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Regioselective Radical Arylation of Anilines with Arylhydrazines

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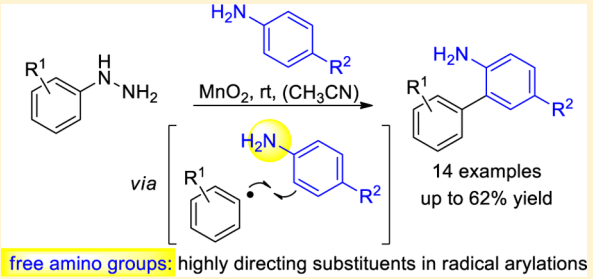
Supporting Information

ABSTRACT: Substituted 2-aminobiphenyls have been prepared from arylhydrazines and anilines via radical arylation reactions under simple oxidative conditions. The strong directing effect of the free and unprotonated amino functionality leads to high regioselectivities, and anilines have been shown to be significantly better aryl radical acceptors than nitrobenzenes or phenyl ethers. The methodology is also applicable to phenols, which react best as phenolates under strongly basic conditions. Finally, radical arylation reactions of anilines and anilinium salts under various conditions have for the first time demonstrated that regioselectivity can also be controlled through the rearomatization step and that the addition of an aryl radical to a substituted benzene might even be reversible.



INTRODUCTION

The Gomberg–Bachmann reaction,[1] which was first reported in 1924, is a well-known method for the preparation of biaryls from aryldiazonium salts by homolytic aromatic substitution.[2,3] Attempts to improve this reaction, e.g., by using phase-transfer conditions,[4] could, however, not significantly increase its attractiveness. The most important reason for this is the advantage of modern organometallic cross-coupling reactions regarding regioselectivity.[5] Despite the fact that the Gomberg–Bachmann reaction can formally be classified as C–H activation[6] so that simple and cheap starting materials can be used, the lack of selectivity limits the scope of suitable substrates to a few compounds among which simple benzene is the by far most important.[7,8] Because of the comparably slow addition of aryl radicals to substituted benzenes,[9] the aromatic substrate often needs to be employed in large excess and is therefore commonly used as solvent. Such limitations even remain for the recently developed organocatalytic biaryl syntheses starting from iodobenzenes.[10]

The fact that selectivity is difficult to achieve in homolytic aromatic substitutions proceeding via reactive aryl radicals prompted us to investigate in more detail which substituents on the aromatic core are suited to control regioselectivity. The first studies in this field revealed that especially amino groups, as they are present in anilines, are highly directing substituents.[11] In combination with aryldiazonium salts,[12] however, special precautions have to be taken to prevent the conversion of these substrates to azobenzenes or triazenes.[13]

Alternative and also well-established sources for aryl radicals are bromo- and iodoarenes, which can be reacted under a wide range of reductive conditions.[14] Recently, arylboronic acids[15] and arylhydrazines[16] have gained considerable interest as reactants in aryl radical reactions under oxidative conditions. Herein, we now describe arylhydrazines as radical sources for the selective arylation of anilines.

RESULTS AND DISCUSSION

The oxidative degradation of arylhydrazines that leads to aryl radicals via the intermediate formation of instable diazenes has been essentially known for a long time.[17] Interestingly, oxidations of arylhydrazines can be carried out under mild conditions and also at low temperatures, which we felt might be a key to achieve or improve selectivity.[18] In addition to the desired regioselectivity of the radical arylation, the oxidant should also preferentially oxidize the hydrazine and not the aniline. In case the aniline remains susceptible toward the chosen oxidant, azo compounds can be expected as major side products from an oxidative dimerization reaction. A number of oxidants including peroxodisulfate,[19a] ferrate salts,[19b] copper salts,[19c] hypervalent iodine species,[19d] manganese dioxide,[19e] potassium permanganate,[19f] and hydrogen peroxide[19g,h] have been reported to enable this conversion in high yield.[19] The results of our first study to identify possible oxidants and reaction conditions are summarized in Table 1.

The results in Table 1 show that 4-chlorophenylhydrazine (**1**) can be oxidized with sufficient selectivity over 4-fluoroaniline (**2**), which is even present in a 20-fold excess. Among the oxidants, potassium superoxide, potassium hexacyanoferrate(III), and hydrogen peroxide even showed perfect selectivity as the azobenzene **4** could not be detected in the crude product mixture (entries 2, 6, and 7). Since all reactions were run until complete conversion of the hydrazine[20] and no major side products could be determined besides azobenzene **4** (for entries 1 and 3–5), we assume that

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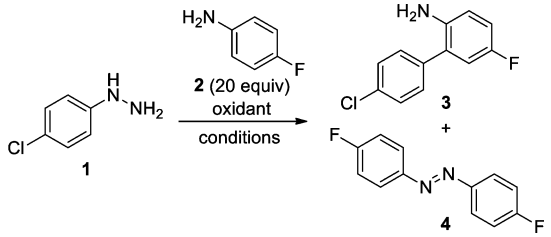
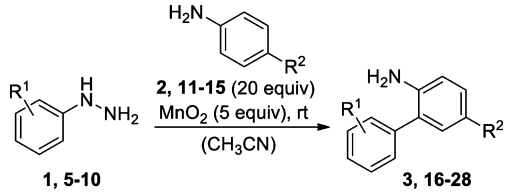
Table 1. Comparison of Oxidants and Reaction Conditions for the Synthesis of Aminobiphenyl 3 from 4-Chlorophenylhydrazine (1) and 4-Fluoroaniline (2)



entry	oxidant (equiv), conditions[a]	aminobiphenyl 3[b] (%)	azobenzene 4[c] (%)
1	MnO_2 (5), CH_3CN, rt	63	11
2	KO_2 (4), CH_3CN, −10 °C	54	
3	$Mn(OAc)_3$ (3), CH_3CN, rt	59	5
4	$KMnO_4$ (3), CH_3CN, rt	56	32
5	$NaIO_4$ (3), (CH_3CN/H_2O = 7:1), rt	54	2
6	$K_3[Fe(CN)_6]$ (3), (CH_3CN/H_2O = 7:1), rt	55	
7	H_2O_2 (10), CH_3CN, rt	36	

[a]Hydrazine **1** (1.00 mmol in 2 mL of CH_3CN) was added to the reaction mixture (5 mL of CH_3CN or CH_3CN/H_2O) over a period of 1 h. Reactions monitored by TLC and continued until total consumption of **1** (ca. 2 h). [b]Yields determined by ^1H NMR with dimethyl terephthalate (δ = 8.10 ppm (s, 4 H)) as internal standard. [c]Yield of azobenzene related to the quantity of aminobiphenyl **3**.

