates could also be coupled in good yields. Moreover, the reaction is not limited to aryl bromides but can also be performed with aryl iodides and even aryl chlorides using the same catalyst system (Table 2, last three entries)

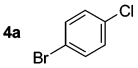
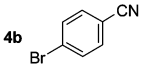
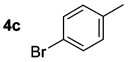
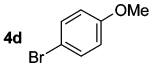
Investigation of the Decarboxylation Step. While varying the aryl halide substrate was surprisingly easy, extending the reaction from 2-nitrobenzoic acid (**10a**) to other carboxylic acids initially proved to be troublesome:[23] A notable but limited range of carboxylic acids could be converted in the presence of stoichiometric amounts of copper, but approaches involving catalytic copper long remained limited to 2-nitrobenzoic acids. This was not unexpected, as a good balance of the rates of the decarboxylation and cross-coupling steps is crucial to achieve high yields of the desired product and to avoid the undesired byproducts **12** and **14** (Scheme 4). In order to design effective catalyst systems for a range of carboxylic acids, we were interested in getting an idea of their relative activity toward decarboxylation in comparison to our model substrate 2-nitrobenzoic acid. Table 3 summarizes the results obtained for the decarboxylation step examined separately from the cross-coupling for a range of acids, in the absence of the Pd catalyst and aryl halide, but otherwise under conditions similar to those of the decarboxylative cross-coupling. As no base was added, protons were amply available allowing an easy formation of the corresponding arenes **11** from the intermediate arylcopper species (see Table 3).

We were excited to find that with our most effective catalyst system consisting of Cu_2O/phenanthroline in a 1:3 mixture of quinoline and NMP, a broad range of carboxylic acids smoothly decarboxylated at a sufficiently high rate (Table 3, first data column). This led us to conclude that there is no intrinsic limitation to the applicability of the decarboxylative cross-coupling reaction with respect to the carboxylate substrate. However, the addition of a halide salt, as would inevitably form in such a process (see Scheme 3), was found to substantially retard the decarboxylation step (Table 3, second and third data columns). For 2-nitrobenzoic acid (**10a**), already an equimolar amount of potassium bromide with regard to the copper slightly slowed down the decarboxylation process with one of our earlier catalysts that contained quinoline as the only copper ligand, and adding excess bromide led to a further drop in conversion (Table 3, numbers in brackets). Using phenanthroline as the ligand,

Table 2. Scope of the Cross-Coupling Reaction with Regard to the Aryl Halide Substrate[a]



10a **4a-u, 4'a-b, 4"c** **7aa-au**

Aryl halide	Method	prod. No Yield (%)	Aryl halide	Method	prod. No Yield (%)
4a 		**7aa**	**4b** 		**7ab**
	A	96		A	96
	B	99		B	93
4c 		**7ac**	**4d** 		**7ad**
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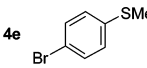
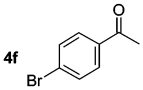
	B	72		B	68
4e 		**7ae**	**4f** 		**7af**
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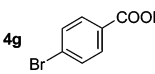
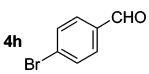
	B	98[b]		B	57
4g 		**7ag**	**4h** 		**7ah**
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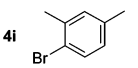
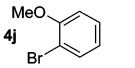
	B	96		B	78
4i 		**7ai**	**4j** 		**7aj**
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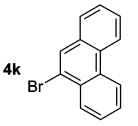
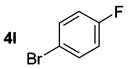
	B	23		B	30
4k 		**7ag**	**4l** 		**7al**
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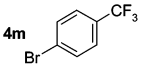
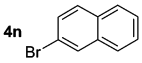
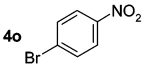
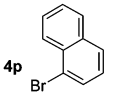
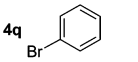
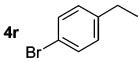
	B	99		B	97
4m 		**7am**	**4n** 		**7an**
	A	83		A	94
	B	93		B	94
4o 		**7ao**	**4p** 		**7ap**
	A	95		A	88
	B	77[b]		B	97
4q 		**7aq**	**4r** 		**7ar**
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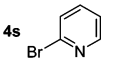
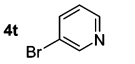
	B	91		B	62
4s 		**7as**	**4t** 		**7at**
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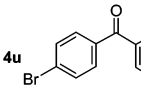
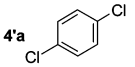
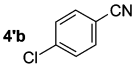
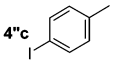
	B	53		B	98
4u 		**7au**	**4'a** 		**7aa**
	A	94		A	0
	B	99		B	66
4'b 		**7ab**	**4"c** 		**7ac**
	A	12		A	84
	B	96		B	38

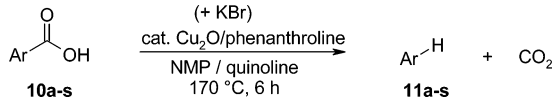
[a] Conditions: Method A: 1.00 mmol aryl bromide, 1.50 mmol carboxylic acid, 0.02 mmol $Pd(acac)_2$, 0.06 mmol P(*i*-Pr)Ph_2, 1.50 mmol $CuCO_3$, 1.50 mmol KF, 500 mg ground 3 Å MS, 3 mL NMP, 120 °C, 24 h, isolated yields. Method B: 1 mmol aryl bromide, 1.50 mmol carboxylic acid, 0.01 mmol $Pd(acac)_2$, 0.03 mmol CuI, 0.05 mmol 1,10-phenanthroline, 1.20 mmol K_2CO_3, 250 mg 3 Å MS, 1.5 mL NMP, 160 °C, 24 h, isolated yields.

the conversion remained unaffected by the presence of bromide, demonstrating the superiority of this catalyst system and explaining why 2-nitrobenzoic acid (**10a**) is such a good substrate for the decarboxylative cross-coupling.

