New Synthesis of Biaryls *via* Rh-Catalyzed Decarbonylative Suzuki-Coupling of Carboxylic Anhydrides with Arylboroxines

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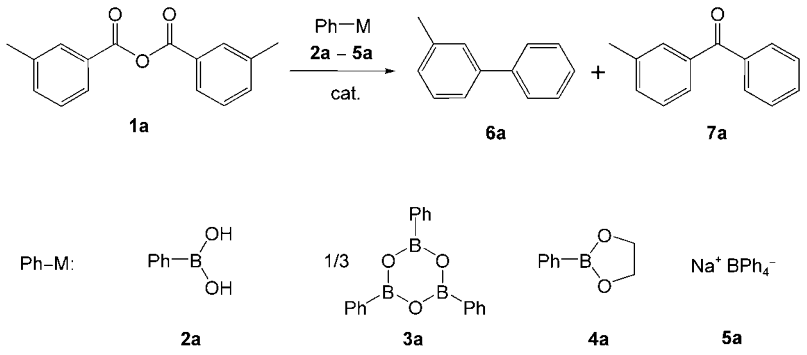
Abstract: The catalytic cross-coupling of aromatic carboxylic anhydrides or acid chlorides with triarylboroxines has been achieved for the first time under decarbonylation, giving rise to the unsymmetrical biaryls rather than the expected diaryl ketones. This new decarbonylative Suzuki coupling, catalyzed by a [Rh(ethylene)$_2$Cl]$_2$/KF system, can be applied to aromatic, heteroaromatic and vinylic carboxylic anhydrides, potentially opening up new perspectives for the use of carboxylic acid derivatives as substrates in biaryl syntheses.

Keywords: biaryls; carboxylic acids; cross-coupling; decarbonylation; rhodium

Substituted biphenyls are a key structural motif in numerous biologically active compounds.[1] Due to the mild reaction conditions, the high yields and the excellent functional group tolerance, the Suzuki coupling of arylboronic acids with aryl halides is usually the method of choice for their synthesis.[2] Besides aryl halides,[3] aryl and alkyl sulfonates,[4] diazonium salts[5] and anilinium salts[6] can be used as the electrophilic coupling partner. Since these do not always satisfy the synthetic needs, an extension of this powerful synthetic methodology to other broadly available substrate classes such as carboxylic acids would be of high interest.

It has recently been demonstrated that carboxylic acid derivatives, e. g., carboxylic anhydrides or esters, can oxidatively add to transition metal catalysts, giving rise to acyl-metal complexes.[7] At elevated temperatures, these intermediates decarbonylate to yield the corresponding alkyl- or aryl-metal species. This behavior has been utilized in decarbonylative Heck olefinations[8,9] and decarbonylative elimination reactions,[10] in which carboxylic acid derivatives serve as synthetic equivalents of aryl or alkyl halides. However, in catalytic cross-coupling reactions, the decarbonylation step was found to be less favorable, so that exclusively aryl ketones are formed in the Suzuki coupling of carboxylic anhydrides with boronic acids.[7,11] To the best of our knowledge, only one special case of a cross-coupling reaction has been reported that proceeds under decarbonylation, but it calls for stoichiometric quantities of nickel salts to trap the carbon monoxide in the form of toxic nickel carbonyl compounds.[12]

Our target was to identify conditions to access biaryls *via* a decarbonylative coupling of aromatic carboxylic anhydrides with arylboronic acids, in the presence of only a catalytic amount of a transition metal complex. A plausible mechanism for this transformation would



Scheme 1. Cross-coupling reaction between 3-methylbenzoic anhydride and boronic acid derivatives.

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Table 1. Decarbonylative Suzuki-coupling of carboxylic anhydrides.

Entry	Ph-M	Precatalyst	Ligand/Additive	Solvent	Yield of **6a** [%]	Yield of **7a** [%]
1	**2a**	$Pd(PPh_3)_4$	–	NMP	< 2[a]	20
2	**2a**	$PdCl_2$	LiCl	NMP	2[a]	2
3	**2a**	$PdCl_2$	DPE-Phos	DMPU	5[a]	15
4	**2a**	$[Rh(ethylene)Cl]_2$	–	mesitylene	10[a]	5
5	**3a**	$PdCl_2$	LiCl	NMP	2	5
6	**3a**	$PdCl_2$	DPE-Phos	DMPU	5	10
7	**3a**	$[Rh(ethylene)_2Cl]_2$	–	mesitylene	40	10
8	**3a**	$RhCl_3$	–	“	0	0
9	**3a**	$(Rh(nbd)Cl)_2$	–	“	20	5
10	**3a**	$(Rh(COD)Cl)_2$	–	“	20	5
11	**3a**	$Rh(acac)(CO)_2$	–	“	40	25
12	**3a**	$[Rh(ethylene)_2Cl]_2$	PPh_3	“	25	25
13	**3a**	“	KF	“	65	20
14[b]	**3a**	“	KF	“	65	20
15	**3a**	“	LiF	“	40	5
16	**3a**	“	NaF	“	55	15
17	**3a**	“	Na_2CO_3	“	40	10
18	**3a**	“	K_3PO_4	“	40	10
19	**3a**	“	KF	diglyme	40	25
20	**3a**	“	KF	n-Bu_2O	60	10
21	**3a**	“	KF	NMP	10	50
22[c]	**3a**	“	KF	mesitylene	30	25
23	**3a**	$PdCl_2$	KF	“	< 2	< 2
24	**4a**	$[Rh(ethylene)_2Cl]_2$	–	“	50[d]	15
25	**5a**	“	–	“	10	15
26[e]	**5a**	“	–	“	65	20

