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Strongly Directing Substituents in the Radical Arylation of Substituted Benzenes

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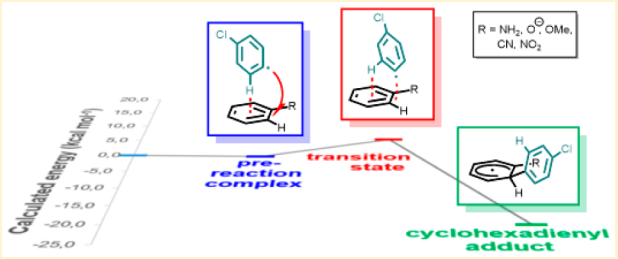
Supporting Information

ABSTRACT: Although general interest in radical arylation reactions has grown rapidly in recent years, poor regioselectivities and the need to use a large excess of the radical-accepting arene have hindered their application to substituted benzenes. We now describe experimental and computational investigations into the substituent effects that lead to regioselective addition based on the recent discovery of anilines as outstanding substrates for radical arylations.



INTRODUCTION

The Gomberg−Bachmann reaction, which dates back to 1924,[1] represents one of the fundamental transformations in aryl radical chemistry.[2,3] Starting from aryl diazonium salts as classical radical sources[4] and arenes or heteroarenes acting as radical acceptors, a broad range of biaryls can be obtained in a reaction[5] whose result is comparable to an aryl-C−H activation.[6] Recent versions of the Gomberg−Bachmann reaction rely on a photocatalytic conversion of diazonium salts,[7] on aryl radical generation from chloro-, bromo-, or iodobenzenes in the presence of strong bases,[8] on arylhydrazines,[9] or on the in situ diazotization of anilines.[10]

Although Gomberg−Bachmann reactions could, on this basis, be very attractive because of their cheap and readily available starting materials, their application, also in the newly developed versions, has remained mostly limited to unsubstituted benzene and selected heteroarenes.[7−10] Explanations for this include the relatively slow addition of aryl radicals to benzene and its derivatives,[11] which requires the use of the radical acceptor in large excess, and the low regioselectivities observed for most substituted benzenes.[5,12] Heteroarenes, on the other hand, and especially electron-rich furans and pyrroles, show increased reactivity toward aryl radicals and far higher regioselectivities.[3e,7,8,13]

The recent extension of the Gomberg−Bachmann reaction to anilines provided motivation to investigate the suitability of substituted benzenes as aryl radical acceptors in more detail.[14] In both of these reactions, and in consecutively developed arylations with arylhydrazines,[15] anilines showed outstanding properties as aryl radical acceptors in two ways: first, the aryl radical addition to anilines was found to proceed about 1 order of magnitude faster than to classically favored substrates such as nitrobenzenes or anisoles,[15a] and second, comparably high regioselectivites were obtained.[14,15]

Little attention has been paid in the literature over the last decades to how substituents affect the regioselectivity in radical arylations of benzene derivatives with the last comprehensive review dating back to 1973.[12] Early studies had shown that variation of substituents on the attacking phenyl radical does influence the substrate selectivity in competition experiments with nitrobenzene and benzene but not the regioselectivity of the substitution at nitrobenzene.[12,16] Such observations led to a discussion of "polarity of free radicals".[17] All substituents on the radical acceptor were considered to be weakly activating,[12] and comparably high regioselectivities were only obtained for particular combinations of donor-substituted phenyl radicals with acceptor-substituted benzenes or vice versa.[18] As these studies have shown that it is particularly difficult to achieve regioselectivity with aryl radicals such as the 4-chlorophenyl radical,[19] this radical was chosen for the experiments reported in this communication. Based on experimental results, we will give insight into the fundamental question as to whether kinetic or thermodynamic factors play a decisive role in the addition step. So far, the low selectivity of phenyl radicals in arylations of substituted benzenes has been attributed to a "little development of the new bond at the transition state",[12] so that "the stability of the product radicals is also of importance".[20]

RESULTS AND DISCUSSION

Three recently developed protocols, starting either from 4-chlorophenyldiazonium chloride (**1**) or 4-chlorophenylhydrazine (**2**), were chosen to collect the required experimental data,

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as these procedures allow in particular the radical arylation of anilines (Scheme 1).[14a,15a,b] All reactions were carried out under air atmosphere to ensure that rearomatization does not become an influential factor.[21] Moreover, the aromatic substrates **3**–**7** were not used as solvents but in a lower excess of 10–20 equiv. In this way, the results also indicate the synthetic applicability, and the relative reactivity of the arenes can be evaluated, as the aryl radicals are not trapped quantitatively.

Tables 1–3 summarize the yields and product ratios obtained with anilines **3** (Table 1), phenols **4**, and phenyl ethers **5** (Table 2) and with benzonitriles **6** and nitrobenzene (**7a**) (Table 3). The conditions A–C refer to the reactions shown in Scheme 1. If available, further data from the literature (conditions D–I) have been added for comparison of regioselectivities.

A comparison of the average yields obtained with the monosubstituted radical acceptors **3a**, **4a**, **5a**, **6a**, and **7a** under all available conditions gave the following trend in overall reactivity: $PhNH_2$ > PhO^- > PhCN > $PhNO_2$ ≈ PhOMe, which is is in agreement with previous experimental studies.[15a] Note that under the reaction conditions B, C, and E, phenol (**4a**) and 4-fluorophenol (**4b**) are present as phenolates.