This trend was amplified in the case of 2-cyanobenzoic acid (**10b**), which is one of the least reactive compounds that we were able to cross-couple successfully. Here, the quinoline system no longer mediated the decarboxylation when a halide salt was present, while the phenanthroline system retained a sufficient level of activity. For even less reactive acids such as 4-nitrobenzoic acid (**10c**), the rates were still too low even with our best ligand system, so that it appeared unlikely that this carboxylic acid could be successfully cross-coupled under decarboxylation using catalytic amounts of a copper phenanthroline system.

The second data column of Table 3 shows that the carboxylic acids tested can be roughly divided into two categories: Some only decarboxylate with the phenanthroline copper catalyst in the absence of bromide ions and will thus probably require a stoichiometric amount of copper in the cross-coupling process, while others tolerate the presence of halides so that catalytic amounts of copper can be expected to suffice. Among the substrates that are least affected by the presence of halides are many ortho-substituted or heterocyclic carboxylic acids, presumably because they are able to coordinate to the copper in a bidentate fashion. This may help them to compete successfully

Table 3. The Decarboxylation Step and the Influence of Bromide Ions[a]



10a-s **11a-s**

Ar (product no.)	yield (%)[b] at the following rel. amount of KBr: 0%	15%	100%
2-NO_2-C_6H_4-(**11a**)	100 (95)	100 (95)	95 (60)
2-CN-C_6H_4-(**11b**)	40 (15)	25 (10)	10 (0)
4-NO_2-C_6H_4-(**11c**)	52 (8)	25 (0)	0 (0)
2-CHO-C_6H_4-(**11d**)	67	67	
2-MeCO-C_6H_4-(**11e**)	79	76	
2-^{i}PrCO$_2$-C_6H_4-(**11f**)	70	70	
2-Et_2NCO-C_6H_4-(**11g**)	68	61	
2-$MeSO_2$-C_6H_4-(**11h**)	54	43	
2-F-C_6H_4-(**11i**)	75	75	
2-MeO-C_6H_4-(**11j**)	28	7	
2-PhNH-C_6H_4-(**11k**)	96	23	
2-CF_3-C_6H_4-(**11l**)	50	15	
2-MeCONH-C_6H_4-(**11m**)	48	0	
2-naphthalene-(**11n**)	61	24	
2-thiophene-(**11o**)	38	34	
Ph-CH_2═CH_2-(**11p**)	40	40	
3-CN-C_6H_4-(**11q**)	72	24	
4-MeO-C_6H_4-(**11r**)	23	0	
3-thiophene-(**11s**)	44	7	

[a] Conditions: 1.00 mmol benzoic acid derivative, 0.075 mmol Cu_2O, 0.15 mmol 1,10-phenanthroline, 0.5 mL quinoline, 1.5 mL NMP, 170 °C, 6 h. Conversions were determined by GC analysis using *n*-tetradecane as the internal standard. Part of the product remained bound to the copper and is not included in the reported yield [b] Numbers in brackets correspond to reactions performed without phenanthroline.

with the halide for the required coordination site at the copper. Following this hypothesis, the key to achieving a generally applicable process catalytic in both metals should be to induce a stronger preference of the copper for carboxylate over bromide ions by tuning its ligand environment.

Scope with Regard to the Carboxylate Substrate. With gradual improvements of the copper catalyst, we were already able to extend the range of carboxylic acids that decarboxylate in the presence of bromide salts from 2-nitrobenzoic acids, which decarboxylate even in the presence of simple CuI, initially to carboxylic acids with other strongly coordinating groups in ortho-position that increase the copper-ligating quality of the carboxylate substrate (2-acyl, 2-formyl), later to carboxylic acids with weakly coordinating ortho-substituents (2-methoxy, 2-cyano), and finally to vinylic or heterocyclic derivatives (cinnamic, thiophenecarboxylic acids). This seems to be the performance limit when employing phenanthroline as the copper ligand, but ongoing work indicates that the use of more elaborate copper ligands leads to a further substantial increase in decarboxylation activity, especially for meta- and para-substituted carboxylic acids.

On the basis of the decarboxylation results in Table 3, we probed the scope of the overall process with regard to the carboxylic acid substrate. Selected results are summarized in Table 4. Previously, we needed to optimize the reaction for each substrate individually and, as a result, reported multiple alternative procedures. Now, we have identified a single protocol involving 10% of a Cu(I)Br/phenanthroline catalyst along with 3% palladium bromide (method B′) that is applicable to a remarkable range of derivatives, among them all derivatives that efficiently decarboxylate in the presence of KBr. For some substrates for which the process catalytic in both Pd and Cu did not give satisfactory yields, reaction turnover was still achieved in the presence of stoichiometric amounts of copper (Table 4, last five entries). We restricted the number of examples for the less desirable stoichiometric processes (method A, C), as ongoing catalyst development in our group seems to indicate that improved copper catalyst will allow a further extension of the substrate scope for the protocol catalytic in both metals. However, the fact that even the notoriously unreactive, electron-rich 4-methoxybenzoic acid (**10r**) could be coupled in moderate yield shows that a process stoichiometric in copper may turn out to have a considerable scope.

