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The Gomberg–Bachmann Reaction for the Arylation of Anilines with Aryl Diazotates

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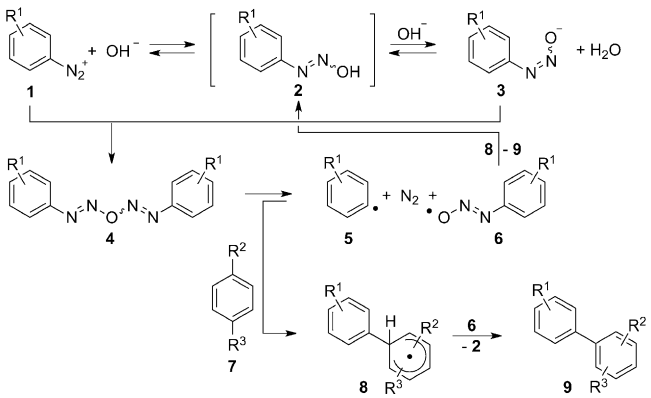
Regarding today's key research areas in organic chemistry, cross-coupling reactions to biaryls should ideally be carried out as C–H activations and not depend on the preparation of haloaromatics.[1] A well-known reaction fully in line with such current requirements is the Gomberg–Bachmann biaryl synthesis, which was first published in 1924.[2–4] However, all later developments and improvements for this reaction type, among which many variants are exploiting phase-transfer effects,[5] could not significantly increase its attractiveness. The main reason for this trend certainly is the superiority of modern organometallic cross-coupling reactions with respect to regioselectivity.[6,7] Even though Gomberg–Bachmann reactions can formally be regarded as C–H activations,[8,9] which enables the use of simple and cheap starting materials, the lack of selectivity narrows the scope of suitable substrates to a few compounds, with simple benzene being by far the most important.[10,11] Moreover, the aromatic substrate needs to be employed in large excess and is often even used as solvent.[12] Although conceptually new, these limitations remain for recently developed organocatalytic biaryl syntheses with iodobenzenes.[13–15] Herein, we present a novel variant of the Gomberg–Bachmann reaction that allows the highly regioselective radical coupling of phenyl diazotates with anilines.

When choosing diazonium salts as one of the most readily available aryl radical sources,[16] reactions with free anilines are basically complicated by the competing formation of triazenes and azo compounds.[17] A known but not generally effective or selective way out is to replace the anilines by anilinium salts.[18] Nevertheless, to enable the use of free anilines as reactants, we reasoned that the diazonium salt needs to be protected from side reactions by a rapid ionic coupling,[19] which, however, does not prevent the later formation of aryl radicals. Interestingly, this prospective reaction course overlaps with the mechanism generally accepted for Gomberg–Bachmann reactions.[20] Under basic conditions, diazonium ions **1** are first converted to a mixture of diazohydroxides **2**, diazotates **3**, and diazo anhydrides **4**



Scheme 1. Mechanism of the Gomberg–Bachmann reaction by Rüchardt.[20]

(Scheme 1). The formation of biphenyl **9** proceeds via the homolytic cleavage of **4** to give aryl radical **5** and azoxy radical **6**, the addition of **5** to the aromatic substrate **7**, and the final rearomatization of **8**.

Preliminary experiments with seven literature-known Gomberg–Bachmann protocols,[21] however, revealed that neither 4-chlorophenyldiazonium chloride nor its corresponding tetrafluoroborate **1** ($R^1=Cl$) were able to give more than trace amounts of the desired 2-aminobiphenyl **9** upon reaction with 4-fluoroaniline (**7**, $R^2=NH_2$, $R^3=F$) under any conditions.[22] To now ensure a reaction course via an aryl diazotate **3** as a protected derivative of diazonium ion **1**, solutions of the specific diazotate **10** were prepared from 4-chlorophenyldiazonium chloride and investigated spectroscopically.[22–24] Selected results from the coupling of **10** with 4-fluoroaniline (**11**) under various conditions are summarized in Table 1. Accordingly, the radical arylation reaction proceeds well at temperatures between 50 and 110 °C (entries 2–5).[25] Slight decreases in yield were observed for a slower or faster addition of diazotate **10** to the reaction mixture (entries 8 and 9) and upon addition of a phase-transfer catalyst or a reductant (entries 13 and 14). Minor improvements compared to the standard conditions resulted from changing to a nitrogen atmosphere (entry 6) or from the use of a higher concentrated alkaline solution (entry 10). A reduction of the excess of 4-fluoroaniline **11** from 12.5 equivalents (standard) to 5.0 equivalents did also only slighly effect the formation of aminobiphenyl **12** (entries 11 and 12).