In terms of regioselectivity, only the anilines **3a,b** (Table 1) and phenolates of **4a,b** (Table 2, entries 1 and 2) were able to suppress the formation of *meta*-isomers (3-isomers), independent of the presence of a substituent in the *para*-position. Arylation of the anisoles **5a,b** (Table 2, entries 3 and 4), benzonitriles **6a,b**, and nitrobenzene (**7a**), in contrast, led to basically all possible regioisomers. Remarkably, the effect of the electron-donating methoxy group differs from those of the electron-withdrawing cyano and nitro groups, as anisole (**5a**) showed a preference for the 2-isomer (2/3/4 = 71:14:15), whereas benzonitrile (**6a**) and nitrobenzene (**7a**) were attacked more frequently in the 4-position via average selectivities of 2/3/4 = 53:14:33 and 2/3/4 = 45:13:42, respectively.[25] This effect may be related to a three-electron interaction between the radical and the oxygen atom of the methoxy group in the transition state. The importance of the 4-position in arylations of electron-deficient arenes also became obvious from the significant decrease in yield caused by blocking this position by a fluorine substituent (Table 3, entries 1 and 2). Arylation experiments with 4-fluoronitrobenzene are not included since they are complicated by competing nucleophilic substitution.

In the next step, density-functional theory (DFT) calculations were carried out to determine whether the experimentally observed substituent effects in radical arylations could be predicted computationally. It was of particular interest in this respect to evaluate the influence of the transition state, **TS**, compared to the stabilization of the cyclohexadienyl radical adduct **CA** (Scheme 2).

Scheme 1. Reaction Conditions A–C Used for Radical Arylations

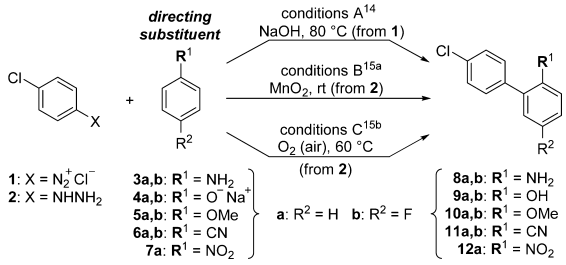
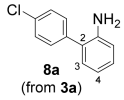
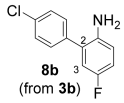
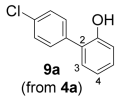
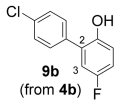
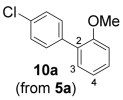
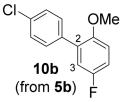


Table 1. Arylation of Aniline (3a) and 4-Fluoroaniline (3b)

biphenyl	isomers	conditions A	B	C	D[a]
 8a (from 3a)		80%	54%	60%	62%
	2 (**8a**)	76	76	85	75
	3 (**8a′**)	--	--	--	--
	4 (**8a′′**)	26	24	15	25
 8b (from 3b)		68%	53%	55%	61%
	2 (**8b**)	100	100	100	100
	3 (**8b′**)	--	--	--	--

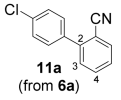
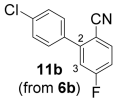
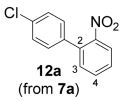
[a]Conditions D: See ref 15c.

Table 2. Arylation of Phenol (4a), 4-Fluorophenol (4b), Anisole (5a), and 4-Fluoroanisole (5b)

biphenyl	isomers	conditions A	B	C	E[a]	F[b]	G[c]
 9a (from 4a)	¤		57%	58%	62%		
	2 (**9a**)		70	76	68		
	3 (**9a′**)		--	--	--		
	4 (**9a′′**)		30	24	32		
 9b (from 4b)			49%	40%	56%		
	2 (**9b**)		100	100	100		
	3 (**9b′**)		--	--	--		
 10a (from 5a)		31%	34%	35%		59%	48%
	2 (**10a**)	64	73	73		68	75
	3 (**10a′**)	17	12	12		17	12
	4 (**10a′′**)	19	15	15		15	13
 10b (from 5b)		36%	31%	36%			
	2 (**10b**)	72	88	89			
	3 (**10b′**)	28	12	11			

[a]Conditions E: Reaction of 4-cyanophenyl radical with phenolate or 4-bromophenolate; see ref 22. [b]Conditions F: Reaction of 4-methylphenyl radical with anisole; see ref 8e. [c]Conditions G: Reaction of 3-chlorophenyl radical with anisole; see ref 5.

Table 3. Arylation of Benzonitrile (6a), 4-Fluorobenzonitrile (6b), and Nitrobenzene (7a)

biphenyl	isomers	conditions A	B	C	H[a]	I[b]
 11a (from 6a)		49%	29%	62%	58%	
	2 (**11a**)	48	62	52	51	
	3 (**11a′**)	16	11	15	14	
	4 (**11a′′**)	36	27	33	35	
 11b (from 6b)		20%	13%	49%		
	2 (**11b**)	61	67	77		
	3 (**11b′**)	39	33	23		
 12a (from 7a)		36%	52%	38%		30%
	2 (**12a**)	44	42	41		55
	3 (**12a′**)	14	16	18		4
	4 (**12a′′**)	42	42	41		41

[a]Conditions H: See ref 5. [b]Conditions I: Reaction of phenyl radical with nitrobenzene; see refs 23 and 24.