Summary and Outlook

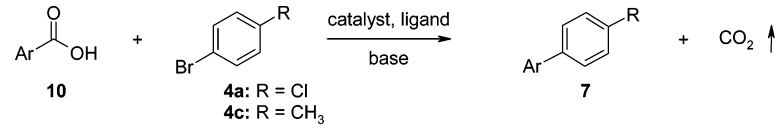
A decarboxylative cross-coupling of arenecarboxylates with aryl halides mediated by a Cu/Pd catalyst was developed as a new strategy for biaryl synthesis. Its key advantage in comparison to existing protocols is that it draws on readily available carboxylic acids as sources of aryl nucleophiles in place of expensive organometallic compounds. Two alternative protocols were developed, one with a stoichiometric and the other with a catalytic amount of copper, both of them broadly applicable with regard to the aryl halide substrate and a growing number of carboxylic acid coupling partners. In the protocol catalytic in copper, best results were obtained with ortho-substituted or heterocyclic carboxylic acids, which are able to coordinate to copper in a chelating fashion allowing them to successfully compete with halides for coordination sites. Current work is directed toward the development of more active catalyst systems with ligands designed to induce a stronger preference of the copper component for carboxylate ions over halides and, alternatively, to the use of aryl sulfonates as halide-free coupling partners. The goal is to extend the scope of the decarboxylative cross-coupling, hopefully to the entire range of aromatic, vinylic, and heteroaromatic acids.

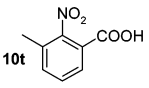
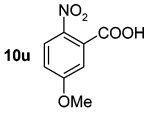
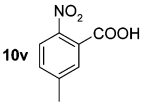
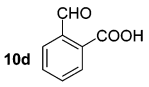
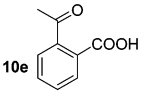
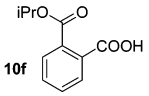
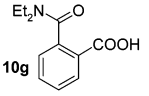
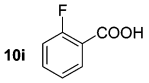
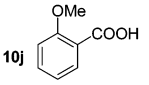
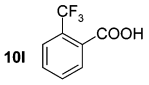
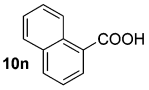
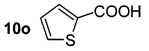
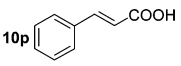
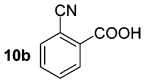
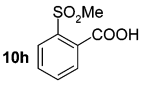
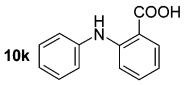
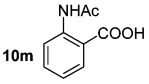
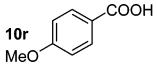
Experimental Section

General Methods. Reactions were performed in oven-dried glassware under a nitrogen atmosphere containing a Teflon-coated stirrer bar and dry septum, unless otherwise specified. 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 ramp to 300 °C and then 3 min at this temperature. Column chromatography was performed using a Combi Flash Companion-Chromatography-System (Isco-Systems) and Redi*Sep* packed columns (12 g). NMR spectra were obtained on Bruker AMX 400 systems using $CDCl_3$ as solvent, with proton and carbon resonances at 400 and 100 MHz, respectively. Mass spectral data were acquired on a GC-MS Saturn 2100 T (Varian).

Biaryl Synthesis from Copper(II) Nitrobenzoate (Method A, Table 1, 2, and 4). An oven-dried 20 mL crimp top vial equipped with a septum cap was charged with 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol), $CuCO_3$ (185 mg, 1.50 mmol), and NMP (1 mL). The resulting mixture was stirred for 0.5 h at 120 °C, then the solvent was evaporated under reduced pressure to remove most of the reaction water.

Table 4. Substrate Scope of the Cross-Coupling Reaction



ArCOOH	Method	prod. No Yield (%)	ArCOOH	prod. No Method	Yield (%)
 **10t**	B	**7ta**[a] 74	 **10u**	B	**7ua**[a] 77
 **10v**	B	**7va**[a] 51	 **10d**	B'	**7dc** 61
 **10e**	B'	**7ec** 69	 **10f**	B'	**7fc** 51
 **10g**	B'	**7gc** 45	 **10i**	B'	**7ic** 76
 **10j**	B'	**7jc** 46	 **10l**	B'	**7lc** 31
 **10n**	B'	**7nc**[b] 57	 **10o**	B'	**7oc** 62
 **10p**	B'	**7pc** 79	 **10b**	B' C	**7bc** 34 55
 **10h**	B' C	**7hc** 42 97	 **10k**	B' C	**7kc** 0 91
 **10m**	B' C	**7mc** 0 42	 **10r**	B' A	**7rc** 0 41[c]

Conditions: Methods A and B: see Table 2; method B′: 1.20 mmol 4-bromotoluene (**4c**), 1.00 mmol carboxylic acid, 0.03 mmol $PdBr_2$, 0.10 mmol CuBr, 0.10 mmol 1,10-phenanthroline, 1.00 mmol K_2CO_3, 250 mg ground 3 Å MS, 1.5 mL NMP, 0.5 mL quinoline, 170 °C, 24 h, isolated yields; method C: 1.00 mmol aryl bromide, 1.30 mmol carboxylic acid, 0.02 mmol $Pd(acac)_2$, 1.20 mmol CuI, 0.10 mmol 2,2′-bipyridine, 1.20 mmol K_2CO_3, 500 mg 3 Å MS, 3 mL NMP, 160 °C, 24 h, isolated yields. [a] Using 4-bromochlorobenzene (**4a**) as coupling partner. [b] At 150 °C. [c] At 160 °C.