Table 2. Synthesis of 2-Aminobiphenyls



entry	hydrazine:[a] R^1 =	aniline: R^2 =	aminobiphenyl[b] (%)
1	**1**: 4-Cl	**2**: F	**3** (53)
2	**5**: 3,4-Cl	**2**: F	**16** (62)
3	**6**: 2-Cl	**2**: F	**17** (56)
4	**7**: 4-CN	**2**: F	**18** (58), (46)[c]
5	**8**: 4-OMe	**2**: F	**19** (32)[c]
6	**1**: 4-Cl	**11**: Cl	**20** (47)
7	**9**: 4-F	**12**: Br	**21** (45)
8	**1**: 4-Cl	**12**: Br	**22** (48), (54)[c]
9	**6**: 2-Cl	**12**: Br	**23** (57)
10	**1**: 4-Cl	**13**: CN	**24** (29), (35)[c]
11	**1**: 4-Cl	**14**: OMe	**25** (39), (35)[c]
12	**10**: 3,4,5-F	**15**: H	**26** (75, *o*:*p* = 59:16)
13	**1**: 4-Cl	**15**: H	**27** (54, *o*:*p* = 41:13)
14	**6**: 2-Cl	**15**: H	**28** (70, *o*:*p* = 49:21)

[a]Hydrazines were added to the reaction mixture over a period of 1 h. Reactions continued until total consumption of the hydrazine (ca. 2 h, TLC control). [b]Isolated yields. Hydrazine used as free base. [c]Hydrazine used as hydrochloride; $NaHCO_3$ (5 equiv) added to the reaction mixture.

hydrogen abstraction by the highly reactive chlorophenyl radicals occurs to a remarkable extent.[12] The resulting volatile chlorobenzene is not found among the products due to a concentration of reaction mixture in vacuo prior to analysis. A repetition of the experiment in enty 1 with a careful workup gave the product **3** and chlorobenzene in 30% yield. Comparative experiments conducted in CD_3CN gave chlorobenzene and 4-deuteriochlorobenzene in a ratio of 37:1, which demonstrates that only a small amount of hydrogen abstraction originates from the solvent and the major amount from the NH_2 group of 4-fluoroaniline (**2**) or from the rearomatization step (Scheme 3).

Because of the simple reaction conditions and easy workup as well as the ready availability and low cost, manganese dioxide was chosen as the preferred oxidant. A series of experiments was conducted to determine scope and limitations of the 2-aminobiphenyl synthesis (Table 2).

For some of the products, we compared the influence of replacing the arylhydrazine by its hydrochloride salt accompanied by 5 equiv of sodium hydrogen carbonate. Minor differences in product formation were observed for aminobiphenyls **22**, **24**, and **25** (entries 8, 10, and 11). Only aminobiphenyl **18** (entry 4) was obtained with a remarkably better yield when starting from hydrazine **7** than from the corresponding hydrochloride. 4-Methoxyphenylhydrazine (**8**) was used as hydrochloride salt due to the low stability of the corresponding free base.

Regarding the substituents on the arylhydrazine, a significantly decreased yield was only found for the 4-methoxy derivative **8** in the series of reactions with 4-fluoroaniline (**2**) (entries 1−5). Changes from halogen substituents on the aniline (entries 1−9) to an electron-withdrawing group, such as cyano (entry 10), or an electron-donating group, such as methoxy (entry 11), also led to lower yields. Not surprisingly, a comparably large amount of accompanying azobenzene (**25**:4,4′-dimethoxyazobenzene = 2:1) was isolated from the arylation of *p*-anisidine (**14**) (entry 11), which represents the most easily oxidizable substrate in the series of anilines. Unexpectedly, however, we could not detect or isolate the regioisomer resulting from the aryl radical attack onto the *meta*-position of *p*-anisidine (**14**). Previous studies had shown that, due to the significant radical stabilizing effect of the methoxy group, *p*-anisidine (**14**) can not be reacted regioselectively with aryl radicals.[11c] The arylation experiments with aniline (**15**) gave a mixture of *ortho*- and *para*-isomers with a clear preference for the *ortho*-product.[21] With an *ortho*-substituent on the arylhydrazine, such as in the 2-chloro derivative **6**, the selectivity is, however, decreased from *ortho*:*para* = 4:1 (entries 12 and 13) to a ratio of 2.5:1 (entry 14).

Since the optimization experiment with potassium superoxide had given aminobiphenyl **3** as pure product without need for further purification (Table 1), although at a slightly lower yield than manganese dioxide, we also used the superoxide for three preparative experiments. Thus, the aminobiphenyls **3**, **16**, and **20** were again obtained in high purity and with yields of 39%, 58%, and 37%, respectively.

To get a better insight in the relative reactivity of the newly investigated anilines, the known aryl radical acceptors furan,[16b,22] phenol,[23] and anisole[4] were submitted to similar reactions conditions (Scheme 1).

The yield of the reaction with furan leading to 2-(4-chlorophenyl)furan (**29**) is comparable to experiments by Demir[16b] with manganese triacetate and hydrazinium chlorides. Phenol and anisole are obviously less reactive aryl radical acceptors than anilines since the biphenyl alcohol **30** and biphenyl ether **31** were obtained in lower yields. The distribution of isomers of **31** in the arylation of anisole is not much different from the product patterns found in Gomberg−

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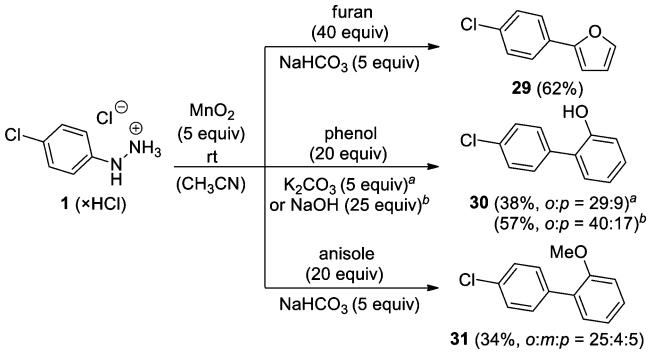
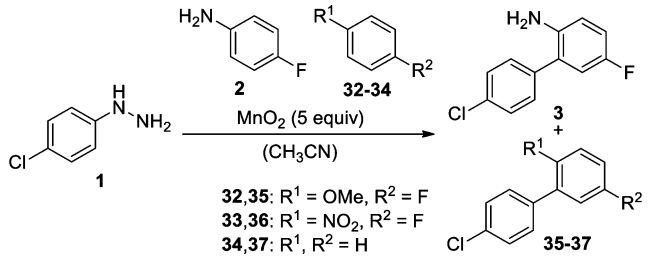
Scheme 1. Arylation of Furan, Phenol, and Anisole



Bachmann arylations of anisole.[4] Not surprisingly, the reactivity of phenol could significantly be improved by the addition of excess sodium hydroxide to the reaction mixture.[23] In this way, more electron-rich phenolate ions act as radical acceptors and the original aromatic hydroxy group of the phenol can no longer stabilize the aryl radical through hydrogen atom transfer. Our initial concern that these two positive aspects might be counterbalanced by an extensive formation of dimerization products from the more easily oxidizable phenolate ions, compared to phenol, did not prove true.[24] Related experiments with 4-fluoroaniline (**2**) in the presence of stronger bases (potassium carbonate or sodium hydroxide) showed that arylation reactions of anilines are independent of base concentration.[25]