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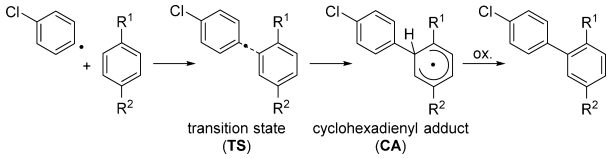
Scheme 2. Reaction Course



All calculations were performed with Gaussian09, revision C.01.[26] Geometries were optimized using the B3LYP functional[27,28] and the aug-cc-pVDZ basis set.[29,30] Structures were shown to be minima or transition states by calculating the normal vibrations within the harmonic approximation. Energies relative to the separated reactants are reported including the vibrational zero-point energy taken from these calculations. B3LYP/aug-cc-pVDZ calculations have been shown to underestimate radical activation energies by several kilocalories per mole in comparison to coupled-cluster reference calculations,[31] although we expect the trends to be correct for such closely related reactions.

Early calculations by James and Suart[32] on the hydrogen atom addition to benzene gave an activation energy of ca. 4 kcal mol^{-1} and suggested that the addition step is exothermic by −28 kcal mol^{-1}. From these values, the activation energy for the attack of a phenyl radical onto benzene was estimated to >3 kcal mol^{-1} and the related reaction energy to −18 kcal mol^{-1}.[33] The results from our calculations are summarized in Figure 1 and Tables 4 and 5.

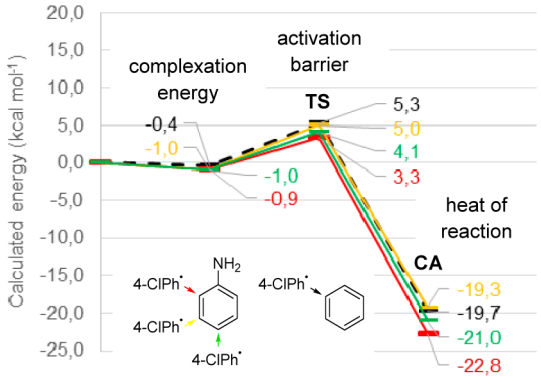


Figure 1. Schematic reaction profiles for the arylation of aniline and benzene with the 4-chlorophenyl radical.

Table 4. Calculated Activation Barriers for the Attack of a 4-Chlorophenyl Radical

	activation barrier[a] for an attack in		
directing substituent R^1 =	2-position	3-position	4-position
3a: NH_2	3.3	5.0	4.1
4a: O^-	−9.8[b]	−2.3	−9.2
5a: OCH_3	3.7	5.4	4.7
6a: CN	4.5	4.8	4.6
7a: NO_2	3.8	5.6	4.3
benzene: H	5.3		

[a]Relative to the separated reactants (B3LYP/aug-cc-pVDZ + zero-point energy). [b]A prereaction complex with a binding energy of −9.8 kcal mol^{-1} is formed (see Figure 2). The activation barrier from this complex to the 2-isomer is essentially zero.

Table 5. Calculated Heats of Reaction for the Attack of a 4-Chlorophenyl Radical

	heats of addition[a] for attack in		
radical acceptor R^1 = , R^2 =	2-position	3-position	4-position
3a: NH_2, H	−22.8	−19.3	−21.0
3b: NH_2, F	−24.0	−20.6	
4a: O^-, H	−35.0[b]	−22.0	−27.7
4b: O^-, F	−37.8[b]	−22.3	
5a: OCH_3, H	−22.3	−18.9	−19.9
5b: OCH_3, F	−23.1	−19.6	
6a: CN, H	−22.1	−20.3	−20.6
6b: CN, F	−21.9	−19.9	
7a: NO_2, H	−22.6	−19.2	−23.5
benzene: H	−19.7		

[a]Relative (B3LYP/aug-cc-pVDZ + zero-point energy) heats of addition and *e* to the separated reactants. [b]A prereaction complex with a binding energy of −9.8 kcal mol^{-1} is formed. The activation barrier from this complex to the *ortho*-product is essentially zero.

The data obtained for the arylation of aniline (**3a**) and benzene with the 4-chlorophenyl radical revealed that the radical attack on electron-rich aromatic systems proceeds via a prereaction complex that has not been considered previously (Figure 2). One of the two more polarized C−H bonds in the

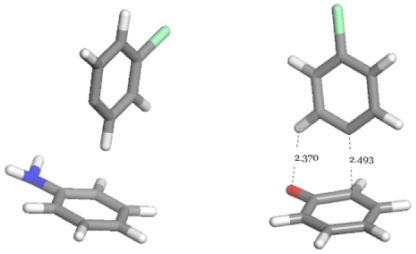


Figure 2. Pre-reaction complex formed on attack of the 4-chlorophenyl radical on aniline (left) and on the *ortho*-position of the phenolate anion (right). Distances are given in angstroms.

position *ortho* to the radical center points to the π-system of the radical-accepting aniline. As shown by the activation energies summarized in Table 4, this complex plays an exceptional role in the arylation of phenolate ions. It is likely that both specific solvation and counterion-effects are important for these reactions, but considering explicit solvent molecules and/or counterions would be outside the scope of this article.

The activation energies (relative to the separated reactants) for the neutral systems lie in the range of 3.3−5.6 kcal mol^{-1}, consistent with the estimated value of >3 kcal mol^{-1} (Table 4). The calculated heats of reaction lie in the range of −18.9 to −24.0 kcal mol^{-1}, again consistent with the experimental estimate of −18 kcal mol^{-1} for the addition of the phenyl radical to benzene.[33,34] The introduction of the fluorine atom in the 4-position generally led to a weak relative stabilization in the range of −0.3 to −1.3 kcal mol^{-1}. A comparison of the heats of reaction to those of benzene (−19.7 kcal mol^{-1}) provided support for the long-standing assumption that all substitutents on the radical acceptor are weakly activating, independent of their electron-donating or -withdrawing character. The activating effect is thereby much more pronounced for 2- and 4-positions than for 3-positions.