Subsequently, the reaction vessel was charged with $Pd(acac)_2$ (6.1 mg, 0.02 mmol), *iso*-propyldiphenylphosphine (13.7 mg, 0.06 mmol), potassium fluoride (87 mg, 1.50 mmol), and pulverized 3 Å molecular sieves (500 mg). After the vessel was flushed with alternating vacuum and nitrogen purge cycles, a solution of the corresponding aryl halide (**4a**−**u**, **4′a,b**, **4″c**) (1.00 mmol) and the internal standard *n*-tetradecane (50 μL) in NMP (3 mL) was added *via* syringe. The resulting mixture was stirred at 120 °C for 24 h, poured into aqueous HCl (1 N, 20 mL), and extracted repeatedly with 20 mL portions of ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and 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.

Biaryl Synthesis Using a Catalytic Amount of Copper (Method B, Table 2 and 4). An oven-dried 20 mL vessel was charged with 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol), potassium carbonate (167 mg, 1.20 mmol), and NMP (1 mL). The resulting mixture was stirred for 0.5 h at 120 °C, and then the solvent was evaporated under reduced pressure to remove the reaction water. Copper(I) iodide (5.7 mg, 0.03 mmol), palladium acetylacetonate (3.0 mg, 0.01 mmol), 1,-10-phenanthroline (9 mg, 0.05 mmol), and pulverized 3 Å molecular sieves (250 mg) were added, and the reaction vessel was evacuated and flushed with nitrogen three times. Subsequently, a solution of the corresponding aryl halide (**4a**−**u**, **4′a,b**, **4″c**) (1.00 mmol) and the internal standard *n*-tetradecane (50 μL) in NMP (1.5 mL) was added *via* syringe. The resulting mixture was stirred at 160 °C for 24 h, diluted with aqueous HCl (1 N, 10 mL), and extracted repeatedly with 20 mL portions of ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and 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′ (Table 4). Method B′ is analogous to Method B but with a higher loading of a modified catalyst and performing the reaction at 170 °C. The following amounts were used: carboxylic acid (**10d**−**r**) (1.00 mmol), potassium carbonate (138 mg, 1.00 mmol), copper(I) bromide (14.3 mg, 0.10 mmol), palladium bromide (8.0 mg, 0.03 mmol), 1,10-phenanthroline (18.0 mg, 0.10 mmol), pulverized 3 Å

molecular sieves (250 mg), and a solution of 4-bromotoluene (**4c**) (205 mg, 1.20 mmol) and the internal standard *n*-tetradecane (50 μL) in a mixture of NMP (1.5 mL) and quinoline (0.5 mL). The residue was again purified by column chromatography (SiO_2, ethyl acetate/hexane gradient), yielding the corresponding biaryl.

Biaryl Synthesis Using a Stoichiometric Amount of Copper (Method C, Table 4). Method C is analogous to Method B but with a stoichiometric amount of copper. The following amounts were used: carboxylic acid (**10**) (1.30 mmol), 4-bromotoluene (**4c**) (171 mg, 1.00 mmol), palladium acetylacetonate (5.3 mg, 0.02 mmol), copper(I) iodide (286 mg, 1.50 mmol), 2,2′-bipyridine (15.6 mg, 0.10 mmol), potassium carbonate (167 mg, 1.20 mmol), pulverized 3 Å molecular sieves (250.0 mg), and a solution of 4-bromotoluene (**4c**) (205 mg, 1.20 mmol) and the internal standard *n*-tetradecane (50 μL) in NMP (3 mL).

Large Scale Procedure for the Synthesis 4-Methyl-2′-nitrobiphenyl (7ac) (Table 1, Entry 24). An oven-dried flask was equipped with an internal thermometer and a Soxhlet apparatus filled with molecular sieves and charged with purified potassium 2-nitrobenzoate (16.4 g, 80.00 mmol), (1,10-phenanthroline)bis-(triphenyl-phosphine)-copper(I) nitrate (199 mg, 0.24 mmol), and palladium acetyl-acetonate (7.3 mg, 0.024 mmol). After the vessel was flushed with alternating vacuum and nitrogen purge cycles, a solution of 4-bromotoluene (**4c**) (13.7 g, 80.00 mmol) in a mixture of toluene (60 mL) and quinoline (60 mL) was added. The vessel was lowered into an oil bath preheated to 175 °C, and part of the solvent was distilled off until the boiling temperature remained constant at 150 °C. After the reaction mixture was stirred for 24 h, it was allowed to cool to room temperature, acidified with aqueous HCl (5 N, 100 mL), and extracted repeatedly with toluene. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The volatiles were removed *in vacuo*, and the residue was purified by Kugelrohr distillation yielding **7ac** (15.6 g, 92%) as a yellow oil.

Synthesis of 4-Chloro-2′-nitrobiphenyl (7aa). Compound **7aa** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 4-bromochlorobenzene (**4a**) (191 mg, 1.00 mmol), yielding **7aa** as a yellow solid (216 mg, 96%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-chloro-2′-nitrobiphenyl [CAS: 6271-80-3]. Compound **7aa** was also prepared using the same amounts following Method B in 99% yield (231 mg).

