Biaryls

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Synthesis of Amino- and Hydroxybiphenyls by Radical Chain Reaction of Arenediazonium Salts**

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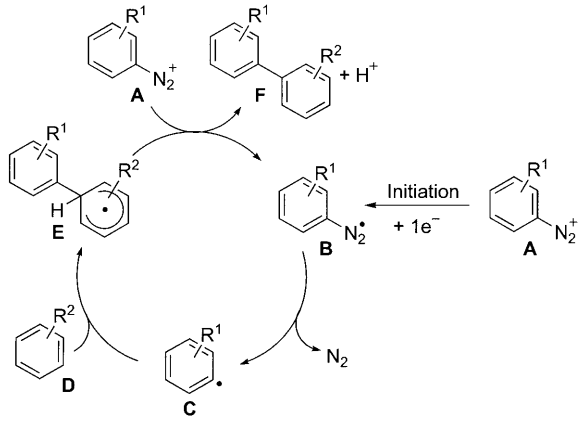
Dedicated to Professor Dr. Wolfgang Steglich on the occasion of his 75th birthday

A wide range of organometallic methods have been developed for the mild and efficient synthesis of biaryl compounds.[1–5] In this context, addition reactions of aryl radicals to aromatic substrates have so far only rarely been applied.[6] Complications in intermolecular radical aryl–aryl couplings occur as a result of the relatively slow addition of aryl radicals to common substrates such as substituted benzenes,[7] which in turn gives rise to side reactions. Successful aryl–aryl couplings therefore often require special conditions; for example, the substrate is used as the solvent[8] or the reaction is modified to an intramolecular conversion.[9]

Aryl–aryl couplings using arenediazonium salts **A** as precursors are known as Gomberg–Bachmann[10,11] or Pschorr[12] reactions (Scheme 1). These reactions are complicated by the fact that a reductant is needed for the generation of radicals **B** and **C**,[13] whereas oxidizing conditions are required for the rearomatization of the cyclohexadienyl intermediate **E**.[14,15] To date, only a few studies have proposed to employ the diazonium salt **A** both as the source of **C** and as an oxidant for intermediate **E**.[16]

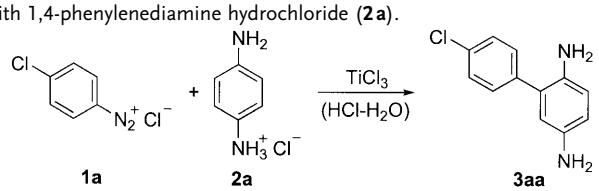


Scheme 1. Radical chain mechanism for biaryl synthesis.

Given that the reactivity of aryl radicals is more controlled in water than in most other organic solvents,[17,18] we decided to evaluate homolytic aromatic substitution reactions in aqueous solution. Our first results on the synthesis of amino- and hydroxybiphenyls are reported herein.

For reasons of solubility and unambiguous regioselectivity, 4-chlorophenyldiazonium chloride (**1a**) and 1,4-phenylenediamine (**2a**) were chosen for the initial study (Table 1).

Table 1: Coupling reaction of 4-chlorophenyldiazonium chloride (**1a**) with 1,4-phenylenediamine hydrochloride (**2a**).



Entry	Equiv $TiCl_3$ (relative to **1a**)	Addition of **1a** over *x* min	**3aa**[a] Yield [%][b]/[%][c]
1	2.5	0	56/54
2	2.5	3	59/–
3	2.5	6	65/58
4	2.5	11	54/–
5	2.5	23	50/–
6	1.0	6	65/–
7	**0.5**	**6**	**70/70**
8	0.25	6	71/–
9	0.0	6	66/64
10	0.0[d]	6	59/60

[a] Reactions conducted according to Method A, see the Supporting Information. [b] Yield determined by GC (internal standard: tetradecane). [c] Yield after purification by column chromatography. [d] Experiment with 10 equiv **2a** instead of 20 equiv.