Figure 3 shows a plot of the calculated energies against the calculated heats of reaction. The correlation between the two

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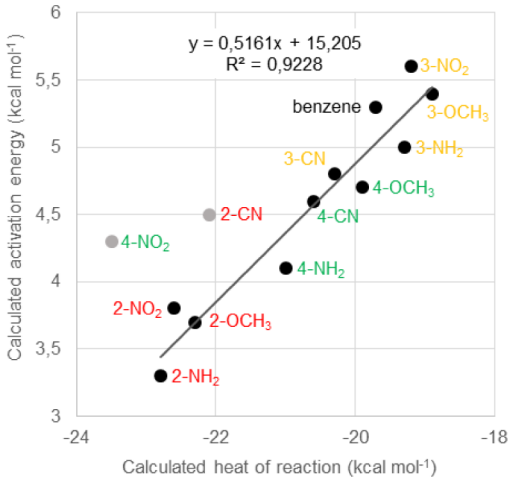

Figure 3. Calculated activation energies plotted vs the calculated heats of reaction (all kcal mol^{-1}) for the addition of the 4-chlorophenyl radical to neutral monosubstituted benzenes. The regression line and the correlation equation do not include the two data points plotted in gray, which represent significant outliers and are both associated with strong π-acceptors, as discussed in the text.

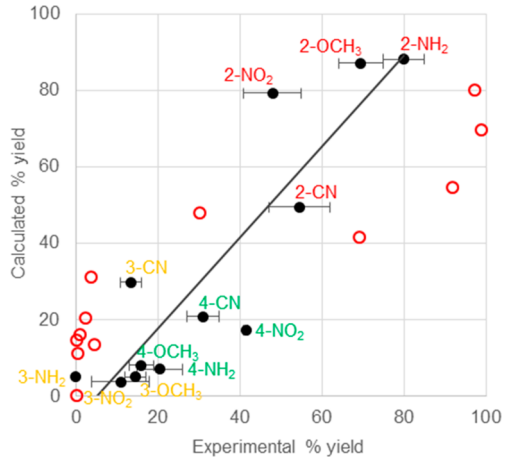

Figure 4. Calculated and experimental yields of the individual neutral arylated products. The black filled circles and the regression line and equation are those obtained from the calculated gas-phase activation energies assuming kinetic control with the addition as the rate-determining step. The red open circles indicate the predicted yields obtained by assuming thermodynamic control of the product radicals. The line is that for perfect 1:1 agreement.

quantities is good, so that we can conclude that the radical addition is compatible with the Bell–Evans–Polanyi principle.[35] However, the 4-nitro and 2-cyano cases deviate significantly and have been omitted from the correlation (indicated in gray in Figure 3). Quite generally, the π-acceptor substituents lie above the correlation line (i.e., the activation energies are higher than would be expected from the heat of reaction). Nevertheless, we can conclude that the differences in calculated activation barriers for the radical addition to substituted benzenes are largely controlled by the stabilization of the product radical without significant specific kinetic effects. The slope of the calculated regression line is approximately 0.5, suggesting that radical stabilization effects by the substituents are approximately 50% developed in the transition states. The π-acceptors are less well able to stabilize the transition states than the other substituents.

The question of whether the product distributions are best described by kinetic or thermodynamic control of the addition reactions can be answered by comparing calculated product distributions with those observed experimentally. Figure 4 shows a plot of the calculated (from transition-state theory) % yield for each product of the addition of *p*-chlorophenyl radical to the monosubstituted benzenes vs the experimental results expressed as the mean of the product distributions for all reaction conditions with error bars that cover the range found experimentally. The agreement (RMSE = 15%) is good, so that we can conclude that the product distributions are kinetically controlled. The corresponding correlation obtained by assuming thermodynamic control gives a significantly worse RMSE (21%). The product yields calculated assuming thermodynamic control are shown as red open circles in Figure 4. Note that a statistical factor of 2:2:1 has been used for the 2-, 3-, and 4-isomers, respectively, in order to account for the fact that there is only one 4-position available for each substituted benzene. The assumption of kinetic control for the arylation of nitrobenzene leads to a predicted 2/4- ratio of 79:16, representing the strongest deviation in this series, compared to 30:69 for thermodynamic control. As experiment (Table 3) gives approximately equal yields of the two isomers with a slight preference for the 2-isomer, and the arylation of nitrobenzene can be considered to proceed with a stronger thermodynamic influence.

The combination of our experimental and theoretical results therefore suggests that the addition of aryl radicals to substituted benzenes largely takes place under kinetic control with the radical addition as the rate-determining step and that substituent effects in the product radicals are approximately 50% effective in the transition states. These conclusions are consistent with those of a previous theoretical study by Zhang[34] on the arylation of aniline. Zhang concluded that aryl radical addition to neutral anilines is the rate-determining step in a kinetically controlled reaction, whereas arylation to protonated anilines may be thermodynamically controlled.

Note that, even though the calculations can predict the product distributions well, the calculated activation energies do not agree completely with the accepted reactivity series $PhNH_2$ > PhO^- > PhCN > $PhNO_2$ ≈ PhOMe;[15a,26,36] in order of increasing calculated activation energy for the most reactive isomer, the calculations predict $PhNH_2$ > $PhOCH_3$ ≈ $PhNO_2$ > PhCN > benzene. PhO^- cannot be treated in the same way as the neutral systems because ion-pairing and solvation effects are likely to be dominant in determining reactions rates for the phenolate anion.

