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Copper-Catalyzed Decarboxylation of Aromatic Carboxylic Acids: En Route to Milder Reaction Conditions

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Abstract: The copper-catalyzed decarboxylation of carboxylic aromatic acids has been advantageously achieved by using aliphatic amines like tetramethylethylenediamine (TMEDA) or hexamethylenetetraamine (HMTA) as ligands instead of the aromatic heterocyclic amines (quinoline, phenanthroline) used until now. The improvement is significant since the reaction can be performed at a lower temperature (*ca.* 50 °C less) and the reaction time is clearly shorter (15 min instead of 12 to 24 h).

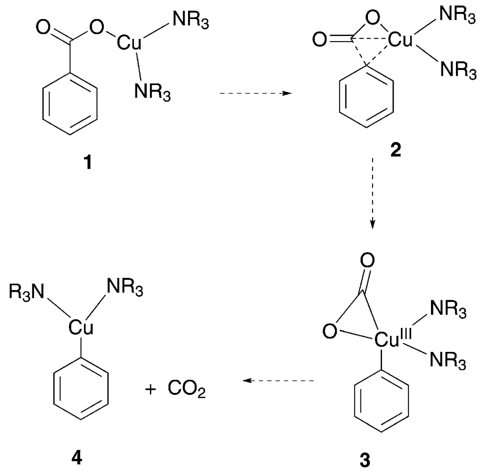
Keywords: aromatic carboxylic acids; aryl–aryl coupling; copper; decarboxylative cross-coupling; palladium

The decarboxylation of copper aromatic carboxylates was extensively investigated from the 1960s[1] by Sheppard,[2] Cohen,[3] Nilsson[4] and others.[5] Sheppard et al. reported that cuprous arylcarboxylates readily decarboxylate on heating. Quinoline is generally used as a solvent or cosolvent since the reaction then occurs faster.[1] It should be noted that the temperature of decarboxylation is clearly dependent on the nature of the starting cuprous aromatic carboxylate (100 to 215 °C).[2,5] The results reported by Cohen, Sheppard and Nilsson support the formation of a σ-bonded arylcopper species as an intermediate in these reactions. Thus, in a seminal report, Nilsson described a one-pot decarboxylation-Ullmann reaction using cuprous 2-nitrobenzoate and iodobenzene or 2- and 4-iodoanisole.[4a] This was the first decarboxylative coupling reaction. A few years later, Sheppard showed that the decarboxylation of cuprous pentafluorobenzoate leads to pentafluorophenyl copper in 72% yield.[2] Thereafter, various studies pointed out that chelating nitrogen ligands such as bipyridine[3b] or 1,10-phenanthroline[3a] greatly enhance the rate of decarboxylation. A breakthrough was recently introduced by Gooßen who showed that the decarboxylation of aromatic carboxylic acids can be performed by using only a catalytic amount of copper to give the protodecarboxylation product. Moreover, he described the first copper/palladium-catalyzed decarboxylative cross-coupling reaction between an aromatic carboxylic acid and an aryl bromide.[6,7] Of course, the use of cheap and readily available carboxylic acids as the source of aryl nucleophiles instead of costly preformed stoichiometric organometallic reagents make this new procedure very attractive from economical and environmental points of view.[3b–d]

Since the seminal reports on the copper-mediated protodecarboxylation of aromatic carboxylic acids,[2–4] almost no change was reported concerning the catalytic system and the reaction was generally performed in NMP or a mixture NMP/quinoline at 170 °C in the presence of bipyridine or 1,10-phenanthroline as a ligand.[5b–d] These last years, only one attempt to improve this catalytic system was performed by Gooßen. He has compared various aromatic diamines and he showed that 4,7-diphenyl-1,10-phenanthroline (bathophenanthroline) is more efficient than 1,10-phenanthroline with non-activated aromatic carboxylic acids.[6b] Currently, one of the main challenge is to lower the reaction temperature and so far, this was only possible by using silver[8] or palladium[9] instead of copper.

The mechanism of the reaction is not clear. However, as suggested by Cohen,[3b] it is reasonable to propose the complexation of the copper atom to the C–COO bond of the carboxylate (**1**→**2**), *via* a π-complexation to the aromatic ring or not.

