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Oxidative Radical Arylation of Anilines with Arylhydrazines and Dioxygen from Air

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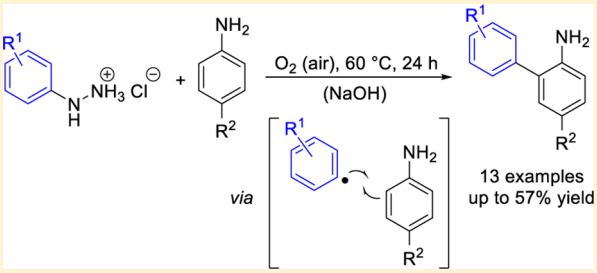
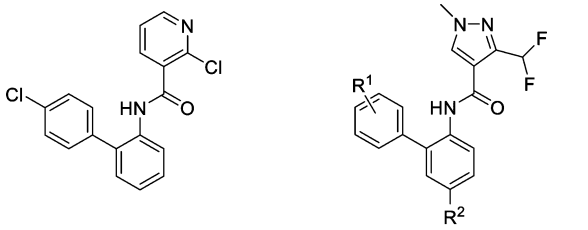
Supporting Information

ABSTRACT: Substituted 2-aminobiphenyls have been prepared from arylhydrazine hydrochlorides and anilines in biphasic radical arylation reactions with dioxygen from air as a most simple and readily available oxidant. Under optimized conditions, the free amino functionality of the aniline leads to high *ortho*:*meta* regioselectivities, now even for anilines bearing a donor substituent in the *para* position. Finally, the mild and metal-free new access to aminobiphenyls was shown to be applicable on a gram scale.



Substituted biphenyls are valuable building blocks in many fields of application.[1] One particularly important subgroup of compounds are 2-aminobiphenyls,[2] which for example, occur as core structures of the three industrially produced fungizides boscalid, bixafen, and Xemium (Figure 1).[3−5] Not surprisingly, the large-scale syntheses of these compounds rely on organometallic cross-coupling reactions as key steps.[6−8]



Boscalid

Bixafen: R^1 = 3,4-Cl_2, R^2 = F
Xemium: R^1 = 3,4,5-F_3, R^2 = H

Figure 1. Boscalid, bixafen, and Xemium.

Since radical arylation reactions[9] can basically offer a much more straightforward access to substituted biphenyls, mainly due to the fact that such arylations are comparable to C−H activation reactions[10,11] and less functionalized starting materials are therefore required, there has recently been increasing interest in improving the reaction type that was first reported by Gomberg and Bachmann about 90 years ago.[12] Important challenges are, in particular, to conduct radical arylations with high regioselectivity[13] and to lower the excess of the arene acting as aryl radical acceptor. Large amounts of aryl radical acceptor are commonly required to counterbalance the relatively slow addition of aryl radicals to most functionalized benzene derivatives.[14] Moreover, new reactions should be sustainable and ideally be feasible under metal-free conditions. Based on the traditional aryl radical sources for arylation reactions, which are aryl diazonium salts,[15] remarkable advances have recently been achieved by employing photocatalysts[16] and optimized Gomberg−Bachmann conditions.[17] In addition, bromo- and iodobenzenes, which had for decades been mainly applied in combination with organostannanes,[18] have now been shown to be valuable aryl radical sources for the preparation of biphenyls under metal-free conditions.[19,20] Regarding aryl radical acceptors, unsubstituted benzene is still the most widely used compound due to the negligibility of regioselectivity issues.[21] In this context, we have recently discovered that anilines are not only highly reactive scavengers for aryl radicals, thereby exceeding the capabilities of phenols, phenyl ethers, and nitrobenzenes,[22] but they do allow arylations to proceed with unprecedented regioselectivities.[17,23] Based the advantages of such substrates, we now report the metal-free arylation of anilines using arylhydrazines as radical sources and dioxygen from air as simple oxidant under mild conditions. In general, radical arylations with arylhydrazines have so far required either pure oxygen atmosphere and catalysts,[24] an excess of an oxidizing agent,[23,25] or harsh conditions.[26] Another aspect that will facilitate future applications is that arylhydrazines are readily available from aryldiazonium salts by reduction with such simple reagents as sodium sulfite.[27]

The oxidation of arylhydrazines that leads to aryl radicals via the intermediate formation of instable diazenes has been known for a long time and studied intensively.[28] Beneficially, such oxidations of arylhydrazines can be carried out under mild conditions and also at low temperatures.[29] Our first experiments under air atmosphere (Table 1, entries 1 and 2) revealed that relatively long reaction times of 60 h are required at room temperature and that chlorobenzene (**4**), arising from hydrogen abstraction by the aryl radical, is formed as major byproduct.[15]