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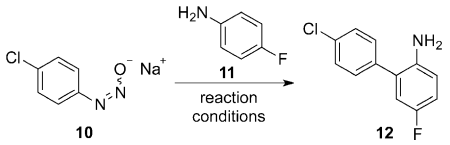
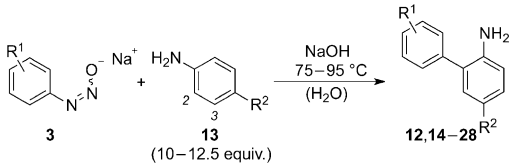
Table 1. Arylation of 4-fluoroaniline (**11**) with diazotate **10**.

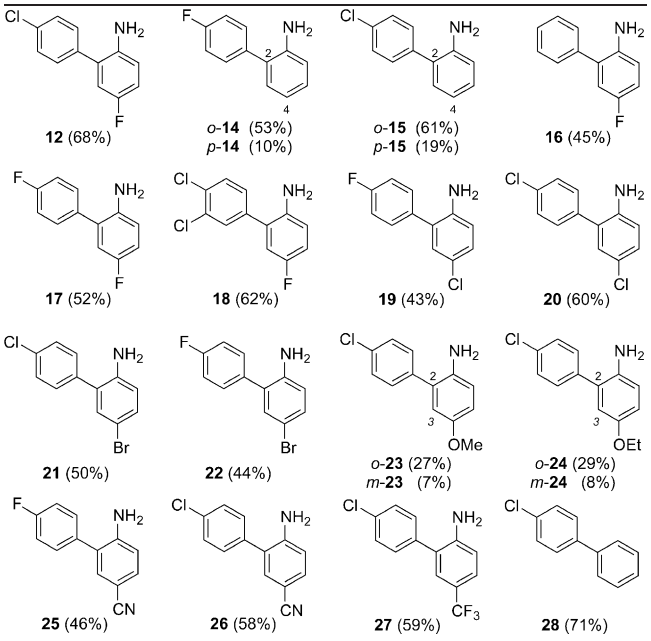


Entry	Variation vs. standard conditions[a]	Yield [%][b]
1	–	74
2	room temperature	36
3	50 °C	70
4	90 °C	78
5	110 °C	74
6	nitrogen atmosphere	78
7	argon atmosphere	73
8	addition of **10** to **11** over 6 min	58
9	addition of **10** to **11** over 24 min	68
10	8 N NaOH used for preparation of **10**	78
11	10 equiv of 4-fluoroaniline (**11**)/**10**	78
12	5 equiv of 4-fluoroaniline (**11**)/**10**	63
13	addition of aliquat 336 (5 mol%)	65
14	addition of iron powder (2.0 mmol)	65
15	addition of diazonium salt to NaOH and **11**	80[c]

[a] Standard conditions: An aqueous solution of **10** [prepared from 4-chlorophenyldiazonium chloride, (0.4 M, 2.00 mmol, 5.00 mL) and aqueous sodium hydroxide (4 N, 3 mL), 62% yield] was added dropwise over 12 min to 4-fluoroaniline (**11**, 25.0 mmol, 2.40 mL, 12.5 equiv) under air at 75 °C. [b] Yield based on diazotate **10** determined by 1H NMR spectroscopy using dimethyl terephthalate [1.00 mmol, $\delta = 8.10$ ppm (s, 4H)] as internal standard. [c] Yield of diazotate intermediate: 64%; yield of **12** based on diazonium salt: 52%.

Table 2. Radical arylation of anilines with diazotates.[a]





[a] Yields of 2-aminobiphenyls and regioisomers (*p*-**14**, *p*-**15**, *m*-**23**, *m*-**24**) after purification by column chromatography. Regioselectivity for the 2-position/3-position > 20:1, in case no yield is given for the regioisomer.[27]

Finally, an experiment showed that the desired aminobiphenyl **12** can even be obtained through the direct addition of 4-chlorophenyldiazonium chloride to a mixture of aqueous sodium hydroxide and 4-fluoroaniline, avoiding the intermediate preparation of a solution of diazotate **10** (entry 15). Up to this point, the diazotate-based arylation demonstrated a remarkable robustness. Additionally, aminobiphenyl **12** was formed with unreached regioselectivities of more than 20:1 related to its regioisomer in all reactions.[26,27] The main difference with respect to previously investigated literature-known Gomberg–Bachmann reactions[21] appears to be the increased base concentration. In this way, the equilibrium between the aryl diazonium salt **1** and the aryl diazotate **3** (Scheme 1) can be shifted largely towards the diazotate **3** and otherwise prevailing ionic side reactions of diazonium ions with anilines are effectively suppressed.[28,29] Supported by the identification of the diazotates in NMR experiments,[24] we therefore propose that not diazo anhydrides **4**, such as in classic Gomberg–Bachmann reactions, but more nucleophile-resistant diazotates **3** or diazohydroxides **2** represent the major intermediates of this reaction type.[20,29,30] Slightly modified standard conditions were then applied to determine the scope and limitations of the biaryl synthesis (Table 2). Halogens, hydrogen, and acceptor substituents in 4-position of the aniline (as in biphenyls **14**–**22** and **25**–**27**) were well tolerated and the products were formed with unchangingly high regioselectivities (>20:1).[27] Reduced selectivities, which partially account for lower yields, were only observed for biphenyls **23** and **24**, deriving from the donor-substituted anilines 4-anisidine (**13**, $R^2 = OMe$) and 4-phenetidine (**13**, $R^2 = OEt$).