To directly compare the effect of the free amino functionality present in anilines on the arylation, and to get a first idea about relative reaction rates, we conducted a few simple competition experiments. The control reaction for this series was run with 10 equiv of 4-fluoroaniline (**2**) (Table 3, entry 1) and showed that a reduction of the excess of aniline does not lead to significantly decreased yields (cf. 53%, Table 2, entry 1). When the arylation was then carried out with a mixture of 4-fluoroaniline (**2**) and equal amounts of 4-fluoroanisole (**32**) (entry 2) or 4-fluoronitrobenzene (**33**) (entry 3), the aniline-derived aminobiphenyl **3** was found as major product with a ratio of ca. 10:1 to the biphenyls **35** and **36**. Although these results clearly suggest that an amino group renders the benzene core much more reactive toward a radical attack than nitro or methoxy groups, as they are present in the competing substrates **32** and **33**, it is difficult to draw a more precise conclusion due to the fact that the combined yields of **3** and **35**, and **3** and **36**, do not amount to the 51% obtained in the control experiment. A possible reason for this decrease in overall yield might be that the competing substrates 4-fluoroanisole (**32**) and 4-fluoronitrobenzene (**33**) have been attacked by the 4-chlorophenyl radical to a comparably larger extent, but the final yield was lowered due to difficulties in the rearomatization step (see below) or a somehow low stability of the products **35** and/or **36** under the given reaction conditions.

Table 3. Competition Experiments for the Addition of the 4-Chlorophenyl Radical to Various Substrates



entry	competing substrates (equiv)	products (%)
1	4-fluoroaniline (**2**) (10) (control)	**3** (51)[a]
2	4-fluoroaniline (**2**) (10) vs 4-fluoroanisole (**32**) (10)	**3** (35)[a] **35** (<3)[b]
3	4-fluoroaniline (**2**) (10) vs 4-fluoronitrobenzene (**33**) (10)	**3** (34)[a] **36** (<4)[b]
4	4-fluoroaniline (**2**) (15) vs benzene (**34**) (5)	**3** (52)[a] **37** (<3)[b]

[a]Isolated yields. [b]Yields of products **35**, **36**, and **37** derived from ^{1}H NMR spectra of the crude reaction mixtures and by comparison with literature data (ref 26).

A more precise conclusion can be drawn from the experiment with benzene (**34**) as competing substrate (Table 3, entry 4), since the aminobiphenyl **3** was obtained in a yield comparable to the control experiment (Table 3, entry 1) and the original preparative attempt (Table 2, entry 1). The ratio of 4-fluoroaniline (**2**)/benzene (**34**) = 3:1 was chosen to account for the six equal positions on the benzene core in relation to the two *ortho*-positions of the aniline. From the ratio of the products **3** and **37** (entry 4), we conclude that an *ortho*-position of 4-fluoroaniline (**2**) is at least 15 times more reactive than a single position on benzene. With this relative rate per (reactive) position, and based on the known rate constant for the addition of aryl radicals to benzene ($k = 4.5 \times 10^5$ M^{-1} s^{-1}),[9] an at least 5-fold value of $k = 2.3 \times 10^6$ M^{-1} s^{-1} can be derived for the addition of aryl radicals to 4-fluoroaniline (**2**).[27]

The results of the oxidative arylation of anilines reported herein as well as a recent study on a new variant of the Gomberg–Bachmann arylation[11c] clearly demonstrate that free amino functionalities, as they are present in anilines, are highly activating and directing substituents for the purpose of radical arylations. Since we have previously also observed a certain regioselectivity for radical arylations of anilines under acidic conditions, under which the aniline was definitely protonated and the directing effect of the free amino group cannot have been operative, we wondered whether the product distribution can also be influenced through the rearomatization step. Generally, there is broad agreement that the key step in all of these reactions is the addition of an aryl radical to the aromatic substrate, and that the resulting cyclohexadienyl-type radicals almost always find a way to rearomatize.[10a]

For this mechanistic study, we used 4-methoxyphenylhydrazine (**8**) as an aryl radical source in combination with ammonium cerium(IV) nitrate. Preliminary experiments had shown that arylhydrazines react sluggishly with other oxidants under strongly acidic conditions (including manganese dioxide) and that nondonor-substituted arylhydrazines are even more difficult to oxidize. A comparison of two reactions depicted in Scheme 2 (eqs 1 and 2) then clearly demonstrated that there remains indeed no directing effect if the amino functionality is protonated, and aminobiphenyl **19** and its regioisomer **19′** were observed in almost equal amounts (Scheme 2, eq 2).

For comparison, the arylation of protonated 4-fluoroaniline (**2**) under reductive conditions using the 4-methoxyphenyldiazonium salt **38** instead of hydrazine **8** as radical source, proceeded regioselectively and aminobiphenyl **19** was found as only regioisomer (Scheme 2, eq 3).[11a] As the reaction above had shown that the aryl radical attacks both ring positions of 4-

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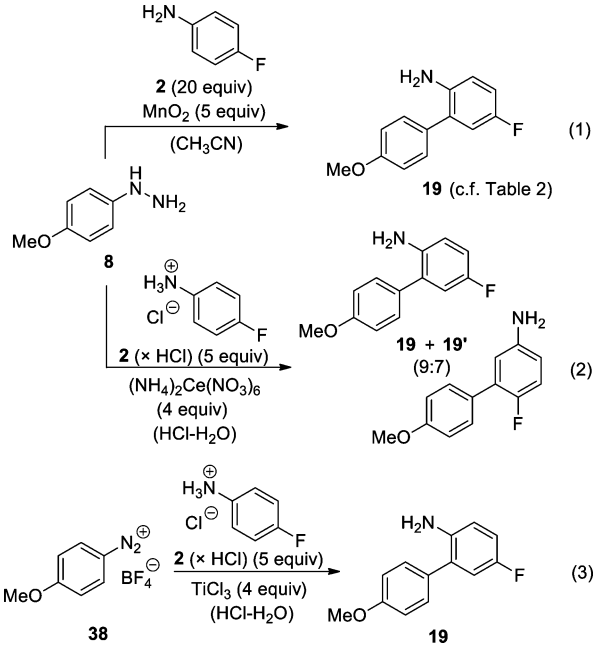
Scheme 2. Regioselectivity under Various Reaction Conditions



fluoroanilinium ions (Scheme 2, eq 2), the differentiation and regiocontrol under reductive conditions (Scheme 2, eq 3) must have occurred in the rearomatization step. For anilines which do not bear directing substituents in the *para*-position (e.g., R^2 = OH, OMe),[11a] the present results can be summarized as depicted in Scheme 3.