The fact that substoichiometric amounts of titanium(III) chloride suffice for the full conversion of the diazonium salt supports the proposed chain mechanism (Scheme 1). Because of its reduction potential **2a** alone can initiate the chain reaction (Table 1, entries 9 and 10). Comparable properties have been observed for 1,4-dimethoxybenzene.[19] The existence of an optimum rate of addition of **1a** to the reaction mixture (Table 1, entries 1–5) is also consistent with general considerations. High concentrations of the diazonium salt, which are created by fast addition, lead to undesired homocoupling of aryl radicals to diazonium salts.[20] Low

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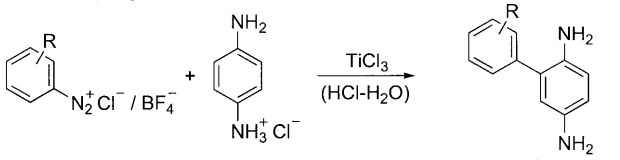
concentrations of the diazonium salt do not effectively propagate the radical chain (**E**→**F**, Scheme 1).

The results obtained with various arenediazonium salts **1a**–**1e** are summarized in Table 2. Since not all diazonium precursors can be prepared as chloride salts in aqueous solution (method A) owing to insufficient solubility, we also conducted the reactions by adding diazonium tetrafluoroborates either as solids (method B) or dissolved in acetonitrile (method C). Given that the diazonium chloride can be prepared as an aqueous solution, method A is the procedure of choice. If this is not the case, method B can be applied instead. Acetonitrile as cosolvent (method C) is suitable only for donor-substituted diazonium salts. Previous syntheses of biaryl-2,5-diamines required a five-step sequence including a Suzuki cross-coupling of doubly benzylidene-protected 2-iodo-1,4-phenylenediamine.[21]

Table 2: Coupling reactions of arenediazonium salts **1a**–**1e** with **2a**.



1a-e **2a** **3aa-3ea**

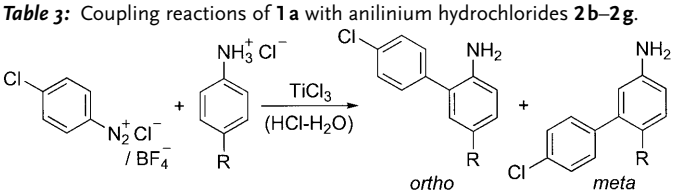
1	R	Method	3	Yield [%][b]
1a	*p*-Cl	A	**3aa**	70[c]
		B	**3aa**	56
		C	**3aa**	22
1b	*p*-F	A	**3ba**	70[c]
		B	**3ba**	60
		C	**3ba**	35
1c	*o*-Cl	B	**3ca**	39
1d	*o*-Br	A	**3da**	45[c]
		B	**3da**	48
1e	*p*-MeO	A	**3ea**	75[c]
		B	**3ea**	49
		C	**3ea**	58

[a] Reactions conducted according to procedures described in the Supporting Information. [b] Yield after purification by column chromatography. [c] Yield over two steps, based on the aniline precursor of the diazonium salt.

In the following series of experiments, 4-chlorophenyldiazonium salts **1a** were reacted with different *para*-substituted anilines (Table 3). The best results were obtained with the donor-substituted anilines anisidine (**2b**) and 4-aminophenol (**2c**); this suggests that the substitution mechansim can also be classified as $S_{RN}1$ type.[22] In contrast, the reactions of the less electron-rich anilines **2d**–**2g** were significantly complicated by homocoupling reactions,[20] indicating that the aryl radical addition step (**C**→**E**, Scheme 1) is too slow. These reactions therefore require more than fivefold excess of the aniline to be efficient.

The predominating *meta* selectivity in the reactions with **2b** and **2c** points to a preferred attack of the aryl radical at positions *ortho* to the more electron-donating group. Attempts to increase the selectivity by running the reaction at 0 °C or 45 °C failed. The virtually complete *ortho* selectivity in the reactions with **2d**, **2f**, and **2g** can be explained by the ineffective rearomatization (**E**→**F**, Scheme 1) of the cyclohexadienyl intermediates arising from the *meta* attack.