CONCLUSIONS

In summary, it has been shown that DFT calculations can be used to predict experimental product distributions in radical arylations of benzenes. Although not as regioselective as arylations of alkenes, the aryl radical addition to substituted benzenes still proceeds with a high degree of kinetically controlled selectivity. Substituent effects in the resulting cyclohexadienyl radical adduct are reflected to about 50% in the transition state. All reactions pass through a prereaction complex, which was found to be particularly strongly stabilized in the case of an aryl radical attack on phenolate ions. These results give more detailed insight into the long-standing question of how substituents affect the regioselectivity in radical arylations of substituted benzenes.

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EXPERIMENTAL SECTION

General Experimental Methods. Solvents and reagents were used as received. ^{1}H NMR spectra were recorded on 360 and 600 MHz spectrometers using $CDCl_3$ and CD_3OD as solvents referenced to TMS (0 ppm), $CHCl_3$ (7.26 ppm), and CHD_2OD (3.31 ppm). Chemical shifts are reported in parts per million (ppm). Coupling constants are reported in hertz (*J*, Hz). The following abbreviations are used for the description of signals: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quadruplet), m (multiplet). ^{13}C NMR spectra were recorded at 90.6 and 150.9 MHz in $CDCl_3$ and CD_3OD using $CDCl_3$ (77.0 ppm) and CD_3OD (49.5 ppm) as standards. Chemical shifts are given in parts per million (ppm). ^{19}F NMR spectra were recorded at 338.8 MHz using $CFCl_3$ (0 ppm) or C_6F_6 (−164.9 ppm) as standards. Mass spectra were recorded using electron impact (EI). Analytical TLC was carried out on Merck silica gel plates using short-wave (254 nm) UV light and ninhydrin to visualize components. Silica gel (Kieselgel 60, 40−63 μm, Merck) was used for flash column chromatography. Yields obtained after purification are summarized in Tables 1−3.

General Procedure for the Synthesis of Biphenyls under Gomberg−-Bachmann Conditions (Conditions a): Preparation of the Aryl Diazotate by Diazotization 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 an additional 20 min at 0 °C. An aliquot of this 0.4 M aryldiazonium 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 was then used for the aryl−aryl coupling. **Radical Arylation of Substituted Benzenes with a Previously Prepared Aryl Diazotate**. The previously prepared solution/suspension of the aryl diazotate (2.00 mmol, 5.00 mL) was added dropwise to the substituted benzene (20.0 mmol) at 75−95 °C under vigorous stirring over a period of 10−15 min. After the addition was complete, the mixture was allowed to stir for an additional 10 min. 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 distillation under reduced pressure or column chromatography on silica gel.

General Procedure for the Synthesis of Biphenyls with MnO_2 under Single-Phase Conditions (Conditions B). To a stirred suspension of the substituted benzene (20.0 mmol) and MnO_2 (435 mg, 5.00 mmol) in acetonitrile (5 mL) at rt was added a solution of the arylhydrazine (1.00 mmol) in acetonitrile (2 mL) dropwise over a period of 1 h. After completion of the reaction, as monitored by TLC, the reaction mixture was filtered over Celite. The filter cake was further washed with ethyl acetate, and the solvents were removed under reduced pressure. The remaining benzene derivative was removed by Kugelrohr distillation, and the products were purified by silica gel chromatography.

General Procedure for the Synthesis of Biphenyls from Arylhydrazine Hydrochlorides under Air (Conditions C). A mixture of the substituted benzene (20.0 mmol) and aqueous sodium hydroxide (1 N, 1.0 mL) was heated to 60−90 °C, and the arylhydrazine hydrochloride was added portion wise in 10 batches over a period of 9 h. The reaction was completed after 24 h at the given temperature, as monitored by TLC. After removal of water under reduced pressure, the remaining aniline was recovered by Kugelrohr distillation, and the crude biphenyls were purified by column chromatography on silica gel.

4′-Chlorobiphenyl-2-amine (**8a**) and 4′-chlorobiphenyl-4-amine (**8a″**) were prepared under conditions A−C. Separation and purification by column chromatography (hexane/ethyl acetate 10:1) gave **8a** and **8a″** as dark solids. 4′-Chlorobiphenyl-2-amine (**8a**): R_f = 0.6 (hexane/EtOAc = 4:1) [UV]; mp =65−67 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.09 (bs, 2 H), 6.80 (dd, *J* = 1.1 Hz, *J* = 8.0 Hz, 1 H), 6.85 (dt, *J* = 1.1 Hz, *J* = 7.5 Hz, 1 H), 7.10 (dd, *J* = 1.6 Hz, *J* = 7.6 Hz, 1 H), 7.15−7.21 (m, 1 H), 7.40 (s, 4 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 115.7 (CH), 118.8 (CH), 126.3 (C_q), 128.8 (CH), 129.0 (2 × CH), 130.3 (CH), 130.4 (2 × CH), 133.1 (C_q), 137.9 (C_q), 143.4 (C_q); MS (EI) *m*/*z* 205 (35) [^{37}Cl-M$^+$], 203 (100) [^{35}Cl-M$^+$], 168 (45), 167 (75); HRMS (ESI) calcd for $C_{12}H_{11}ClN$ [M$^+$ + H] 204.0575, found 204.0569. 4′-Chlorobiphenyl-4-amine (**8a″**): R_f = 0.3 (hexane/EtOAc = 4:1) [UV]; mp =118−120 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.09 (bs, 2 H), 6.81 (d, *J* = 8.6 Hz, 2 H), 7.35 (d, *J* = 8.5 Hz, 2 H), 7.39 (d, *J* = 8.6 Hz, 2 H), 7.45 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 115.4 (2 × CH), 127.5 (2 × CH), 127.8 (2 × CH), 128.7 (2 × CH), 130.2 (C_q), 132.1 (C_q), 139.6 (C_q), 146.1 (C_q); MS (EI) *m*/*z* 205 (30) [^{37}Cl-M$^+$], 203 (100) [^{35}Cl-M$^+$], 167 (18); HRMS (ESI) calcd for $C_{12}H_{11}ClN$ [M$^+$ + H] 204.0575, found 204.0582. The spectral data obtained are in agreement with those reported in the literature.[15b]