Synthesis of 4-Chloro-2′-nitrobiphenyl (7aa) from 1,4-Dichlorobenzene (4′a). Compound **7aa** was also prepared from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 1,4-dichlorobenzene (**4′a**) (441 mg, 3.00 mmol) following Method B to give 154 mg (66%).

Synthesis of 4-Cyano-2′-nitrobiphenyl (7ab). Compound **7ab** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 1-bromo-4-cyanobenzene (**4b**) (181 mg, 1.00 mmol), yielding **7ab** as a yellow solid (216 mg, 96%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-cyano-2′-nitrobiphenyl [CAS: 75898-34-9]. Compound **7ab** was also prepared using the same amounts following Method B in 93% yield (208 mg).

Synthesis of 4-Cyano-2′-nitrobiphenyl (7ab) from 1-Chloro-4-cyanobenzene (4′b). Compound **7ab** was also prepared from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 1-chloro-4-cyanobenzene (**4′b**) (137 mg, 1.00 mmol), to give 27 mg (12%) following Method A, and 216 mg (96%) following Method B.

Synthesis of 4-Methyl-2′-nitrobiphenyl (7ac). Compound **7ac** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 4-bromotoluene (**4c**) (171 mg, 1.00 mmol), yielding **7ac** as a yellow oil (206 mg, 97%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methyl-2′-nitrobiphenyl [CAS: 70680-21-6]. Compound **7ac** was also prepared using the same amounts following Method B in 72% yield (153 mg).

Synthesis of 4-Methyl-2′-nitrobiphenyl (7ac) from 4-Iodotoluene (4′′c). Compound **7ac** was also prepared from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 4-iodotoluene (**4′′c**) (218 mg, 1.00 mmol), to give 179 mg (84%) following Method A, and 81 mg (38%) following Method B.

Synthesis of 4-Methoxy-2′-nitrobiphenyl (7ad). Compound **7ad** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 4-bromoanisole (**4d**) (187 mg, 1.00 mmol), yielding **7ad** as a yellow oil (181 mg, 79%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methoxy-2′-nitrobiphenyl [CAS: 20013−55-2]. Compound **7ad** was also prepared using the same amounts following Method B in 68% yield (156 mg).

Synthesis of 4-Methylthio-2′-nitrobiphenyl (7ae). Compound **7ae** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 1-bromo-4-methylsulfanyl benzene (**4e**) (203 mg, 1.00 mmol), yielding **7ae** as a yellow solid (201 mg, 82%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methylthio-2′-nitrobiphenyl [CAS: 911217-03-3]. Compound **7ae** was also prepared using the same amounts following Method B in 98% yield (240 mg).

Synthesis of 4-Acetyl-2′-nitrobiphenyl (7af). Compound **7af** was prepared following Method A from (250 mg, 1.50 mmol) and 4-bromoacetophenone (**4f**) (199 mg, 1.00 mmol), yielding **7af** as a yellow solid (208 mg, 86%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-acetyl-2′-nitrobiphenyl [CAS: 5730-96-1]. Compound **7af** was also prepared using the same amounts following Method B in 57% yield (137 mg).

Synthesis of 4-(Ethoxycarbonyl)-2′-nitrobiphenyl (7ag). Compound **7ag** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 4-bromobenzoic acid ethyl ester (**4g**) (229 mg, 1.00 mmol), yielding **7ag** as a yellow solid (263 mg, 97%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-(ethoxycarbonyl)-2′-nitrobiphenyl [CAS: 108621-65-4]. Compound **7ag** was also prepared using the same amounts following Method B in 96% yield (260 mg).

Synthesis of 4-Formyl-2′-nitrobiphenyl (7ah). Compound **7ah** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 4-bromobenzaldehyde (**4h**) (185 mg, 1.00 mmol), yielding **7ah** as a yellow solid (212 mg, 93%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-formyl-2′-nitrobiphenyl [CAS: 169188-17-4]. Compound **7ah** was also prepared using the same amounts following Method B in 78% yield (177 mg).

Synthesis of 2,4-Dimethyl-2′-nitrobiphenyl (7ai). Compound **7ai** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 4-bromo-*m*-xylene (**4i**) (185 mg, 1.00 mmol), yielding **7ai** as a yellow solid (212 mg, 93%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2,4-dimethyl-2′-nitrobiphenyl [CAS: 911217-05-5]. Compound **7ai** was also prepared using the same amounts following Method B in 23% yield (52 mg).

Synthesis of 2-Methoxy-2′-nitrobiphenyl (7aj). Compound **7aj** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 2-bromoanisole (**4j**) (187 mg, 1.00 mmol), yielding **7aj** as a yellow oil (184 mg, 80%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-methoxy-2′-nitrobiphenyl [CAS: 6460-92-0]. Compound **7aj** was also prepared using the same amounts following Method B in 30% yield (69 mg).

Synthesis of 1-(9-Phenanthryl)-2-nitrobenzene (7ak). Compound **7ak** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 9-bromophenanthrene (**4k**) (257 mg, 1.00 mmol), yielding **7ak** as a yellow solid (257 mg, 86%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 1-(9-phenanthryl)-2-nitrobenzene [CAS: 911217-05-5]. Compound **7ak** was also prepared using the same amounts following Method B in 99% yield (299 mg).