Table 3: Coupling reactions of **1a** with anilinium hydrochlorides **2b**–**2g**.



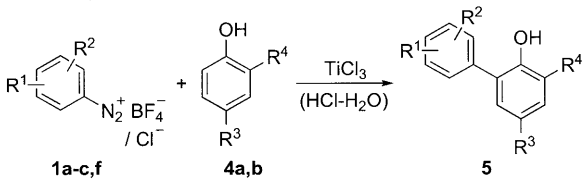
1a **2b-g** **3ab-3ag**

2	R	Method	3	Yield [%][b]	Selectivity *ortho*/*meta*
2b	OMe	A (45 °C)	**3ab**	64	15:85
		A	**3ab**	66	16:84
		A (0 °C)	**3ab**	57	37:63
		B	**3ab**	68	22:78
2c	OH	A (45 °C)	**3ac**	75	15:85
		A	**3ac**	64	13:87
		A (0 °C)	**3ac**	50	21:79
2d	F	A	**3ad**	18	>95:5[c]
		B	**3ad**	23	>95:5[c]
2e	Cl	A	**3ae**	22	80:20
		B	**3ae**	19	78:22
2f	CO_2Me	A	**3af**	10	>95:5[c]
		B	**3af**	28	>95:5[c]
2g	COMe	B	**3ag**	35	>95:5[c]

[a] Reactions conducted according to procedures described in the Experimental Section. [b] Yields after purification by column chromatography. [c] The *meta* isomer was not detected by GC-MS nor by NMR spectroscopy.

Examples for applications of this methodology to polyhydroxylated biaryls are sumarized in Table 4. Method A, which proceeded with substoichiometric amounts of titanium(III) chloride, was found to be less effective than method B, in which an excess of titanium was used. In contrast to 1,4-phenylendiamine, hydroquinones **4** are unable to initiate the chain reaction.[19,23] 4′-Chlorobiphenyl-2,3-diol (**5ab**), which is

Table 4: Coupling reactions of arenediazonium salts **1a**–**c**,**f** with hydroquinones **4a**,**b**.



1a-c,f **4a,b** **5**

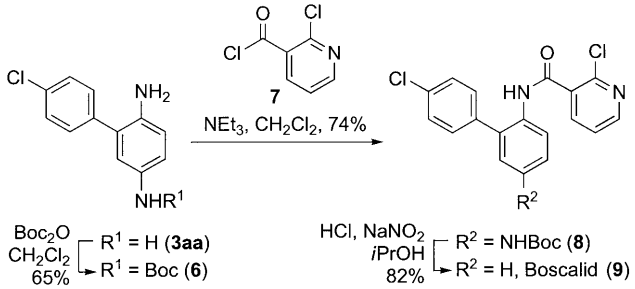
1	R^1, R^2	4	R^3, R^4	Method	5	Yield [%][b]	Selectivity *ortho*/*meta*
1a	*p*-Cl, H	**4a**	OH, H	A	**5aa**	60	–
				B	**5aa**	79	–
1b	*p*-F, H	**4a**	OH, H	B	**5ba**	85	–
1c	*o*-Cl, H	**4a**	OH, H	B	**5ca**	81	–
1f	*p*-Cl, *m*-Cl	**4a**	OH, H	B	**5fa**	80	–
1a	*p*-Cl, H	**4b**	H, OH	A	**5ab**	54	70:30
				B	**5ab**	63	75:25

[a] Yields after purification by column chromatography. Reactions conducted according to procedures described in the Supporting Information.

obtained as the main product from the arylation of *ortho*-hydroquinone (**4b**), was previously synthesized by a significantly more demanding four-step procedure from 1,2-dimethoxybenzene and 4-chloroiodobenzene.[24] Photochemically initiated $S_{RN}1$-type reactions of phenoxides with azosulfides in dimethylsulfoxide have been reported by Petrillo et al.[25]