Then, a copper(III) intermediate **3** would be formed by oxidative addition. Finally, a rapid reductive elimination would give an arylcopper **4** and carbon dioxide (Scheme 1). By considering this putative mechanism, the role of a σ-donor ligand like 1,10-phenanthroline would be to favour the oxidative



Scheme 1. Putative mechanism for the Cu-catalyzed decarboxylation of aromatic carboxylic acids.

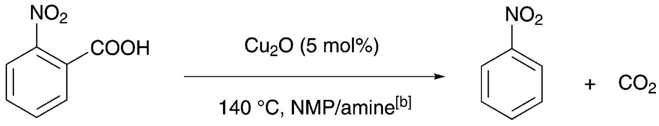
addition of the C–C bond which is probably the limiting step of the mechanism described above (Scheme 1). Indeed, the insertion of copper into the C–C bond is due to a π back-donation from a filled metal orbital into the σ* orbitals of the C–C bond. Such a process is favoured by increasing the electronic density of the copper atom and it should be favoured by the presence of σ-donor ligands on copper. Thus, the good results obtained with quinoline, bypyridine or 1,10-phenanthroline are not surprising since amines are good σ-donor ligands. On the other hand, it seemed to us very surprising to use aromatic amines instead of aliphatic amines since the latter are expected to be more efficient. In the light of these considerations, we decided to study the influence of various amines on the copper-catalyzed protodecarboxylation of aromatic carboxylic acids.

In a first set of experiments, we performed the copper-catalyzed decarboxylation of 2-nitrobenzoic acid in NMP in the presence of stoichiometric amounts of various simple amines at 140 °C (ratio ArCOOH/amine ≈ 1:30).

As shown in Table 1, the improvement observed by adding quinoline is not spectacular. The yield of protodecarboxylation product was slightly enhanced (89% instead of 72%) but the reaction time remained unchanged (Table 1, entries 1 and 2). In fact, all the other amines tested gave better results.

As expected, aliphatic amines are more efficient than aromatic amines (Table 1, entries 2–9). The disappointing result obtained with (i-Pr)$_2$EtN, a good σ-donor ligand (Table 1, entry 4) can probably be explained by steric hindrance. Similar effects were reported with bulky ligands such as 2,9-dimethyl-1,10-phenanthrolines.[6b] The best result (99% in 5 min) was achieved by using TMEDA, a good bidentate σ-donor ligand (Table 1, entry 9). Of course, it was important to lower the amount of both copper and TMEDA. As shown in Table 2, 10 mol% TMEDA and 5 mol% Cu$_2$O (ligand/Cu = 1:1) are enough to perform quantitatively the reaction at 140 °C in 5 min (Table 2, entry 2). Even more interestingly, a satisfactory yield was obtained in the presence of only 0.5% Cu$_2$O and 1% TMEDA (ligand/Cu = 1:1), however the reaction lasts 1.5 h instead of 5 min (Table 2, entry 3). To the best of our knowledge, this reaction had never been done with such a low copper catalyst

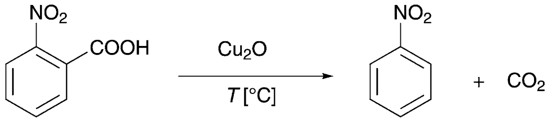
Table 1. Influence of various amines on Cu-catalyzed protodecarboxylation of 2-nitrobenzoic acid.[a]



Entry	Ligand	Time	Yield [%][c]
1	none	2 h	72
2	quinoline	2 h	89
3	*N,N*-dimethylaniline	45 min	82
4	*N,N*-diisopropylethylamine	45 min	82
5	DBU[d]	45 min	94
6	*N,N*-dimethylpiperazine	1 h	99
7	DABCO[e]	1 h	99
8	triethylamine	1 h	99
9	TMEDA[f]	5 min	99

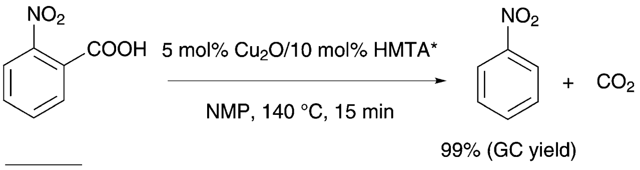
[a] Reactions performed on a 2.5 mmol scale (c = 0.5 M).
[b] Amine/ArCOOH ≈ 30:1.
[c] Yield determined by GC (decane as internal standard).
[d] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.
[e] DABCO = 1,4-diazabicyclo[2.2.2]octane (DABCO/Cu = 1:1).
[f] TMEDA = *N,N,N′,N′*-tetramethylethylenediamine.