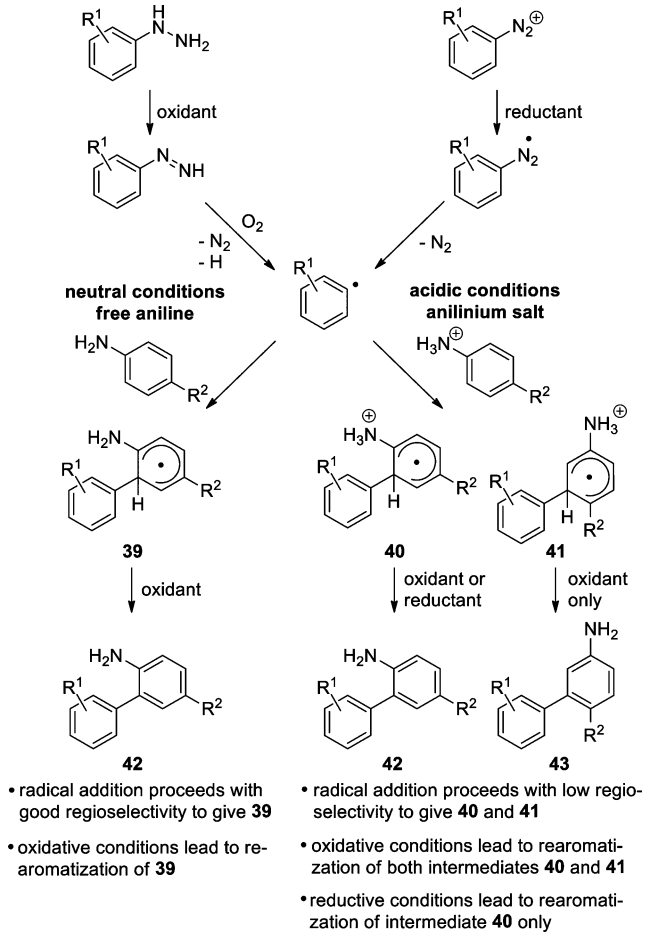
Obviously, it is therefore possible to achieve regioselectivity in the arylation of anilines in two ways, either by running the reaction under neutral or basic conditions to exploit the strongly directing effect of the amino functionality or by applying acidic and reductive conditions that allow rearomatization only for cyclohexadienyl intermediate **40**. Because no side products were so far isolated that could give insight into the fate of the cyclohexadienyl-type radical **41** under acidic reductive conditions, radical **41** might decompose or even reversibly evolve back to an aryl radical and a fluoroanilinium ion. Such reversibility has so far only been reported for the attack of alkyl radicals to benzenes.[28] In general, higher yields can be expected from the arylation of free anilines. The aryl radical addition to anilines is certainly several times faster than to anilinium ions (cf. Table 3), and important side reactions such as hydrogen abstraction are thus far more effectively suppressed.

An important application for 2-aminobiphenyls is the synthesis of fungicides.[29] Scheme 4 shows the conversion of the readily available aminobiphenyl **26** with pyrazolecarboxylic acid chloride **44** into the recently introduced Xemium (**45**).[30] To date, the aminobiphenyl precursors for fungizides such as Xemium have been produced by palladium-catalyzed cross-coupling reactions that rely on more elaborate starting materials.

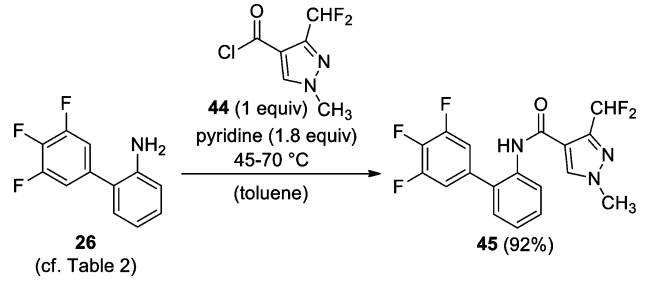
SUMMARY

In summary, we have described a new synthetic access to 2-aminobiphenyls[31] that is based on the arylation of anilines using arylhydrazines as radical sources under oxidative conditions. The directing effect of the free (and unprotonated) amino

Scheme 3. Regioselectivity under Neutral and Acidic Conditions



Scheme 4. Synthesis of Xemium (45)



functionality allows the reactions to proceed with good regioselectivity, and anilines were found to be significantly better aryl radical acceptors than commonly employed substrates such as nitrobenzenes or phenyl ethers. Furthermore, radical arylation reactions under strongly oxidizing conditions showed that regioselectivity can be controlled through the rearomatization step and that the addition of an aryl radical to a substituted benzene might even be reversible. From a synthetic point of view, the methodology is attractive due to the use of cheap and readily available starting materials. Since it is especially suited for halogenated arylhydrazines and anilines, it represents a valuable extension to known palladium-catalyzed cross-coupling reactions.

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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 $CDCl_3$ as solvent referenced to TMS (0 ppm) or $CHCl_3$ (7.26 ppm). ^{13}C NMR spectra were recorded at 90.6 and 150.9 MHz in $CDCl_3$ using $CDCl_3$ (77.0 ppm) as standard. ^{19}F NMR spectra were recorded at 338.8 MHz using $CFCl_3$ (0 ppm) or C_6F_6 (−164.9 ppm) as standard. Chemical shifts are reported in parts per million (ppm). Coupling constants are in hertz (*J*, Hz). The following abbreviations are used for the description of signals: s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quadruplet), m (multiplet). Mass spectra were recorded using a GC mate II GC−MS system with electron-impact ionization (EI) and a sector field mass analyzer for MS and HRMS measurements. Analytical TLC was carried out on silica gel plates using short wave (254 nm) UV light and $KMnO_4$ to visualize components. Silica gel (Kieselgel 60, 40−63 μm) was used for flash column chromatography.

General Procedure for the Synthesis of Arylhydrazines (GP 1). To a solution of the aniline (20.0 mmol) in acetic acid (10 mL) at rt was added concd HCl (50 mL). After cooling to 0 °C, a solution of $NaNO_2$ (1.38 g, 20.0 mmol) in water (4 mL) was added dropwise and stirring at 0 °C was continued for 1 h. The cold mixture was filtered, and a precooled solution of $SnCl_2 \times 2\ H_2O$ (10.0 g, 44.3 mmol) in concd HCl (10 mL) was added dropwise to the filtrate at 0 °C. After 1 h, the formed precipitate was collected by filtration and washed with saturated aqueous NaCl (30 mL). The hydrazine hydrochloride was dissolved in diluted aqueous NaOH (2 M, 100 mL) and extracted with diethyl ether (2 × 100 mL). The combined organic phases were washed with water and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the hydrazine was used without further purification.[32]

General Procedure for the Synthesis of Aminobiphenyls from Arylhydrazines with MnO_2 (GP 2). To a stirred suspension of the aniline derivative (20.0 mmol) and MnO_2 (435 mg, 5.00 mmol) in acetonitrile (5 mL) at rt was added dropwise a solution of the arylhydrazine (1.00 mmol) in acetonitrile (2 mL) 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 aniline was recovered by Kugelrohr distillation, and the products were purified by column chromatography on silica gel (as described with each product).