To demonstrate the synthetic potential of the described method, we converted the biarylamines **3aa** and **3ac** into the fungizide Boscalid[26,27] (industrial production exceeds 1000 tons annually) and the antimalarial agent tebuquine, respectively.[28]

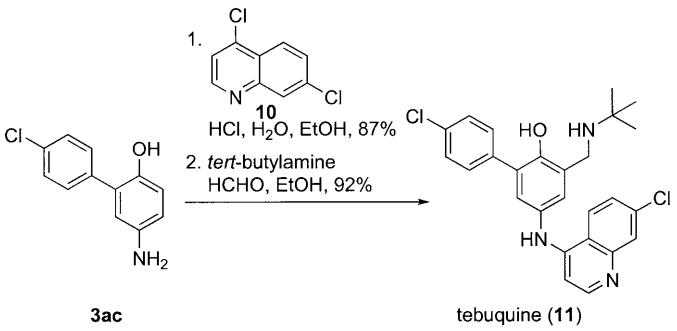
Monoprotection of diamine **3aa** with di-*tert*-butyl pyrocarbonate (Boc_2O) gave **6**, which upon reaction with 2-chloronicotinic acid chloride (**7**) furnished amide **8** (Scheme 2). Boscalid (**9**) was accessible in a one-pot procedure consisting of deprotection, diazotization, and reduction.



Scheme 2. Three-step synthesis of the fungizide Boscalid (**9**) from 4′-chlorobiphenyl-2,5-diamine (**3aa**).

Starting from aminophenol **3ac**, tebuquine (**11**) was accessible by a simple sequence (Scheme 3). Nucleophilic aromatic substitution of 4,7-dichloroquinoline (**10**) followed by Mannich aminomethylation led to the desired target compound **11** after acidic workup. Tebuquine (**11**) has shown subnanomolar activity against chloroquine-resistant strains of *Plasmodium falciparum* and represents a lead structure for the development of new antimalarial drugs.[28–30]

In summary, we have developed a previously unknown access to functionalized biarylamines and alcohols. Electron-rich phenols and aniline derivatives were shown to be best suited precursors. This methodology is of particular value since conventional organometallic cross-coupling reactions are difficult to accomplish with electron-rich aromatics. Regarding the availability and price of the starting materials, the radical chain reactions offer an economically interesting new pathway to many biarylamines and alcohols. Further investigations in the control of regioselectivity in reactions of *para*-subsituted anilinium salts are currently underway and will be reported in due course.



Scheme 3. Two-step conversion of 5-amino-4′-chlorobiphenyl-2-ol (**3ac**) to the antimalarial agent tebuquine (**11**).

Experimental Section

Method A for the radical arylation of anilines (Table 3): a) Preparation of the arenediazonium chloride: An ice-cooled degassed solution of the aniline (20.0 mmol) in 10% hydrochloric acid (20 mL) and water (20 mL) was stirred, and a degassed solution of sodium nitrate (1.38 g, 20.0 mmol) in water (10 mL) was added dropwise over 10 min. After the reaction mixture had been stirred an additional 20 min at 0°C, the solution was used for the aryl–aryl coupling reaction. b) Aryl–aryl coupling: A mixture of the aniline **2** (10.0 mmol) in degassed water (16 mL) and titanium(III) chloride (4 mL, ca. 1M solution in 10% hydrochloric acid) was stirred, and the solution of the arenediazonium chloride (5 mL, ca. 2.00 mmol) was added by syringe pump over 5 min. The resulting mixture was left to stir for 15 min, and a solution of sodium hydroxide (2.0 g) and sodium sulfite (2.0 g) in water (20 mL) was added. The crude product mixture was extracted three times with diethyl ether (3 × 30 mL), and the combined organic phases were subsequently washed with saturated sodium chloride solution (30 mL) and dried over sodium sulfate. Concentration in vacuo and purification by column chromatography furnished the biphenylamines **3**.

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