Table 2. Cu-catalyzed protodecarboxylation of 2-nitrobenzoic acid in the presence of TMEDA.[a]



Entry	Solvent	Cu$_2$O [mol%]	TMEDA [mol%]	Temp. [°C]	Time	Yield [%][b]
1	NMP	5	340	140	5 min	99
2	NMP	5	10	14	5 min	99
3	NMP	0.5	1	140	1.5 h	93c)
4	NMP	5	10	120	15 min	99
5	NMP	5	10	110	8 h	99
6	NMP	5	10	100	12 h	99
7	DMSO	5	10	140	5 min	99
8	toluene	5	10	110	24 h	61

[a] The reactions were performed on a 5 mmol scale (c = 0.5 M).
[b] Yield determined by GC (decane as internal standard).
[c] The reaction was performed on a 15 mmol scale.



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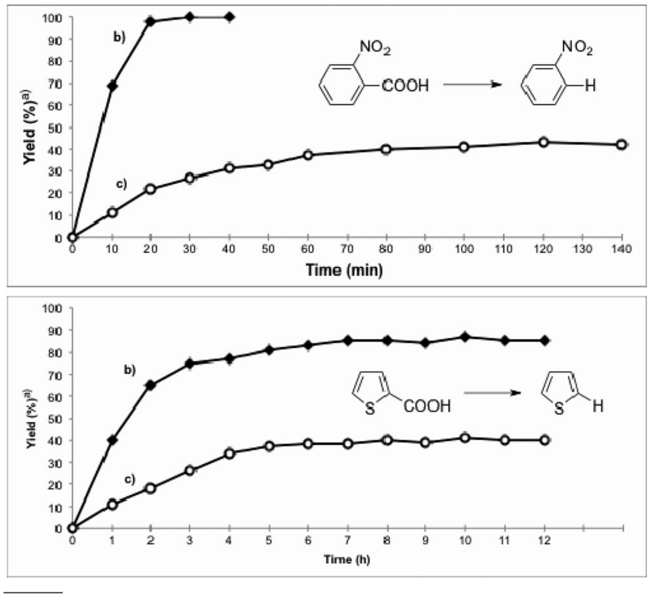
* HMTA = hexamethylenetetraamine.[10]

Scheme 2. Cu-catalyzed protodecarboxylation of 2-nitrobenzoic acid by using HMTA as ligand.

loading. The new catalytic system also allowed us to lower the reaction temperature down to 100 °C (Table 2, entry 6). The yield of protodecarboxylation product is then still quantitative but the decarboxylation takes place in 12 h instead of 5 min at 140 °C. NMP was used as a solvent but other high boiling polar solvents like DMSO can be used (Table 2, entry 7). On the other hand, non-polar solvents such as toluene led to unsatisfactory results (Table 2, entry 8).

It should be noted that HMTA,[10] a good σ-donor ligand since the lone pair of the nitrogen is very accessible, is as efficient as TMEDA (Scheme 2). Finally, by comparison with the previous procedures described by Gooßen,[6b] the use of TMEDA allows to lower the reaction temperature of 50–70 °C.

The examples depicted in Figure 1 show that TMEDA is much more efficient at 120 °C. It must be emphasized that, up to now, the only way to obtain a similar result was to replace copper salts by silver salts.[8,9]



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a) Yield determined by GC (decane as internal standard).

b) 5 mol% Cu_2O/TMEDA (1:2), NMP, 120°C.

c) 5 mol% Cu_2O/*o*-phenanthroline (1:2), NMP/quinoline (3:1), 120 °C.

Figure 1. Protodecarboxylation of 2-nitrobenzoic and 2-thiophenecarboxylic acids. Comparison of two catalytic sytems: *o*-phenanthroline/Cu_2O and TMEDA/Cu_2O.

We applied our decarboxylation procedure to various activated aromatic and heteroaromatic carboxylic acids (Table 3).

In most cases, the protodecarboxylation product is formed rapidly in high yields. All experiments were performed at 140 °C to avoid optimizing the temperature of the reaction for each case. However, it should be noted that in many cases it is possible to work at a lower temperature. For instance, 2-nitrobenzoic acid led to 99% of nitrobenzene in 12 h at 100 °C and 2-acetoxybenzoic acid gave 86% of acetophenone in 3 h at 120 °C.