In principle, acceptor substituents on the aniline (e.g., 4-aminobenzonitrile **13**, $R^2 = CN$) could similarly lead to a decrease in selectivity, since the cyclohexadienyl radical adduct (compare **8**, Scheme 1), arising from the undesired addition of aryl radicals in 3-position of **13,** again receives better stabilization.[31] In previous work, in which the arylation of 4-anisidine (**13**, $R^2 = OMe$) had to be conducted under acidic conditions to avoid side reactions, the radical-stabilizing effect of the methoxy group clearly predominated the influence of the protonated amino functionality, and *m*-**23** was consequently formed as major product.[18a] In contrast, under the basic conditions described herein, it has been possible for the first time to advantageously exploit the highly radical-stabilizing effect of the amino group to effectively direct the arylation into the *ortho* position of the aniline.[9c,27]

Structural variations of the diazotate **3** led to the conclusion that lipophilic atoms or groups represent the preferred substituents on the aromatic core. Aryl diazotates bearing polar functional groups (e.g., $R^1 = 4\text{-}NO_2$ or 4-CN) gave increasing yields of undesired azo coupling compounds and triazenes. This observation further supports the proposed reaction course via diazohydroxides **2** or diazotates **3**, because these intermediates are likely to require lipophilic substitu-

ents to allow their entry into the organic (aniline-containing) phase for the later generation of aryl radicals.[32] The phase-transfer step itself is confirmed by the successful arylation of benzene (biphenyl **28**) under otherwise identical conditions.

For a comparison of *para*-substituted anilines and benzene as radical acceptors, a competition experiment was conducted by using a mixture of 4-fluoroaniline (**11**) and benzene as aromatic substrates. This experiment shows that 4-fluoroaniline (**11**), in contrast to what one would expect from the yields reported in Table 2, is about five times more reactive towards aryl radicals than benzene, although it possesses only two (activated) *ortho* positions compared to the six equivalent sites of benzene (ratio of reaction rate per aromatic site is 16:1).[33] Taking into account literature-known rate constants, anilines can be integrated into the reactivity row of commonly used substrates for aryl radicals as follows: benzene ($5\times10^5\,M^{-1}s^{-1}$),[12] *para*-substituted anilines ($2\times10^6\,M^{-1}s^{-1}$),[33] nonactivated alkenes and furan ($2–3\times10^7\,M^{-1}s^{-1}$), and activated alkenes ($1–3\times10^8\,M^{-1}s^{-1}$).[34]

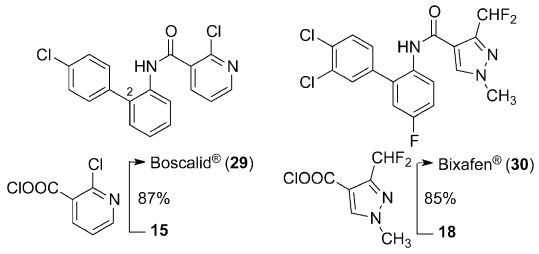
Beneficially, mainly with regard to an application of the radical arylation on a larger scale, the intermediate preparation of the diazotate solution can be avoided by a modified experimental procedure (Table 1, entry 15).[35] The results from a comparison of both variants, each conducted with five aminobiphenyls, are summarized in Table 3. For a better insight, the yields of the one-pot variant were calculated on the basis of the diazotate and the diazonium salt. By measuring the gas evolution in reactions of variant **B**, we could further show that the diazonium salt, upon entry into the reaction mixture, is immediately converted under loss of nitrogen.[22,36] An accumulation of reactive intermediates, such as diazo anhydrides, can therefore be ruled out.[35] By applying variant **B**, the synthesis of aminobiphenyl **12** was finally carried out on a 50-fold (100 mmol) scale leading to an unchanged yield.

Table 3. Comparison of variants **A** and **B**.