Synthesis of 4-Fluoro-2′-nitrobiphenyl (7al). Compound **7al** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 4-bromo-fluorobenzene (**4l**) (175 mg, 1.00 mmol), yielding **7al** as a yellow oil (145 mg, 67%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-fluoro-2′-nitrobiphenyl [CAS: 390-38-5]. Compound **7al** was also prepared using the same amounts following Method B in 97% yield (211 mg).

Synthesis of 2′-Nitro-4-trifluoromethylbiphenyl (7am). Compound **7am** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 4-bromo-trifluorotoluene (**4m**) (225 mg, 1.00 mmol), yielding **7am** as a yellow oil (222 mg, 83%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2′-nitro-4-trifluoromethylbiphenyl [CAS: 189575-69-7]. Compound **7am** was also prepared using the same amounts following Method B in 93% yield (248 mg).

Synthesis of 2-(2-Nitrophenyl)naphthalene (7an). Compound **7an** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 2-bromo-naphthalene (**4n**) (206 mg, 1.00 mmol), yielding **7an** as a yellow solid (234 mg, 94%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-(2-nitrophenyl)naphthalene [CAS: 94064−83-2]. Compound **7an** was also prepared using the same amounts following Method B in 94% yield (233 mg).

Synthesis of 2,4′-Dinitrobiphenyl (7ao). Compound **7ao** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 1-bromo-4-nitrobenzene (**4o**) (202 mg, 1.00 mmol), yielding **7ao** as a yellow solid (232 mg, 95%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2,4′-dinitrobiphenyl [CAS: 606-81-5]. Compound **7ao** was also prepared using the same amounts following Method B in 77% yield (156 mg).

Synthesis of 1-(2-Nitrophenyl)naphthalene (7ap). Compound **7ap** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 1-bromo-naphthalene (**4p**) (207 mg, 1.00 mmol), yielding **7ap** as a yellow solid (220 mg, 88%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 1-(2-nitrophenyl)naphthalene [CAS: 5415-59-8]. Compound **7ap** was also prepared using the same amounts following Method B in 97% yield (241 mg).

Synthesis of 2-Nitrobiphenyl (7aq). Compound **7aq** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and bromobenzene (**4q**) (157 mg, 1.00 mmol), yielding **7aq** as a yellow solid (170 mg, 85%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-nitrobiphenyl [CAS: 86-00-0]. Compound **7aq** was also prepared using the same amounts following Method B in 91% yield (181 mg).

Synthesis of 2-Nitro-4′-propylbiphenyl (7ar). Compound **7ar** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 1-bromo-4-propylbenzene (**4r**) (199 mg, 1.00 mmol), yielding **7ar** as a yellow oil (228 mg, 95%). Compound **7ar** was also prepared using the same amounts following Method B in 62% yield (148 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (dd, J = 8.4, 1.2 Hz, 1H), 7.56−7.63 (m, 1H), 7.41−7.48 (m, 2H), 7.23 (s, 4H), 2.60−2.65 (m, 2H), 1.63−1.72 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.3, 142.8, 136.2, 134.4, 132.1, 132.0, 131.8, 128.7, 128.6, 128.1, 128.0, 127.8, 127.6, 123.9, 37.8, 24.4, 14.0 ppm. HRMS (EI) for $C_{15}H_{15}NO_2$, 241.110276, found 241.110025. MS (Ion trap, EI): m/z (%) = 241 (60, [M+]), 212 (57), 165 (100), 139 (12), 115 (13), 76 (7).

Synthesis of 2-(2-Nitrophenyl)pyridine (7as). Compound **7as** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 2-bromopyridine (**4s**) (158 mg, 1.00 mmol), yielding **7as** as a yellow oil (25 mg, 13%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-(2-nitrophenyl)-pyridine [CAS: 4253-81-0]. Compound **7as** was also prepared using the same amounts following Method B in 53% yield (106 mg).

Synthesis of 3-(2-Nitrophenyl)pyridine (7at). Compound **7as** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 3-bromopyridine (**4t**) (158 mg, 1.00 mmol), yielding **7at** as a yellow solid (19 mg, 10%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3-(2-nitrophenyl)-pyridine [CAS: 4253-80-9]. Compound **7at** was also prepared using the same amounts following Method B in 98% yield (196 mg).

Synthesis of 4-(2-Nitrophenyl)benzophenone (7au). Compound **7au** was prepared following Method A from 2-nitrobenzoic acid (**10a**) (250 mg, 1.50 mmol) and 4-bromobenzophenone (**4u**) (261 mg, 1.00 mmol), yielding **7au** as a yellow solid (285 mg, 94%). Compound **7au** was also prepared using the same amounts following Method B in 99% yield (300 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.89−7.95 (m, 1H), 7.84 (t, J = 8.4 Hz, 4H), 7.62−7.66 (m, 1H), 7.55−7.59 (m, 1H), 7.40−7.53 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.0, 148.8, 141.6, 137.3, 137.0, 135.4, 132.6, 132.5, 131.7, 130.3, 130.0, 128.8, 128.3, 127.9, 124.3 ppm. HRMS (EI) for $C_{19}H_{13}NO_3$, 303.089541, found 303.089823. MS (Ion trap, EI): m/z (%) = 303 (39, [M$^+$]), 226 (36), 152 (16), 105 (100), 77 (44).