Compared with the procedure developed by Gooßen[6b] which was generally used until now to decarboxylate activated aromatic acids, the catalytic system Cu_2O/TMEDA can be used at lower temperatures (100–140 °C instead of 170 °C).

Moreover, the reactions are faster (often less than 1 h instead of 12 h) and lead to higher yields. For example, 2-methoxybenzoic and 2-thiophenecarboxylic acids were decarboxylated in respectively 75% and 87% yields instead of 24% and 58% with the Gooßen's procedure.[5b] Moreover, the scope of the reaction is larger, thus, 2,6-dimethoxybenzoic acid led to 92% yield whereas it does not react by using Cu_2O/*o*-phenanthroline as a catalyst.[8c] The results listed in Table 3 show that the reaction is chemoselective since various functional groups (nitro, chloro, acetoxy, ester or methoxy) are tolerated. Finally, it is interesting to note that the reaction was successfully applied to cinnamic acid (Table 3, entry 13).

We then tried to use the efficient catalytic system described above to perform some palladium-catalyzed decarboxylative cross-coupling reactions. Of course, to avoid the rapid protonation of the arylcopper intermediates formed in the reaction mixture, it is not possible to start from the free carboxylic acid and we replaced them by their potassium salts. In the case of potassium 2-nitrobenzoate the coupling occured at 120 °C in the presence of 10% CuBr,[11] 10% TMEDA and 3% $Pd(acac)_2$ but the reaction was very slow and led to low yield of 2-nitrobiphenyl (22%, Scheme 3).

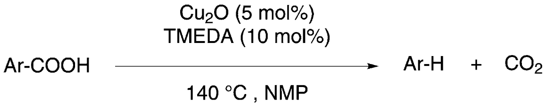
This unsatisfactory result is mainly due to the poor solubility of potassium carboxylates in NMP. Thus, it is possible to improve the yield by working in DMPU[12] (40%) but to obtain good yields (90%) it is necessary to heat to 170 °C in NMP or DMPU.

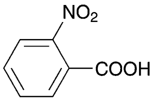
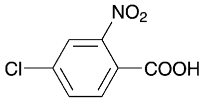
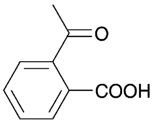
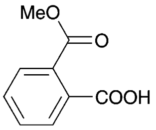
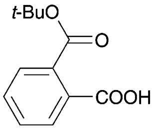
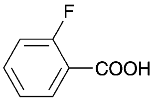
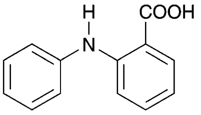
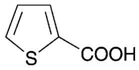
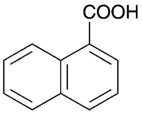
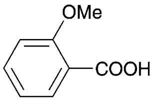
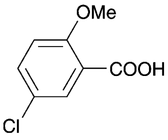
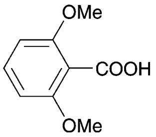
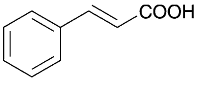
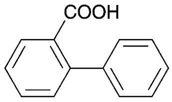
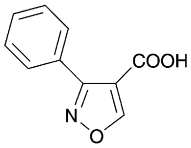
Accordingly, to achieve the coupling efficiently at a lower temperature, it is necessary to use a more soluble metal carboxylate such as caesium 2-nitrobenzoate (Scheme 4).

The coupling product was then formed at 130 °C in 92% yield.

Various decarboxylative cross-coupling reactions were efficiently achieved according to this procedure.

Table 3. Cu-catalyzed protodecarboxylation of various aromatic and heteroaromatic carboxylic acids.[a]



Entry	ArCOOH	Time	Yield [%][b]
1		5 min	99
2		20 min	83
3		20 min	98
4		45 min	81
5		45 min	87
6		1 h	95
7		4 h	90[c]
8		30 min	87
9		6 h	99[c]
10		40 min	75[d]
11		1 h	68[e]
12		2 h	92[f]
13		24 h	70[c]
14		40 h	89[c]
15		1 h	93[f]

[a] The reactions were performed on a 5 mmol scale ($c = 0.5$ M).

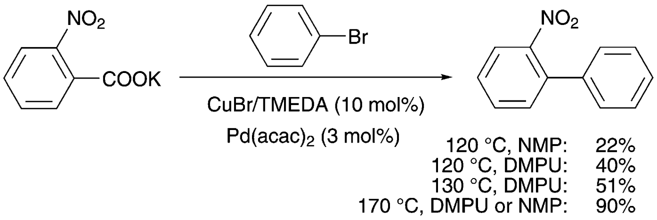
[b] Yield determined by GC (decane or hexadecane as internal standards).