Conditions: 1.00 mmol 3-methylbenzoic anhydride, 1.50 mmol **2a**–**5a**, 0.03 mmol precatalyst, 0.10 mmol additive, 160 °C, 16 h; GC yields using n-hexadecane as internal standard.

[a] Main product: benzoic acid.

[b] 1.00 mmol additive.

[c] 140 °C.

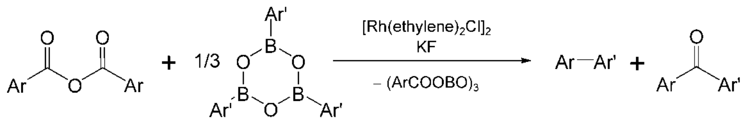
[d] Side product: 3,3′-dimethylbiphenyl (15%).

[e] With 1.00 mmol 3-methylbenzoyl chloride (**8a**) instead of **1a**.

involve the oxidative addition of the carboxylic anhydride to a transition metal catalyst, followed by decarbonylation of the resulting acyl-metal species and transmetallation with the boronic acid derivative. Thus, the key to high product selectivity would be to assist the decarbonylation step and avoid premature transmetallation. The biaryl product would finally be liberated by reductive elimination, regenerating the initial transition metal complex.

We chose the reaction of 3-methylbenzoic anhydride **1a** with several benzeneboronic acid derivatives **2a**–**5a** as our model system (Scheme 1) and screened various transition metal complexes under different conditions to elucidate the factors facilitating the formation of decarbonylated product **6a** over the ketone **7a**. Selected results are displayed in Table 1.

Using benzeneboronic acid (**2a**) as the carbon nucleophile, hydrolysis of the carboxylic anhydride predominated under various conditions, and only small quantities of cross-coupling products were observed despite using anhydrous solvents (Table 1, entries 1–4). This was not unexpected, since boronic acids are known to liberate water at elevated temperatures to form cyclic boroxines. We attempted to work around this side reaction of the carboxylic anhydrides by directly using preformed triphenylboroxine (**3a**). Indeed, use of **3a** led to less hydrolysis and improved yields of the cross-coupling products (entries 5–23). In the presence of various Pd catalysts, predominantly the non-decarbonylated product **7a** was formed even under conditions that had been successfully used in decarbonylative Heck olefinations or decarbonylative eliminations of carboxylic anhydrides (entries 5 and 6).[8e,10] Only in the presence of $[Rh(ethylene)_2Cl]_2$ and under conditions similar to those used for decarbonylative Heck olefinations of acid chlorides,[9] were significant amounts of the desired biaryl **6a** formed (entry 7). Encouraged by this finding, we set out to further optimize the catalytic system and tested various rhodium complexes in combination with several additives (entries 7–18). Best results were obtained with $[Rh(ethylene)_2Cl]_2$, while similar complexes with more strongly bound ligands showed significantly



1a – f **3a – i** **6a – n** **7a – n**

Scheme 2. Cross-coupling reaction of carboxylic anhydrides and aryl boroxines.

lower activities (entries 7–12). The addition of catalytic quantities of fluoride salts and in particular KF appeared to improve the activity of the rhodium catalyst, leading to significantly higher yields of the product **6a**, whereas the addition of other inorganic halides or bases show no enhancement of the catalytic activity (entries 13–18). At this point, we cannot provide an unambiguous explanation for this interesting counter ion effect.

Mesitylene proved to be the optimal solvent for this reaction in terms of yield. The highest selectivity (6:1) for the decarbonylated product was reached in *n*-Bu$_2$O, albeit with a slightly lower overall yield (entry 20). More strongly coordinating solvents such as NMP apparently retarded the decarbonylation step so that more ketone **7a** was formed (entry 21). Similar to other decarbonylative processes, elevated temperatures are essential (entry 22).