4′-Chloro-5-fluorobiphenyl-2-amine (**8b**) was prepared under conditions A−C. Purification by column chromatography (hexane/ethyl acetate 10:1) gave **8b** as a dark brown oil. 4′-Chloro-5-fluorobiphenyl-2-amine (**8b**): R_f = 0.6 (hexane/EtOAc = 4:1) [UV]; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.54 (bs, 2 H), 6.69 (dd, J_{HF} = 4.7 Hz, *J* = 8.5 Hz, 1 H), 6.83 (dd, *J* = 2.8 Hz, J_{HF} = 9.0 Hz, 1 H), 6.88 (ddd, *J* = 3.0 Hz, J_{HF} = 8.1 Hz, *J* = 8.7 Hz, 1 H), 7.37 (d, *J* = 8.7 Hz, 2 H), 7.42 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 115.3 (d, J_{CF} = 22.2 Hz, CH), 116.5 (d, J_{CF} = 22.6 Hz, CH), 116.7 (d, J_{CF} = 7.7 Hz, CH), 127.4 (d, J_{CF} = 7.2 Hz, C_q), 129.1 (2 × CH), 130.3 (2 × CH), 133.6 (C_q), 136.9 (d, J_{CF} = 1.7 Hz, C_q), 139.4 (d, J_{CF} = 2.2 Hz, C_q), 156.4 (d, J_{CF} = 236.9 Hz, C_q); MS(EI) *m*/*z* 224 (6), 223 (29) [^{37}Cl-M$^+$], 222 (18), 221 (100) [^{35}Cl-M$^+$], 220 (10), 219 (20), 187 (8), 186 (45), 185 (60), 184 (13), 159 (5), 157 (7), 126 (6), 110 (10), 93 (37); HRMS (EI) calcd for $C_{12}H_9ClFN$ [M$^+$] 221.0407, found 221.0409. The spectral data obtained are in agreement with those reported in the literature.[15b]

4′-Chloro-2-hydroxybiphenyl (**9a**) and 4′-chloro-4-hydroxybiphenyl (**9a″**) were prepared under conditions B and C. Purification by column chromatography (hexane/EtOAc = 10:1 → 4:1) gave a mixture of **9a** and **9a″**. 4′-Chloro-2-hydroxybiphenyl (**9a**): R_f = 0.5 (hexane/EtOAc = 4:1) [UV]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.06 (bs, 1 H), 6.95 (dd, *J* = 0.9 Hz, *J* = 8.1 Hz, 1 H), 6.99 (dt, *J* = 1.2 Hz, *J* = 7.5 Hz, 1 H), 7.21 (dd, *J* = 1.7 Hz, *J* = 7.6 Hz, 1 H), 7.23−7.29 (m, 1 H), 7.41 (d, *J* = 8.7 Hz, 2 H), 7.44 (d, *J* = 8.6 Hz, 2 H). 4′-Chloro-4-hydroxybiphenyl (**9a″**): R_f = 0.5 (hexane/EtOAc = 4:1) [UV]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.82 (bs, 1 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 7.37 (d, *J* = 8.7 Hz, 2 H), 7.43 (d, *J* = 8.7 Hz, 2 H), 7.45 (d, *J* = 8.7 Hz, 2 H). The spectral data obtained are in agreement with those reported in the literature.[37,38]

4′-Chloro-5-fluorobiphenyl-2-ol (**9b**) was prepared under the conditions B and C. Purification by column chromatography (dichloromethane 100%) gave **9b** as a light yellow oil. 4′-Chloro-5-fluorobiphenyl-2-ol (**9b**): R_f = 0.3 (DCM) [UV]; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.70 (bs, 1 H), 6.74−6.78 (m, 1 H), 6.85 (dd, *J* = 3.1 Hz, J_{HF} = 6.2 Hz, 1 H), 7.01 (dd, *J* = 8.8 Hz, J_{HF} = 10.0 Hz, 1 H), 7.40 (d, *J* = 8.7 Hz, 2 H), 7.46 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 115.5 (d, J_{CF} = 8.2 Hz, CH), 116.5 (d, J_{CF} = 3.1 Hz, CH), 116.9 (d, J_{CF} = 25.0 Hz, CH), 127.9 (d, J_{CF} = 7.7 Hz, C_q), 129.3 (2 × CH), 130.3 (2 × CH), 134.3 (C_q), 134.6 (C_q), 148.3 (C_q), 156.0 (d, J_{CF} = 239.2 Hz, C_q); HRMS (EI) calcd for $C_{12}H_9ClFN$ [M$^+$] 221.01779, found 221.01749. The spectral data obtained are in agreement with those reported in literature.[39]