[c] 170 °C.

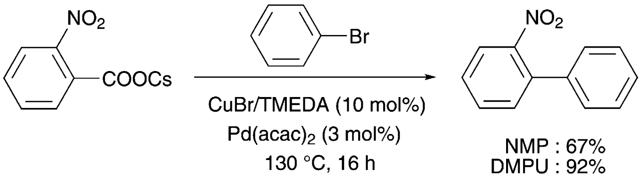
[d] 20 mol% of Cu_2O was used.

[e] 15 mol% of Cu_2O was used.

[f] The reaction was performed on a 15 mmol scale, isolated yield.



Scheme 3. Cu/Pd-catalyzed decarboxylative cross-coupling reaction between potassium 2-nitrobenzoate and bromobenzene.



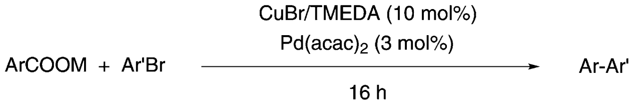
Scheme 4. Cu/Pd-catalyzed decarboxylative cross-coupling reaction between caesium 2-nitrobenzoate and bromobenzene.

The examples depicted in Table 4 show that the reaction is chemoselective since fluoro, chloro, nitro, cyano, ester or keto groups are tolerated. It should be noted that various heterocyclic substrates were used successfully.

This procedure can be used to synthezise polyaromatic molecules. Thus, 1,3-bisthienylbenzene was easily prepared from 1,3-dibromobenzene (Scheme 5).

The last example (Scheme 6) shows that the catalytic system described above can be used efficiently on a preparative scale (0.1 mol). Interestingly, it is then

Table 4. Cu/Pd-catalyzed decarboxylative cross-coupling reactions.[a]



$$\text{ArCOOM} + \text{Ar'Br} \xrightarrow[\text{16 h}]{\text{CuBr/TMEDA (10 mol\%)}, \ \text{Pd(acac)}_2 \text{ (3 mol\%)}} \text{Ar-Ar'}$$

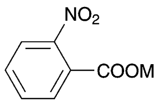
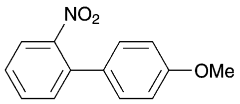
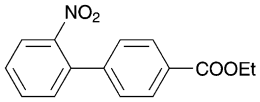
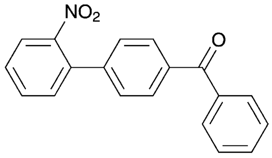
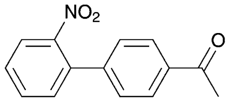
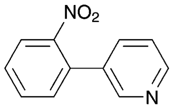
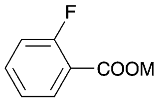
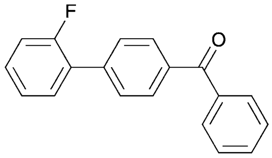
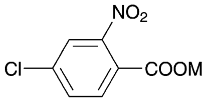
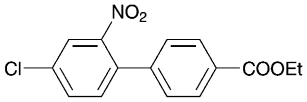
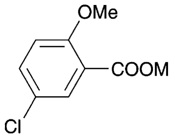
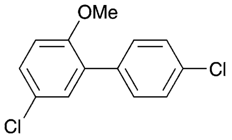
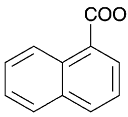
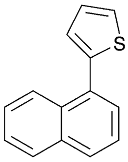
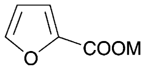
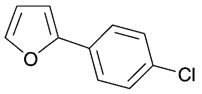
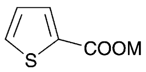
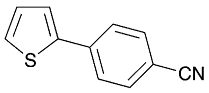
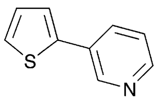
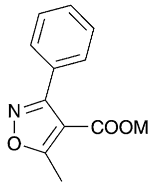
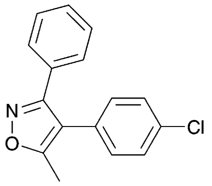
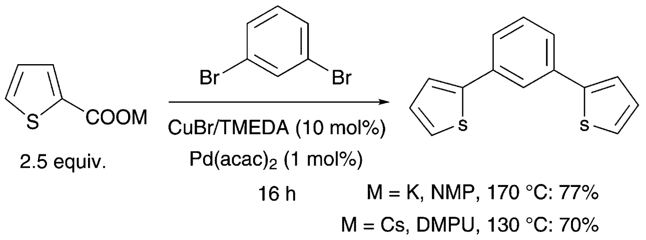
Entry	ArCOOM	Coupling Product	Yield [%][b] M = Cs[c]	Yield [%][b] M = K[d]
1			77	80
2			89	91
3			90	91
4			77	88
5			91	96
6			90[e]	91
7			82	74
8			71[f]	81[f]
9			–	70
10			69[f]	73[f]
11			70	–
12			61	66