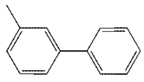
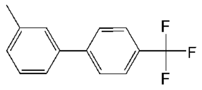
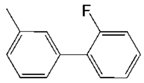
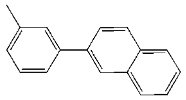
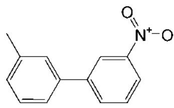
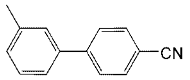
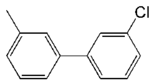
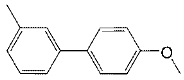
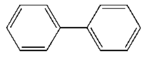
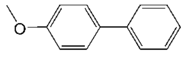
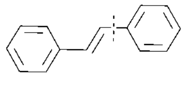
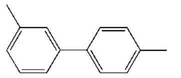
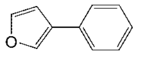
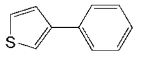
Under optimized conditions, satisfactory yields of biaryl **6a** were also obtained when employing the cyclic phenyl boronate **4a** or sodium tetraphenylborate (**5a**) (entries 24 and 25) as carbon nucleophiles. Furthermore, 3-methylbenzoyl chloride (**8a**) can also serve as the aryl source instead of the carboxylic anhydride **1a**, especially in combination with sodium tetraphenylborate (**5a**) (entry 26).

Having established an efficient reaction protocol for the transformation depicted in Scheme 2, we next set out to investigate its scope. Various functionalized arylboroxines **3a–i** were generated from commercially available boronic acids **2a–i** by heating them under reduced pressure, or alternatively by azeotropic distillation of a toluene solution of **2a–i**. The boroxines were successfully coupled with aromatic, heteroaromatic and vinylic carboxylic acid anhydrides **1a–f**, giving rise to the corresponding biaryls **6a–m** in moderate to good yields.[13] Selected results are shown in Table 2.

The selectivity of decarbonylated product **6** *vs.* ketone **7** was found to be higher for electron-poor than for electron-rich boroxines (e.g., entries **6b** and **6 h**). This can be rationalized by the higher nucleophilicity of electron-rich boroxines, favoring transmetallation over the competing decarbonylation.

In summary, for the first time, a reaction protocol has been identified for the cross-coupling of aromatic carboxylic acid derivatives with organometallic species that proceeds mainly under extrusion of carbon monoxide to give a biaryl product. The reaction is not only interesting from a mechanistic standpoint, it moreover bears the potential of becoming the basis for the use of aromatic carboxylic acid derivatives as substrates for biaryl synthesis. Improvement of the reaction protocol towards *in situ* activation of carboxylic acids is currently under investigation in our laboratory.

Table 2. Scope of the reaction according to Scheme 2.

Anhydride + Boroxine	Product **6** Ar–Ar'		Yield of **6** [%][a]	Yield of **7** [%][a]
1a + **3a**		**6a**	65 (64)	20
1a + **3b**		**6b**	70 (66)	<5
1a + **3c**		**6c**	65 (48)	<5
1a + **3d**		**6d**	65 (55)	20
1a + **3e**		**6e**	70 (61)	<5
1a + **3f**		**6f**	65 (57)	<5
1a + **3g**		**6g**	70 (55)	15
1a + **3h**		**6h**	50 (37)	40
1b + **3a**		**6i**	60 (55)	25
1c + **3a**		**6j**	40 (35)	15
1d + **3a**		**6k**	30 (16)	<5
1a + **3i**		**6l**	60 (57)	25
1e + **3a**		**6m**	25 (21)	15
1f + **3a**		**6n**	25 (21)	5

Conditions: 1.00 mmol carboxylic anhydride, 0.50 mmol boroxine, 0.015 mmol [Rh(ethylene)$_2$Cl]$_2$, 0.10 mmol KF, 4 mL mesitylene, 160 °C, 8 h.

[a] GC yields, isolated yields in brackets. The residue derived from the anhydride is displayed on the left hand side of the structures.

Experimental Section

Synthesis of 3-Methylbiphenyl (6a)

A flame-dried, 20-mL reaction vessel equipped with a pressure equalizer and magnetic stirrer was charged with 2,4,6-triphenylboroxine (**3a**; 0.50 mmol, 155 mg), and dry potassium fluoride (0.10 mmol, 5.80 mg). The reaction vessel was closed and dried for 15 minutes under vacuum at 100 °C. After cooling to room temperature, di-μ-chlorotetrakis(η^2-ethylene)dirhodium(I) (5.80 mg, 0.015 mmol) and 3-methylbenzoic anhydride (**1a**; 254 mg, 1.00 mmol) were added *via* syringe as a stock solution in 4 mL anhydrous mesitylene. The mixture was then stirred at 160 °C and the progress of the reaction was monitored by GC. After completion of the reaction (usually after 8 h), the volatiles were removed under vacuum and the residue was purified by column chromatography (SiO_2, hexane), affording **6a** as a white solid; yield: 108 mg (64%). The product was identified by means of ^1H and ^{13}C NMR as well as by GC-MS and HRMS to be 3-methylbiphenyl, CAS registry number [643-93-6].

The side product **7a** (40 mg, 20%), CAS registry number [643-65-2], was isolated after further elution with hexanes/ethyl acetate.

Compounds **6b–n** were synthesized accordingly (see Supporting Information).

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References and Notes

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[13] The difference to 100% yield is made up mostly by carboxylic acid, probably due to hydrolysis caused by incomplete dehydration of the boronic acid in the preceding step.