2-Aminobiphenyl	**A**: Addition of the diazotate solution to the aniline (compare Table 2) [%][a,b]	**B**: Addition of the diazonium salt solution to the aniline and NaOH (one-pot procedure) [%][a,b]	[%][a,c]
12	68	64	41
		83[d]	53[d]
o-**15**/*p*-**15**	61/19	54/10	35/7
17	52	51	42
19	43	42	34
20	60	62	39

[a] Yield after purification by column chromatography. [b] For comparsion: yield based on the diazotate intermediate [yield for the diazotate determined by gas evolution: 62% (**A**) and 64% (**B**)]. [c] Yield based on the diazonium salt. [d] Reaction on a 100 mmol scale (50-fold); yield determined as in Table 1, entry 15.

An important field for the application of 2-aminobiphenyl derivatives is crop protection.[37,38] Biphenyls **15** and **18**, which represent the key intermediates for Boscalid® (**29**)[37] and Bixafen® (**30**)[38] (Scheme 2), currently have to be prepared by classical palladium-catalyzed cross-coupling reactions. Through the radical arylation described herein, the same compounds are now available from much simpler starting materials and by using cheap sodium hydroxide instead of a precious catalyst.[39] Further applications of 2-aminobiphenyls in heterocyclic,[40] organometallic,[41] and medicinal[42] chemistry have also been reported.



Scheme 2. Synthesis of Boscalid® and Bixafen® from 2-aminobiphenyls.

In summary, aryl diazotates were found to be valuable starting materials for the direct arylation of unprotonated or unprotected anilines. Owing to the highly radical-stabilizing effect of the free amino group, which until now could not be exploited effectively in Gomberg–Bachmann reactions, the radical arylation proceeded with so far unreached regioselectivity. This new synthetic access to 2-aminobiphenyls formally proceeds in the sense of a C–H activation, but without the requirements to use catalysts and to previously prepare bromo- or iodoarenes or even more elaborate precursors.[1]

Experimental Section

Preparation of the aryl diazotate by diazotization (aryl diazonium chloride) and addition of base: A degassed solution of sodium nitrite (20.0 mmol, 1.38 g) in water (10 mL) was added dropwise to an ice-cooled degassed solution of the aniline (20.0 mmol) in hydrochloric acid (3 N, 20 mL) and water (20 mL) over a period of 15 min. The clear solution was stirred for 20 more minutes at 0 °C. An aliquot of this 0.4 M aryl diazonium chloride solution (2.00 mmol, 5.00 mL) was treated with a precooled aqueous solution of sodium hydroxide (4 N, 3 mL). The resulting solution/suspension of the aryl diazotate can be used for the aryl–aryl coupling.

Radical arylation of anilines with a previously prepared aryl diazotate: The previously prepared solution/suspension of the aryl diazotate was added dropwise to the aniline derivative (20.0–25.0 mmol) at 75–95 °C under vigorous stirring over a period of 10–15 min. After the addition was complete, the mixture was left to stir for 10 more minutes. The resulting reaction mixture was then extracted with organic solvents (e.g. diethyl ether or ethyl acetate, 3×75 mL). The combined organic phases were washed with saturated aqueous sodium chloride and dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting product was dried in vacuo. Depending on the product, further purification was carried out by destillation in vacuo or column chromatography on silica gel.

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Keywords: anilines · aryl diazotates · biaryls · Gomberg—Bachmann reaction · radical reactions

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[33] The arylation of 4-fluoroaniline (**11**, 20.0 mmol) in the presence of benzene (6.66 mmol) led to a product ratio of **12**/**28** = 16:1. The rate of addition to 4-fluoroaniline ($k = 2.4 \times 10^6\,M^{-1}s^{-1}$) has been calculated on the basis of the known value for benzene ($k = 4.5 \times 10^5\,M^{-1}s^{-1}$, see reference [12]).

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[36] Using variant **A**, the diazotates are also immediately decomposed upon entry into the reaction mixture at temperatures above 75 °C.

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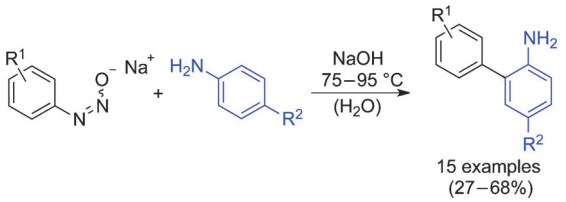
Radical Reactions

*G. Pratsch, T. Wallaschkowski, M. R. Heinrich** ..... ▮▮▮▮–▮▮▮▮

The Gomberg–Bachmann Reaction for the Arylation of Anilines with Aryl Diazotates



Simply aqueous sodium hydroxide is sufficient to exclude ionic side reactions and to prepare 2-aminobiphenyls from aryl diazotates and anilines through a new variant of the Gomberg–Bachmann reaction (see scheme). The metal-free reaction under basic conditions allows to exploit the highly radical-stabilizing effect of the aniline's free amino function for the first time, which leads to a so far unreached regioselectivity.