General Procedure for the Synthesis of Aminobiphenyls from Arylhydrazine Hydrochlorides with MnO_2 and $NaHCO_3$ (GP 3). To a stirred suspension of the aniline derivative (20.0 mmol), $NaHCO_3$ (420 mg, 5.00 mmol) and MnO_2 (435 mg, 5.00 mmol) in acetonitrile (5 mL) at rt was added the arylhydrazine hydrochloride (1.00 mmol) in portions over a period of 10 min. 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. The organic layer was washed with water (30 mL) and saturated aqueous NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure. The remaining aniline was recovered by Kugelrohr distillation, and the products were purified by column chromatography on silica gel (as described with each product).

4′-Chloro-5-fluorobiphenyl-2-amine (3). According to GP 2, the title compound was prepared from 4-chlorophenylhydrazine (**1**) (143 mg, 1.00 mmol), 4-fluoroaniline (**2**) (1.92 mL, 20.0 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification by column chromatography (hexane/EtOAc = 10:1) gave **3** as a black amorphous solid (118 mg, 0.53 mmol, 53%), mp 49−51 °C. The analytical data obtained are in agreement with those reported in ref 11a.

3′,4′-Dichloro-5-fluorobiphenyl-2-amine (16). According to GP 2, the title compound was prepared from 3,4-dichlorophenylhydrazine (**5**) (177 mg, 1.00 mmol), 4-fluoroaniline (**2**) (1.92 mL, 20.0 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification by column chromatography (hexane/EtOAc = 10:1) gave **16** as a black crystalline solid (158 mg, 0.62 mmol, 62%), mp 55−58 °C. The analytical data obtained are in agreement with those reported in ref 11c.

2′-Chloro-5-fluorobiphenyl-2-amine (17). According to GP 2, the title compound was prepared from 2-chlorophenylhydrazine (**6**) (143 mg, 1.00 mmol), 4-fluoroaniline (**2**) (1.92 mL, 20.0 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification by column chromatography (hexane/EtOAc = 10:1) gave **17** (124 mg, 0.56 mmol, 56%): dark purple oil; R_f = 0.4 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.73 (dd, J_{HF} = 4.8 Hz, J = 8.8 Hz, 1 H), 6.81 (dd, J = 3.0 Hz, J_{HF} = 8.9 Hz, 1 H), 6.93 (dt, J = 3.0 Hz, J_{HF} = 8.4 Hz, 1 H), 7.30−7.36 (m, 3 H), 7.48−7.52 (m, 1 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 115.7 (d, J_{CF} = 22.2 Hz, CH), 116.7 (d, J_{CF} = 7.8 Hz, CH), 116.8 (d, J_{CF} = 22.7 Hz, CH), 126.5 (d, J_{CF} = 7.3 Hz, C_q), 127.3 (CH), 129.5 (CH), 130.0 (CH), 131.7 (CH), 133.7 (C_q), 136.8 (d, J_{CF} = 1.6 Hz, C_q), 139.6 (C_q), 156.1 (d, J_{CF} = 237.2 Hz, C_q); ^{19}F NMR (339 MHz, $CDCl_3$) δ −129.6; MS (EI) *m*/*z* 252 (15), 250 (9), 223 (13) [^{37}Cl-M$^+$], 221 (39) [^{35}Cl-M$^+$], 187 (13), 186 (100), 185 (64), 184 (13), 157 (9), 92 (13); HRMS (EI) calcd for $C_{12}H_9ClFN$ [M$^+$] 221.0407, found 221.0407.

4′-Cyano-5-fluorobiphenyl-2-amine (18). According to GP 2, the title compound was prepared from 4-cyanophenylhydrazine (**7**) (133 mg, 1.00 mmol), 4-fluoroaniline (**2**) (1.92 mL, 20.0 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification by column chromatography (hexane/EtOAc = 10:1) gave **18** (123 mg, 0.58 mmol, 58%): brown crystalline solid; mp 163−165 °C; R_f = 0.2 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.68 (bs, 2 H), 6.73 (dd, J_{HF} = 4.7 Hz, J = 8.7 Hz, 1 H), 6.84 (dd, J = 2.9 Hz, J_{HF} = 9.0 Hz, 1 H), 6.93 (dt, J = 2.9 Hz, J = 8.4 Hz, J_{HF} = 8.4 Hz, 1 H), 7.59 (d, J = 8.2 Hz, 2 H), 7.75 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 111.4 (C_q), 116.2 (d, J_{CF} = 18.3 Hz, CH), 116.4 (d, J_{CF} = 18.9 Hz, CH), 117.1 (d, J_{CF} = 7.6 Hz, CH), 118.6 (C_q), 126.3 (d, J_{CF} = 11.3 Hz, C_q), 129.7 (2 × CH), 132.7 (2 × CH), 139.4 (d, J_{CF} = 2.0 Hz, C_q), 143.5 (d, J_{CF} = 1.7 Hz, C_q), 156.4 (d, J_{CF} = 237.4 Hz, C_q); ^{19}F NMR (339 MHz, $CDCl_3$) δ −128.6; MS (EI) *m*/*z* 213 (15), 212 (100) [^{35}Cl-M$^+$], 211 (38), 210 (18), 185 (5), 184 (9), 158 (4), 157 (4), 85 (9), 83 (12); HRMS (EI) calcd for $C_{13}H_9\ F\ N_2$ [M$^+$] 212.0750, found 212.0750.

5-Fluoro-4′-methoxybiphenyl-2-amine (19). According to GP 3, the title compound was prepared from 4-methoxyphenylhydrazine hydrochloride (**8**(× HCl)) (175 mg, 1.00 mmol), 4-fluoroaniline (**2**) (1.92 mL, 20.0 mmol), $NaHCO_3$ (420 mg, 5.00 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification by column chromatography (hexane/EtOAc = 10:1) gave **19** (69.2 mg, 0.32 mmol, 32%): black amorphous solid; mp 63−65 °C; R_f = 0.3 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.85 (s, 3 H), 6.68 (dd, J_{HF} = 4.9 Hz, J = 9.2 Hz, 1 H), 6.80−6.88 (m, 2 H), 6.98 (d, J = 8.8 Hz, 1 H), 7.36 (d, J = 8.9 Hz, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.3 (CH_3), 114.3 (2 × CH), 114.5 (d, J_{CF} = 22.2 Hz, CH), 116.4 (d, J_{CF} = 7.8 Hz, CH), 116.7 (d, J_{CF} = 22.2 Hz, CH), 128.5 (d, J_{CF} = 7.3 Hz, C_q), 130.0 (2 × CH), 130.8 (C_q), 139.6 (d, J_{CF} = 2.3 Hz, C_q), 156.4 (d, J_{CF} = 236.2 Hz, C_q), 159.1 (C_q); ^{19}F NMR (339 MHz, $CDCl_3$): δ −129.6; MS (EI) *m*/*z* 218 (15), 217 (100) [M$^+$], 216 (10), 202 (28), 186 (8), 185 (8), 174 (10), 172 (10), 147 (12), 146 (10); HRMS (EI) calcd for $C_{13}H_{12}FNO$ [M$^+$] 217.0903, found 217.0902.