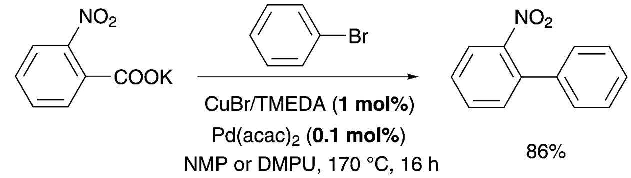
Table 4. (Continued)

Entry	ArCOOM	Coupling Product	Yield [%][b] M = Cs[c]	 M = K[d]
13			72[g]	73

[a] The reactions were performed on a 2 mmol scale.
[b] Yield of isolated product.
[c] The reaction was performed at 130 °C in DMPU.
[d] The reaction was performed at 170 °C in NMP.
[e] 20% CuBr/TMEDA, 40 h.
[f] 20% CuBr/TMEDA, 140 °C.
[g] 2 equiv. of caesium carboxylate were used.



Scheme 5. Cu/Pd-catalyzed decarboxylative cross-coupling reaction from 1,3 dibromobenzene.



Scheme 6. Example of preparative Cu/Pd-catalyzed decarboxylative cross-coupling reaction.

possible to lower the charge of CuBr/TMEDA up to 1% and the one of $Pd(acac)_2$ to 0.1%.

In conclusion, we have shown that the use of TMEDA as a ligand allows us to lower significantly the temperature of the copper-catalyzed decarboxylation of activated aromatic carboxylic acids. Thus, in the case of 2-nitrobenzoic acid the decarboxylation takes place at 100 °C instead of 170 °C with the previous procedures. This new catalytic system was developed owing to an analysis of the reaction mechanism.

Until now, such a result was only possible by using silver salts instead of copper salts.[8] Concerning the reaction temperature, it should be noted that it is the first significant improvement since the seminal reports in the 1960s.[2-4] The reaction conditions described herein also allow us to perform copper-palladium-catalyzed decarboxylative cross-coupling reactions between 120 to 140 °C instead of 170 °C. The results reported above could open the way to the development of low temperature procedures. It is worthy of note that, for large scale applications, it is very advantageous to replace 1,10-phenanthroline by TMEDA which is clearly less expensive.

Experimental Section

Typical Procedure: Synthesis of 2-Nitrobiphenyl (Scheme 6)

An oven-dried, nitrogen-flushed, 500-mL four-necked flask equipped with a mechanical stirrer, a thermometer and a condenser was charged with potassium 2-nitrobenzoic acid (26.7 g, 130.00 mmol), bromobenzene (15.7 g, 100.00 mmol), copper(I) bromide (144 mg, 1.00 mmol), TMEDA (116 mg, 1.00 mmol), $Pd(acac)_2$ (30.5 mg, 0.1 mmol) and NMP (130 mL). The resulting mixture was stirred at 170 °C for 20 h. When the reaction was complete, the mixture was cooled to room temperature and filtered through celite. The solid was rinsed with ethyl acetate (3 × 50 mL) and the resulting filtrate was concentrated under vacuum,. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, gradient 98:2 to 95:5) furnishing 2-nitrobiphenyl as a yellow oil; yield: 17.1 g (86%).

Acknowledgements

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[11] With metal carboxylates, CuBr was used in place of Cu_2O since the reaction is generally faster and gives better yields. For instance from potassium 2-nitrobenzoate, at 120 °C, the yield of coupling product was respectively 22% and 10%.

[12] DMPU = *N,N'*-dimethylpropyleneurea.

8 Copper-Catalyzed Decarboxylation of Aromatic Carboxylic Acids: En Route to Milder Reaction Conditions

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