4′-Chloro-2-methoxybiphenyl (**10a**), 4′-chloro-3-methoxybiphenyl (**10a′**), and 4′-chloro-4-methoxybiphenyl (**10a″**) were prepared under conditions A−C. Purification by column chromatography (hexane/EtOAc = 12:1 → 4:1) gave a mixture of **10a**, **10a′**, and **10a″**. 4′-Chloro-2-methoxybiphenyl (**10a**): R_f = 0.2 (hexane) [UV]; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.81 (s, 3 H), 6.98 (dd, *J* = 0.9 Hz, *J* = 8.3 Hz, 1 H), 7.02 (dt, *J* = 1.1 Hz, *J* = 7.5 Hz, 1 H), 7.28 (dd, *J* = 1.8 Hz, *J* = 7.6 Hz, 1 H), 7.30−7.34 (m, 1 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 7.46 (d, *J* = 8.8 Hz, 2 H). 4′-Chloro-3-methoxybiphenyl (**10a′**): R_f = 0.2 (hexane) [UV]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.86 (s, 3 H), 6.91 (ddd, *J* = 0.9

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Hz, J = 2.4 Hz, J = 8.2 Hz, 1 H), 7.08 (dd, J = 1.9 Hz, J = 2.4 Hz, 1 H), 7.14 (ddd, J = 0.9 Hz, J = 1.9 Hz, J = 7.6 Hz, 1 H), 7.35 (d, J = 7.9 Hz, 1 H), 7.40 (d, J = 8.7 Hz, 2 H), 7.51 (d, J = 8.7 Hz, 2 H). 4′-Chloro-4-hydroxybiphenyl (**10a″**): R_f = 0.2 (hexane) [UV]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.85 (s, 3 H), 6.97 (d, J = 8.9 Hz, 2 H), 7.37 (d, J = 8.7 Hz, 2 H), 7.45−7.50 (m, 4 H). The spectral data obtained are in agreement with those reported in literature.[40−42]

4′-Chloro-5-fluoro-2-methoxybiphenyl (**10b**) and 4′-chloro-6-fluoro-3-methoxybiphenyl (**10b′**) were prepared under conditions A−C. Separation and purification by column chromatography (hexane/ethyl acetate 10:1) gave **10b** and **10b′** as a brown solids. 4′-Chloro-5-fluoro-2-methoxybiphenyl (**10b**): R_f = 0.6 (hexane/EtOAc = 4:1) [$KMnO_4$]; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.78 (s, 3 H), 6.88−6.94 (m, 1 H), 6.97−7.04 (m, 2 H), 7.38 (d, J = 8.9 Hz, 2 H), 7.46 (d, J = 8.8 Hz, 2 H);^{13}C NMR (151 MHz, $CDCl_3$) δ 56.2 (CH_3), 112.4 (d, J_{CF} = 8.3 Hz, CH), 114.6 (d, J_{CF} = 22.6 Hz, CH), 117.2 (d, J_{CF} = 23.5 Hz, CH), 128.3 (2 × CH), 128.6 (C_q), 130.7 (2 × CH), 133.4 (C_q), 135.8 (d, J_{CF} = 1.6 Hz, C_q), 152.5 (d, J_{CF} = 8.1 Hz, C_q), 157.3 (d, J_{CF} = 240.4 Hz C_q); MS(EI) m/z 237 (14), 236 (100), 221 (19), 186 (98), 157 (24); HRMS (EI) calcd for $C_{13}H_{10}ClFO$ [M^+] 236.0404, found 236.0404. 4′-Chloro-5-fluoro-2-methoxybiphenyl (**10b′**): R_f = 0.5 (hexane/EtOAc = 4:1) [$KMnO_4$]; ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.83 (s, 3 H), 6.83−6.87 (m, 1 H), 6.88−6.94 (m, 1 H), 7.08 (dd, J = 8.9 Hz, J_{HF} = 10.0 Hz, 1 H), 7.42 (d, J = 8.9 Hz, 2 H), 7.47 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 55.8 (CH_3), 114.8 (C_q), 115.3 (d, J_{CF} = 8.0 Hz, CH), 116.8 (d, J_{CF} = 23.5 Hz, CH), 120.4 (d, J_{CF} = 7.9 Hz, CH), 129.2 (2 × CH), 130.4 (2 × CH), 133.9 (C_q), 135.7 (d, J_{CF} = 1.6 Hz, C_q), 146.3 (d, J_{CF} = 20.2 Hz, C_q), 153.8 (d, J_{CF} = 240.4 Hz, C_q); MS(EI) m/z 237 (8), 236 (14), 235 (4), 234 (9), 199 (5), 193 (7), 163 (9), 137 (6), 127 (5), 117 (5), 76 (6), 57 (4), 53 (6), 43 (4) 27 (6), 18 (100); HRMS (EI) calcd for $C_{13}H_{10}ClFO$ [M^+] 236.0404, found 236.0405. The spectral data obtained are in agreement with those reported in literature.[15b]