4′,5-Dichlorobiphenyl-2-amine (20). According to GP 2, the title compound was prepared from 4-chlorophenylhydrazine (**1**) (143 mg, 1.00 mmol), 4-chloroaniline (**11**) (2.55 g, 20.0 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification by column chromatography (hexane/EtOAc = 10:1) gave **20** as a brown amorphous solid (112 mg, 0.47 mmol, 47%), mp 77−80 °C. The analytical data obtained are in agreement with those reported in ref 11a.

5-Bromo-4′-fluorobiphenyl-2-amine (21). According to GP 2, the title compound was prepared from 4-fluorophenylhydrazine (**9**) (126 mg, 1.00 mmol), 4-bromoaniline (**12**) (3.44 g, 20.0 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification by column chromatography (hexane/EtOAc = 10:1) gave **21** (119 mg, 0.45 mmol, 45%): brown amorphous solid; mp 73−74 °C; R_f = 0.5 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.93 (bs, 2 H), 6.65 (d, J = 8.5 Hz, 1 H), 7.13 (t, J = 8.8 Hz, J_{HF} = 8.8 Hz, 2 H), 7.21 (d, J = 2.3 Hz, 1 H), 7.24 (dd, J = 2.3 Hz, J = 8.5 Hz, 1 H), 7.38 (dd, J_{HF} = 5.4 Hz, J = 8.8 Hz, 2 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 110.6 (C_q), 115.9 (d, J_{CF} = 21.4 Hz, 2 × CH), 117.4 (CH), 128.7 (C_q), 130.7 (d, J_{CF} = 8.0 Hz, 2

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× CH), 131.2 (CH), 132.8 (CH), 133.9 (d, J_{CF} = 3.4 Hz, C_q), 142.2 (C_q), 162.3 (d, J_{CF} = 247.3 Hz, C_q); ^{19}F-NMR (339 MHz, $CDCl_3$) δ −117.3; MS (EI) *m*/*z* 327 (10), 268 (13), 267 (81) [^{81}Br-M$^+$], 266 (23), 265 (91) [^{79}Br-M$^+$], 264 (12), 252 (43), 250 (23), 235 (27), 233 (16), 219 (16), 186 (27), 185 (100), 184 (23), 167 (19), 166 (16), 158 (11), 157 (21), 139 (11), 133 (13), 93 (22), 92 (37), 85 (19), 83 (29); HRMS (EI) calcd for $C_{12}H_9BrFN$ [M$^+$] 264.9902, found 264.9903.

5-Bromo-4′-chlorobiphenyl-2-amine (22). According to GP 3, the title compound was prepared from 4-chlorophenylhydrazine hydrochloride (**1**(× HCl)) (179 mg, 1.00 mmol), 4-bromoaniline (**12**) (3.44 g, 20.0 mmol), $NaHCO_3$ (420 mg, 5.00 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification by column chromatography (hexane/EtOAc = 10:1) gave **22** as a black oil (152 mg, 0.54 mmol, 54%). The analytical data obtained are in agreement with those reported in ref 11c.

5-Bromo-2′-chlorobiphenyl-2-amine (23). According to GP 2, the title compound was prepared from 2-chlorophenylhydrazine (**6**) (143 mg, 1.00 mmol), 4-bromoaniline (**12**) (3.44 g, 20.0 mmol) and MnO_2 (435 mg, 5.00 mmol). Purification by column chromatography (hexane/EtOAc = 10:1) gave **23** (162 mg, 0.57 mmol, 57%): dark brown oil; R_f = 0.4 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.77 (bs, 2 H), 6.69 (d, *J* = 8.6 Hz, 1 H), 7.18 (d, *J* = 2.3 Hz, 1 H), 7.27−7.36 (m, 4 H), 7.47−7.52 (m, 1 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 129.7 (C_q), 136.8 (CH), 146.8 (C_q), 146.9 (CH), 149.1 (CH), 149.5 (CH), 151.3 (CH), 151.3 (CH), 152.4 (CH), 153.3 (C_q), 156.0 (C_q), 162.0 (C_q); MS (EI) *m*/*z* (%): 285 (23), 284 (12) [^{37}Cl-M$^+$], 283 (90), 282 (10) [^{35}Cl-M$^+$], 281 (73), 248 (73), 247 (40), 246 (69), 245 (34), 168 (37), 167 (100), 166 (71), 164 (10), 140 (28), 139 (52), 138 (10), 101 (13), 83 (40), 83 (23), 82 (20), 69 (21), 63 (11); HRMS (EI) calcd for $C_{12}H_{10}BrClN$ [M$^+$] 280.9607, found 280.9607.

4′-Chloro-5-cyanobiphenyl-2-amine (24). According to GP 3, the title compound was prepared from 4-chlorophenylhydrazine hydrochloride (**1**(× HCl)) (179 mg, 1.00 mmol), 4-aminobenzonitrile (**13**) (1.18 g, 20.0 mmol), $NaHCO_3$ (420 mg, 5.00 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification by column chromatography (hexane/EtOAc = 10:1) gave **24** as reddish crystalline solid (91.2 mg, 0.35 mmol, 35%), mp 154−157 °C. The analytical data obtained are in agreement with those reported in ref 11c.

4′-Chloro-5-methoxybiphenyl-2-amine (25). According to GP 2, the title compound was prepared from 4-chlorophenylhydrazine (**1**) (143 mg, 1.00 mmol), *p*-anisidine (**14**) (2.46 g, 20.0 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification by column chromatography (hexane/EtOAc = 10:1) gave **25** as a brown oil (91.2 mg, 0.39 mmol, 39%). The analytical data obtained are in agreement with those reported in ref 11a.