Synthesis of 2-Cyano-4′-methylbiphenyl (7bc). Compound **7bc** was prepared following Method B′ from 2-cyanobenzoic acid (**10b**) (147 mg, 1.00 mmol) and 4-bromotoluene (**4c**) (205 mg, 1.20 mmol), yielding **7bc** as a white solid (65 mg, 34%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-cyano-4′-methylbiphenyl [CAS: 114772-53-1]. Compound **7bc** was also prepared following Method C from 2-cyanobenzoic acid (**10b**) (191 mg, 1.30 mmol) and 4-bromotoluene (**4c**) (171 mg, 1.00 mmol), yielding **7bc** in 55% (106 mg).

Synthesis of 4′-Methyl-2-formylbiphenyl (7dc). Compound **7dc** was prepared following Method B′ from 2-carboxybenzaldehyde (150 mg, 1.00 mmol) and 4-bromotoluene (**4c**) (205 mg, 1.20 mmol), yielding **7dc** as a white solid (120 mg, 61%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′-methyl-2-formylbiphenyl [CAS: 16191−28-9].

Synthesis of 2-Acetyl-4′-methylbiphenyl (7ec). Compound **7ec** was prepared following Method B′ from 2-acetylbenzoic acid (**10e**) (164 mg, 1.00 mmol) and 4-bromotoluene (**4c**) (205 mg, 1.20 mmol), yielding **7ec** as a white solid (144 mg, 69%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-acetyl-4′-methylbiphenyl [CAS: 16927-79-0].

Synthesis of Isopropyl 4′-Methylbiphenyl-2-carboxylate (7fc). Compound **7fc** was prepared following Method B′ from isopropyl phenyl 2-carboxylate (**10f**) (246 mg, 1.00 mmol) and 4-bromotoluene (**4c**) (205 mg, 1.20 mmol), yielding **7fc** as a white solid (129 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84−7.90 (m, 1H), 7.51−7.57 (m, 1H), 7.40−7.47 (m, 2H), 7.25−7.33 (m, 4H), 5.04−5.14 (m, 1H), 2.47 (s, 3H), 1.14 (d, J = 6.2 Hz, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.2, 142.2, 138.6, 136.6, 132.0, 130.6, 130.4, 129.3, 128.6, 128.5, 128.3, 126.7, 68.3, 21.3, 20.9 ppm. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1. Found: C, 80.3; H, 7.2. MS (Ion trap, EI): m/z (%) = 254 (100, [M+]), 212 (22), 211 (20), 196 (18), 195 (55), 165 (27), 152 (16).

Synthesis of *N*,*N*-Diethyl-2-(4′-methylbiphenyl)carboxamide (7gc). Compound **7gc** was prepared following Method B′ from 2-(diethylcarbamoyl)benzoic acid (**10g**) (221 mg, 1.00 mmol) and 4-bromotoluene (**4c**) (205 mg, 1.20 mmol), yielding **7gc** as a white solid (119 mg, 45%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.39−7.42 (m, 1H), 7.33−7.38 (m, 5H), 7.17 (d, J = 7.9 Hz, 2H), 3.73 (dd, J = 13.5, 6.7 Hz, 1H), 3.02 (dd, J = 13.6, 6.8 Hz, 1H), 2.95 (dd, J = 14.3, 7.2 Hz, 1H), 2.65 (dd, J = 14.3, 7.0 Hz, 1H), 2.36 (s, 3H), 0.91 (t, J = 7.1 Hz, 3H), 0.73 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 170.7, 138.3, 137.3, 136.9, 136.3, 129.4, 129.0, 128.9, 128.7, 127.3, 127.0, 42.2, 38.3, 21.1, 13.4, 12.0 ppm. Anal. Calcd for $C_{18}H_{21}NO$: C, 80.9; H, 7.9; N, 5.2. Found: C, 80.7; H, 7.8; N, 5.3. MS (Ion trap, EI): m/z (%) = 267 (35, [M+]), 266 (15), 196 (100), 195 (32), 167 (20), 166 (22), 152 (20).

Synthesis of 2′-Methylsulfonyl-4-methylbiphenyl (7hc). Compound **7hc** was prepared following Method B′ from 2-methylsulfonylbenzoic acid (**10h**) (200 mg, 1.00 mmol) and 4-bromotoluene (**4c**) (205 mg, 1.20 mmol), yielding **7hc** as a white solid (102 mg, 42%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2′-methylsulfonyl-4-methylbiphenyl [CAS: 632339-04-9]. Compound **7hc** was also prepared following Method C from 2-methylsulfonylbenzoic acid (**10h**) (260 mg, 1.30 mmol) and 4-bromotoluene (**4c**) (171 mg, 1.00 mmol), yielding **7hc** as a white solid (239 mg, 97%).

Synthesis of 2-Fluoro-4′-methylbiphenyl (7ic). Compound **7ic** was prepared following Method B′ from 2-fluorobenzoic acid (**10i**) (140 mg, 1.00 mmol) and 4-bromotoluene (**4c**) (205 mg, 1.20 mmol), yielding **7ic** as a colorless oil (143 mg, 76%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-fluoro-4′-methylbiphenyl [CAS: 720937-41-5].

Synthesis of 4-Methyl-2′-methoxybiphenyl (7jc). Compound **7jc** was prepared following Method B′ from 2-methoxybenzoic acid (**10j**) (152 mg, 1.00 mmol) and 4-bromotoluene (**4c**) (205 mg, 1.20 mmol), yielding **7jc** as a white solid (92 mg, 46%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methyl-2′-methoxybiphenyl [CAS: 92495-53-9].