4′-Chlorobiphenyl-2-carbonitrile (**11a**), 4′-chlorobiphenyl-3-carbonitrile (**11a′**), and 4′-chlorobiphenyl-4-carbonitrile (**11a″**) were prepared under conditions A−C. Purification by column chromatography (hexane/EtOAc = 10:1 → 4:1) gave a mixture of **11a**, **11a′**, and **11a″**. 4′-Chlorobiphenyl-2-carbonitrile (**11a**): R_f = 0.5 (hexane/EtOAc = 4:1) [UV]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44−7.51 (m, 6 H), 7.65 (dt, J = 1.4 Hz, J = 8.5 Hz, 1 H), 7.77 (ddd, J = 0.5 Hz, J = 1.4 Hz, J = 7.8 Hz 1 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 111.2 (C_q), 118.4 (CH), 123.4 (CH), 127.9 (CH), 129.9 (CH), 130.1 (2 × CH), 132.9 (2 × CH), 133.9 (C_q), 135.0 (C_q), 136.5 (C_q), 144.2 (C_q). 4′-Chlorobiphenyl-3-carbonitrile (**11a′**): R_f = 0.5 (hexane/EtOAc = 4:1) [UV]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (t, J = 7.8 Hz, 1 H), 7.63−7−67 (m, 3 H), 7.73 (d, J = 0.9 Hz, J = 8.7 Hz, 2 H), 7.77 (d, J = 7.9 Hz, 1 H), 7.83 (t, J = 1.5 Hz, 1 H). 4′-Chlorobiphenyl-4-carbonitrile (**11a″**): R_f = 0.5 (hexane/EtOAc = 4:1) [UV]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, J = 8.7 Hz, 2 H), 7.52 (d, J = 8.8 Hz, 2 H), 7.65 (d, J = 8.7 Hz, 2 H), 7.73 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 111.3 (C_q), 118.7 (C_q), 127.6 (2 × CH), 128.5 (2 × CH), 129.3 (2 × CH), 132.7 (2 × CH), 134.9 (C_q), 137.6 (C_q), 146.1 (C_q). The spectral data obtained are in agreement with those reported in the literature.[43,44]

4′-Chloro-5-fluorobiphenyl-2-carbonitrile (**11b**) and 4′-chloro-6-fluorobiphenyl-3-carbonitrile (**11b′**) were prepared under conditions A−C. Purification by column chromatography (hexane/EtOAc = 10:1) gave a mixture of **11b** and **11b′**. 4′-Chloro-5-fluorobiphenyl-2-carbonitrile (**11b**): R_f = 0.6 (Hexan/EtOAc = 4:1) [UV]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (ddd, J = 2.6 Hz, J_{HF} = 7.8 Hz, J = 8.6 Hz, 1 H), 7.19 (dd, J = 2.6 Hz, J_{HF} = 9.5 Hz, 1 H), 7.46−7.50 (m, 4 H), 7.77 (dd, J_{HF} = 5.5 Hz, J = 8.6 Hz, 1 H); DEPTQ (151 MHz, $CDCl_3$) δ 107.3 (C_q), 115.5 (d, J_{CF} = 22.5 Hz, CH), 117.2 (d, J_{CF} = 23.2 Hz, CH), 117. (C_q), 129.2 (2 × CH), 129.9 (2 × CH), 135.5 (d, J_{CF} = 1.6 Hz, C_q), 135.6 (C_q), 136.2 (d, J_{CF} = 9.7 Hz, C_q), 147.2 (d, J_{CF} = 9.1 Hz, C_q), 164.8 (d, J_{CF} = 257.4 Hz, C_q); GC-MS (EI) m/z: 233 (^{37}Cl-M^+), 231 (^{35}Cl-M^+), 196, 176, 169, 149, 97; HRMS (EI) calcd for $C_{13}H_7ClFNNa$: 254.0143, found: 254.0148. 4′-Chloro-6-fluorobiphenyl-3-carbonitrile (**11b′**): R_f = 0.6 (Hexan/EtOAc = 4:1) [UV]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (m, 1 H), 7.43−7.45 (m, 4 H), 7.64 (ddd, J = 2.2 Hz, J_{HF} = 4.5 Hz, J = 8.5 Hz, 1 H), 7.73 (dd, J_{HF} = 2.1 Hz, J = 7.1 Hz, 2 H).

4′-Chloro-2-nitrobiphenyl (**12a**), 4′-chloro-3-nitrobiphenyl (**12a′**). and 4′-chloro-4-nitrobiphenyl (**12a″**) were prepared under conditions A−C. Purification by column chromatography (hexane/EtOAc = 15:1) gave a mixture of **12a**, **12a′**, and **12a″**. 4′-Chloro-2-nitrobiphenyl (**12a**): R_f = 0.6 (hexane/EtOAc = 4:1) [UV]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16−7.19 (m, 2 H), 7.31−7.34 (m, 3 H), 7.43 (dt, J = 1.2 Hz, J = 8.0 Hz, 1 H), 7.54 (td, J = 1.2 Hz, J = 7.6 Hz 1 H), 7.80 (dd, J = 1.2 Hz, J = 8.0 Hz 1 H). 4′-Chloro-3-nitrobiphenyl (**12a′**): R_f = 0.6 (hexane/EtOAc = 4:1) [UV]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, J = 7.6 Hz, 2 H), 7.55 (d, J = 7.6 Hz, 2 H), 7.61 (t, J = 8.6 Hz, 1 H), 7.87 (d, J = 7.6 Hz, 1 H), 8.20 (m, 1 H), 8.39 (t, 1 H). 4′-Chloro-4-nitrobiphenyl (**12a″**): R_f = 0.6 (hexane/EtOAc = 4:1) [UV]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 77.47 (d, J = 8.4 Hz, 2 H), 7.55 (d, J = 8.4 Hz, 2 H), 7.70 (d, J = 8.4 Hz, 2 H), 8.29 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 124.2 (2 × CH), 127.6 (2 × CH), 128.6 (2 × CH), 129.4 (2 × CH), 135.3 (C_q), 137.2 (C_q), 146.3 (C_q), 147.3 (C_q). The spectral data obtained are in agreement with those reported in the literature.[44−46]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01840.

Computational results of the density-functional calculations, NMR spectra of biaryl compounds, and GC chromatograms of biaryl compounds **10b** and **10b′** (PDF)

Tables of atom coordinates and absolute energies (PDF)

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Notes

The authors declare no competing financial interest.

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