3′,4′,5′-Trifluorobiphenyl-2-amine (26). According to GP 2, the title compound was prepared from 3,4,5-trifluorophenylhydrazine (**10**) (146 mg, 0.90 mmol), aniline (**15**) (1.64 mL, 18.0 mmol) and MnO_2 (392 mg, 4.50 mmol). Purification of the regioisomers by column chromatography (hexane/EtOAc = 10:1 → 4:1) gave **26** (118 mg, 0.53 mmol, 59%) and 3′,4′,5′-trifluorobiphenyl-4-amine (**26′**) (32.5 mg, 0.15 mmol, 16%). 3′,4′,5′-Trifluorobiphenyl-2-amine (**26**): brown crystalline solid; mp 69−72 °C; R_f = 0.6 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.79 (bs, 2 H), 6.77 (dd, *J* = 0.8 Hz, *J* = 8.0 Hz, 1 H), 6.83 (dt, *J* = 1.0 Hz, *J* = 7.5 Hz, 1 H), 7.06 (dd, *J* = 1.6 Hz, *J* = 7.6 Hz, 1 H), 7.07−7.13 (m, 2 H), 7.19 (ddd, *J* = 1.6 Hz, *J* = 7.4 Hz, *J* = 8.0 Hz, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 113.2 (dd, J_{CF} = 4.5 Hz, J_{CF} = 16.4 Hz, 2 × CH), 116.0 (CH), 118.9 (CH), 124.4 (d, J_{CF} = 1.0 Hz, C_q), 129.4 (CH), 130.1 (CH), 135.5 (dt, J_{CF} = 4.9 Hz, J_{CF} = 7.9 Hz, C_q), 138.9 (td, J_{CF} = 15.3 Hz, J_{CF} = 251.6 Hz, C_q), 143.2 (C_q), 151.3 (ddd, J_{CF} = 4.4 Hz, J_{CF} = 9.9 Hz, J_{CF} = 250.5 Hz, 2 × C_q); ^{19}F-NMR (339 MHz, $CDCl_3$) δ −137.1, −165.4; MS (EI) *m*/*z* 268 (23), 266 (13), 224 (15), 223 (100) [M$^+$], 222 (26), 221 (12), 204 (12), 203 (18), 85 (21), 83 (30); HRMS (EI) calcd for $C_{12}H_8F_3N$ [M$^+$] 223.0609, found 223.0609. 3′,4′,5′-Trifluorobiphenyl-4-amine (**26′**): brown crystalline solid; mp 75−80 °C; R_f = 0.2 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.82 (bs, 2 H), 6.74 (d, *J* = 8.7 Hz, 2 H), 7.11 (dd, *J* = 6.5 Hz, J_{HF} = 9.3 Hz, 2 H), 7.31 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 109.9 (dd, J_{CF} = 4.3 Hz, J_{CF} = 16.9 Hz, 2 × CH), 115.5 (2 × CH), 127.7 (2 × CH), 128.4 (C_q), 137.3 (dt, J_{CF} = 4.4 Hz, J_{CF} = 8.0 Hz, C_q), 138.4 (td, J_{CF} = 15.5 Hz, J_{CF} = 250.0 Hz, C_q), 146.5 (C_q), 151.3 (ddd, J_{CF} = 4.4 Hz, J_{CF} = 9.9 Hz, J_{CF} = 248.5 Hz, 2 × C_q); ^{19}F NMR (339 MHz, $CDCl_3$) δ −138.0, −167.7; MS (EI) *m*/*z* 272 (14), 270 (47), 268 (26), 235 (27), 233 (15) [M$^+$], 224 (13), 223 (100), 219 (10), 195 (10), 85 (44), 83 (62); HRMS (EI) calcd for $C_{12}H_8F_3N$ [M$^+$] 223.0609, found 223.0610.

4′-Chlorobiphenyl-2-amine (27). According to GP 2, the title compound was prepared from 4-chlorophenylhydrazine (**1**) (143 mg, 1.00 mmol), aniline (**15**) (1.82 mL, 20.0 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification of the regioisomers by column chromatography (hexane/EtOAc = 10:1 → 4:1) gave **27** as a dark brown amorphous solid (83.9 mg, 0.41 mmol, 41%)[33] (mp 37−38 °C) and 4′-chlorobiphenyl-4-amine (**27′**) as a black oil (26.2 mg, 0.13 mmol, 13%).[11c] The analytical data obtained for **27** and **27′** are in agreement with those reported in refs 11c and 33.

2′-Chlorobiphenyl-2-amine (28). According to GP 2, the title compound was prepared from 2-chlorophenylhydrazine (**6**) (143 mg, 1.00 mmol), aniline (**15**) (1.82 mL, 20.0 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification of the regioisomers by column chromatography (hexane/EtOAc = 10:1 → 4:1) gave 2′-chlorobiphenyl-4-amine (**28′**) as a black oil (41.8 mg, 0.21 mmol, 21%) and **28** as a black amorphous solid (98.7 mg, 0.49 mmol, 49%) (mp 52−53 °C). The analytical data obtained for **28** are in agreement with those reported in ref 31e. 2′-Chlorobiphenyl-4-amine (**28′**): R_f = 0.3 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.73 (bs, 2 H), 6.73 (d, *J* = 8.6 Hz, 2 H), 7.21 (ddd, *J* = 1.8 Hz, *J* = 7.3 Hz, *J* = 7.9 Hz, 1 H), 7.25−7.28 (m, 3 H), 7.31 (dd, *J* = 1.8 Hz, *J* = 7.4 Hz, 1H), 7.43 (dd, *J* = 1.1 Hz, *J* = 7.9 Hz, 1H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 114.5 (2 × CH), 126.7 (CH), 127.8 (CH), 129.6 (C_q), 129.9 (CH), 130.4 (2 × CH), 131.3 (CH), 132.5 (C_q), 140.5 (C_q), 145.9 (C_q); MS (EI) *m*/*z* 205 (32) [^{37}Cl-M$^+$], 204 (13), 203 (100) [^{35}Cl-M$^+$], 168 (11), 167 (21), 139 (8), 115 (6), 101 (6), 83 (10), 44 (25); HRMS (EI) calcd for $C_{12}H_{10}ClN$ [M$^+$] 203.0502, found 203.0502.

2-(4-Chlorophenyl)furan (29). According to GP 3, the title compound was prepared from 4-chlorophenylhydrazine hydrochloride (**1**(× HCl)) (179 mg, 1.00 mmol), furan (2.90 mL, 40.0 mmol), $NaHCO_3$ (420 mg, 5.00 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification by column chromatography (hexane/EtOAc = 19:1) gave **29** as an orange crystalline solid (110 mg, 0.62 mmol, 62%) (mp 80−85 °C). The analytical data obtained are in agreement with those reported in ref 22.

4′-Chlorobiphenyl-2-ol (30). Method *a* (Scheme 1): According to GP 3, the title compounds were prepared from 4-chlorophenylhydrazine hydrochloride (**1**(× HCl)) (179 mg, 1.00 mmol), phenol (1.88 g, 20.0 mmol), $NaHCO_3$ (420 mg, 5.00 mmol), and MnO_2 (435 mg, 5.00 mmol). Purification by column chromatography (hexane/EtOAc = 10:1) gave **30** (60.2 mg, 0.29 mmol, 29%)[34] and **30′** (19.0 mg, 0.09 mmol, 9%).[35] The analytical data obtained are in agreement with those reported in refs 34 and 35.