Synthesis of 4′-Methyl-2′-(*N*-phenylamino)biphenyl (7kc). Compound **7kc** was prepared following Method C from diphenylamine-2-carboxylic acid (**10k**) (276 mg, 1.30 mmol) and 4-bromotoluene (**4c**) (171 mg, 1.00 mmol), yielding **7kc** as a white solid (237 mg, 91%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′-methyl-2′-(*N*-phenylamino)biphenyl [CAS: 911217-14-6].

Synthesis of 4-Methyl-2′-(trifluoromethyl)biphenyl (7lc). Compound **7lc** was prepared following Method B′ from 2-(trifluoromethyl)-benzoic acid (**10l**) (190 mg, 1.00 mmol) and 4-bromotoluene (**4c**) (205 mg, 1.20 mmol), yielding **7lc** as a white solid (73 mg, 31%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methyl-2′-(trifluoromethyl)biphenyl [CAS: 145486-55-1].

Synthesis of *N*-(4′-Methylbiphenyl-2-yl)acetamide (7mc). Compound **7mc** was prepared following method C from *N*-acetylanthranilic acid (**10** m) (232 mg, 1.30 mmol) and 4-bromotoluene (**4c**) (171 mg, 1.00 mmol), yielding **7mc** as a white solid (94 mg, 42%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for *N*-(4′-methylbiphenyl-2-yl)acetamide [CAS: 76472-82-7].

Synthesis of 1-*p*-Tolylnaphthalene (7nc). Compound **7nc** was prepared following Method B′ (preformed at 150 °C) from 1-naphtoic acid (**10n**) (190 mg, 1.00 mmol) and 4-bromotoluene (**4c**) (205 mg, 1.20 mmol), yielding **7nc** as a white solid (124 mg, 57%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 1-*p*-tolylnaphthalene [CAS: 27331-34-6].

Synthesis of 2-*p*-Tolylthiophene (7oc). Compound **7oc** was prepared following Method B′ from thiophene-2-carboxylic acid (**10o**) (128 mg, 1.00 mmol) and 4-bromotoluene (**4c**) (205 mg, 1.20 mmol), yielding **7oc** as a white solid (109 mg, 62%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-*p*-tolylthiophene [CAS: 16939-04-1].

Synthesis of 1-Methyl-4-*trans*-styrylbenzene (7pc). Compound **7pc** was prepared following Method B′ from *trans*-cinnamic acid (**10p**) (148 mg, 1.00 mmol) and 4-bromotoluene (**4c**) (205 mg, 1.20 mmol), yielding **7pc** as a white solid (157 mg, 80%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 1-methyl-4-*trans*-styrylbenzene [CAS: 1657-45-0].

Synthesis of 4-Methyl-4′-methoxybiphenyl (7rc). Compound **7rc** was prepared following Method A (preformed at 160 °C) from 4-methoxybenzoic acid (**10r**) (228 mg, 1.50 mmol) and 4-bromotoluene (**4c**) (171 mg, 1.00 mmol), yielding **7rc** as a colorless oil (82 mg, 41%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methyl-4′-methoxy-biphenyl [CAS: 53040-92-9].

Synthesis of 4′-Chloro-3-methyl-2-nitrobiphenyl (7ta). Compound **7ta** was prepared following Method B from 3-methyl-2-nitrobenzoic acid (**10t**) (272 mg, 1.50 mmol) and 4-bromochlorobenzene (**4a**) (191 mg, 1.00 mmol), yielding **7ta** as a yellow solid (184 mg, 74%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′-chloro-5-methoxy-2-nitro-biphenyl [CAS: 911217-06-6].

Synthesis of 4′-Chloro-5-methoxy-2-nitrobiphenyl (7ua). Compound **7ua** was prepared following Method B from 5-methoxy-2-nitrobenzoic acid (**10u**) (296 mg, 1.50 mmol) and 4-bromochlorobenzene (**4a**) (191 mg, 1.00 mmol), yielding **7ua** as a yellow solid (204 mg, 77%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′-chloro-5-methoxy-2-nitro-biphenyl [CAS: 911217-07-7].

Synthesis of 4′-Chloro-5-methyl-2-nitrobiphenyl (7va). Compound **7va** was prepared following Method B from 5-methyl-2-nitrobenzoic acid (**10v**) (271 mg, 1.50 mmol) and 4-bromochlorobenzene (**4a**) (191 mg, 1.00 mmol), yielding **7va** as a yellow solid (126 mg, 77%). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4′-chloro-5-methyl-2-nitrobiphenyl [CAS: 70690-00-5].

General Procedure for the Decarboxylation Study (Table 3). An oven-dried vessel was charged with the carboxylic acid (**10a**−**s**) (1.00 mmol), Cu_2O (10.7 mg, 0.075 mmol), phenanthroline (27.0 mg, 0.15 mmol), and the appropriate amount of potassium bromide (0, 0.15, or 1.00 mmol, see Table 3). After the vessel was flushed with alternating vacuum and nitrogen purge cycles, a degassed solution of *n*-tetradecane in a mixture of NMP (1.5 mL) and quinoline (0.5 mL) was added *via* syringe. The resulting mixture was stirred at 170 °C for 6 h. Then the reaction mixture was allowed to cool to room temperature and was diluted with ethyl acetate (2 mL). A sample of the reaction mixture (0.25 mL) was dissolved in ethyl acetate (2 mL), washed with HCl (1 N, 2 mL), dried over $MgSO_4$/$NaHCO_3$, and analyzed by GC.

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