Method *b* (Scheme 1): To a stirred suspension of phenol (1.88 g, 20.0 mmol), aqueous NaOH (8 M, 3.13 mL, 25.0 mmol), and MnO_2 (435 mg, 5.00 mmol) in acetonitrile (5 mL) at rt was added 4-chlorophenylhydrazine hydrochloride (**1**(× HCl)) (179 mg, 1.00 mmol) in portions over a period of 10 min. 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. The organic layer was washed with water (30 mL) and saturated aqueous NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure. The remaining substrate was removed by Kugelrohr distillation and purification by column chromatography (hexane/EtOAc = 10:1) gave **30** as a brown amorphous solid (81.9 mg, 0.40 mmol, 40%)[34] (mp 45−47 °C) and **30′** as a brown amorphous solid (34.9 mg, 0.17 mmol, 17%)[35] (mp 130−135 °C). The analytical data obtained are in agreement with those reported in refs 34 and 35.

4′-Chloro-2-methoxybiphenyl (31). According to GP 3, the title compounds were prepared from 4-chlorophenylhydrazine hydrochloride (**1**(× HCl)) (179 mg, 1.00 mmol), anisole (2.18 mL, 20.0 mmol), $NaHCO_3$ (420 mg, 5.00 mmol), and MnO_2 (435 mg, 5.00

mmol). Purification by column chromatography (100% hexane) gave **31** as a yellow amorphous solid (53.7 mg, 0.25 mmol, 25%) (mp 50−52 °C),[36] along with a mixture of 4'-chloro-3-methoxybiphenyl (8.7 mg, 0.04 mmol, 4%)[37] and 4'-chloro-4-methoxybiphenyl (10.9 mg, 0.05 mmol, 5%).[38] The analytical data obtained are in agreement with those reported in refs 36−38.

Synthesis of 5-Fluoro-4′-methoxybiphenyl-2-amine (19) and 2-Fluoro-4′-methoxybiphenyl-5-amine (19′) with Ammonium Cerium(IV) Nitrate (Scheme 2). To a stirred solution of 4-methoxyphenylhydrazine hydrochloride (**8**(× HCl)) (175 mg, 1.00 mmol) and 4-fluoroaniline (**2**) (555 mg, 5.00 mmol) in water (10 mL) and HCl (10%, 2 mL) at rt was added dropwise a solution of ammonium cerium(IV) nitrate (2.19 g, 4.00 mmol) in water (4 mL) over a periode of 15 min. Stirring was continued for further 15 min, the solution was diluted with water (30 mL), and Na_2SO_3 was used to adjust the pH to a value of 7. The resulting mixture was extracted with diethyl ether, and the combined organic phases were washed with saturated aqueous NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure. The remaining substrate was removed by Kugelrohr distillation, and purification by column chromatography (pentane/EtOAc = 3:1) gave **19** as a brown oil (39 mg, 0.18 mmol, 18%) and **19′** as a brown oil (30 mg, 0.14 mmol, 14%). 2-Fluoro-4′-methoxybiphenyl-5-amine (**19′**): R_f = 0.3 (pentane/EtOAc = 3:1) (UV); ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.85 (s, 3 H), 6.88 (ddd, J = 3.0 Hz, J_{HF} = 3.8 Hz, J = 8.9 Hz, 1 H), 6.71 (dd, J = 3.0 Hz, J_{HF} = 6.6 Hz, 1 H), 6.93 (dd, J = 8.7 Hz, J_{HF} = 10.3 Hz, 1 H), 6.96 (d, J = 8.9 Hz, 2 H), 7.46 (dd, J = 1.6 Hz, J = 8.9 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.3 (CH_3), 113.8 (2 × CH), 114.7 (d, J_{CF} = 7.8 Hz, CH), 116.5 (d, J_{CF} = 22.4 Hz, CH), 116.6 (d, J_{CF} = 5.0 Hz, CH), 128.5 (d, J_{CF} = 1.3 Hz, C_q), 129.0 (d, J_{CF} = 14.7 Hz, C_q), 130.0 (2 × CH), 142.4 (d, J_{CF} = 2.5 Hz, C_q), 153.4 (d, J_{CF} = 237.5 Hz, C_q), 159.2 (C_q); MS (EI) m/z 217 (100) [M^+], 202 (41), 175 (4), 174 (25), 146 (8), 109 (5), 93 (6), 63 (3), 44 (7).

***N*-(3′,4′,5′-Trifluorobiphenyl-2-yl)-3-difluoromethyl-1-methyl-1*H*-pyrazole-4-carboxamide (45).** To a stirred solution of 3′,4′,5′-trifluorobiphenyl-2-amine (**26**) (100 mg, 0.45 mmol) and pyridine (65 μL, 0.81 mmol) in toluene (1 mL) at 55 °C was added dropwise a solution of 3-difluoromethyl-1-methyl-1*H*-pyrazole-4-carboxylic acid chloride (**44**) (87.9 mg, 0.45 mmol) in toluene (300 μL) over a period of 10 min. After completion of the reaction, as monitored by TLC, the solution was heated to 70 °C and was washed with HCl (2 N), saturated aqueous $NaHCO_3$, and water. After being cooled to rt, the solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by column chromatography (hexane/EtOAc = 2:1) gave **45** (158 mg, 0.41 mmol, 92%): white amorphous solid; mp 137−140 °C; R_f = 0.4 (hexane/EtOAc = 1:1) (UV); ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.92 (s, 3 H), 6.65 (t, J_{HF} = 54.2 Hz, 1 H), 6.92−7.06 (m, 2 H), 7.19−7.25 (m, 2 H), 7.38−7.47 (m, 1 H), 7.81 (bs, 1 H), 7.95 (s, 1 H), 8.19 (d, J = 8.2 Hz, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 39.5 (CH_3), 111.6 (t, J_{CF} = 232.9 Hz, CH), 113.7 (dd, J_{CF} = 4.7 Hz, J_{CF} = 16.6 Hz, 2 × CH), 116.5 (C_q), 123.4 (CH), 125.2 (CH), 129.2 (CH), 130.0 (CH), 131.2 (C_q), 134.1 (dt, J_{CF} = 4.9 Hz, J_{CF} = 7.9 Hz, C_q), 134.5 (CH), 136.1 (C_q), 139.5 (td, J_{CF} = 15.3 Hz, J_{CF} = 252.5 Hz, C_q), 142.3 (t, J_{CF} = 29.3 Hz, C_q), 151.2 (ddd, J_{CF} = 4.3 Hz, J_{CF} = 10.0 Hz, J_{CF} = 251.2 Hz, 2 × C_q), 159.4 (C_q); ^{19}F NMR (339 MHz, $CDCl_3$) δ −111.8, −136.9, −164.7; MS (EI) m/z 382 (20), 381 (96) [M^+], 222 (5), 221 (11), 160 (35), 159 (100), 139 (10), 83 (5), 44(4), 43 (14); HRMS (EI) calcd for $C_{18}H_{12}F_5N_3O$ [M^+] 381.0901, found 381.0901.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for new compounds **17**−**19**, **21**, **23**, **26**, **28**, and **45** and ^{1}H NMR spectra for known compounds **3**, **16**, **20**, **22**, **24**, **25**, **27**, and **29**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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