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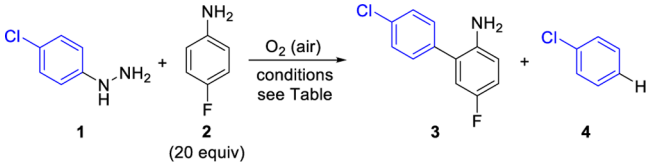
Table 1. Optimization of Reaction Conditions for Neat Reactions in Aniline



entry	conditions[a]	aminobiphenyl **3**[b] (%)	chlorobenzene **4** (%)
1	rt, 18 h	20[c]	25[c]
2	rt, 60 h	53[c]	38[c]
3	rt, 60 h, stream of air	39[d]	nd[e]
4	60 °C, 24 h	46	46
5	60 °C, 24 h, 5 equiv of H_2O	49	50
6	60 °C, 24 h, 20 equiv of H_2O	49	40
7	60 °C, 24 h, addition of **1** over 4 h	61	37
8	60 °C, 24 h, addition of **1** over 9 h	55	35
9	12 min, air, micromixer	0[c]	0[c]

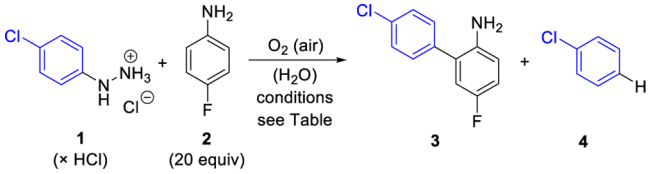
[a]Standard conditions: 4-chlorophenylhydrazine (**1**) (1 mmol), 4-fluoroaniline (**2**) (20 mmol) under air. [b]Yields determined by ^{1}H NMR using dimethyl terephthalate as internal standard. [c]Yield determined by ^{1}H NMR referenced to 4-fluoroaniline. [d]Yield determined after purification by column chromatography. [e]Not detected due to volatility of **4** in the stream of air.

While passing a stream of air through the reaction mixture did not significantly reduce the reaction time (entry 3), this was achieved by raising the temperature to 60 °C (entry 4). Attempts to decrease the amount of undesired chlorobenzene (**4**) through the addition of water, which can potentially stabilize the N–H bonds in the aniline and hydrazine by hydrogen bonding,[30] did not lead to improved product ratios of **3**:**4** (entries 5 and 6). Since previous studies had given a hint that arylhydrazines are far more susceptible to hydrogen atom abstraction than anilines,[23,31] hydrazine **1** was then added to the reaction mixture in five batches over 4 h. Based on the now improved ratio of 61:37 for **3**:**4** (entry 7), we tried to further exploit this effect by adding **1** even more slowly in 10 batches over 9 h (entry 8). The observation that the yield of **3** could not be further increased appeared to be due to a partial decomposition of the phenylhydrazine **1** under air, prior to the addition to the reaction mixture. An exemplary attempt to run the reaction in a microreactor failed completely (entry 9).

Having observed a remarkable instability of the arylhydrazines under air, which is crucial in the reaction mixture but an undesired property before addition, we turned to explore the use of the corresponding air-stable hydrazine hydrochloride **1** (×HCl). Upon addition of the hydrochloride **1** to biphasic mixtures of the aniline **2** and different inorganic bases in water (Table 2, entries 1–3), the best results were obtained for sodium hydroxide. Raising the reaction temperature to 60 °C again shortened the reaction time (entry 4), and the slow addition of **1** had the beneficial effect of further lowering the amount of undesired chlorobenzene (**4**). When the ratios of **3**:**4** in all biphasic attempts (Table 2) are compared with those observed in the homogeneous reactions (Table 1), hydrogen abstraction by the aryl radical appears to be less pronounced in aqueous biphasic systems.

With optimized conditions available, we then turned to investigate the scope and the limitations of this metal-free

Table 2. Optimization of Reaction Conditions for Biphasic Reactions

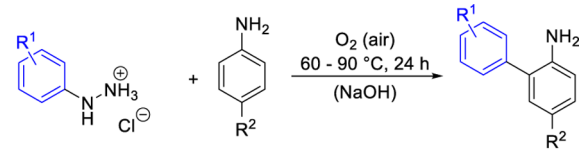


entry	conditions[a]	aminobiphenyl **3**[b] (%)	chlorobenzene **4** (%)
1	rt, 60 h, NaOH (1 M)	54	27
2	rt, 60 h, NH_3 (1 M)	46	25
3	rt, 60 h, Na_2CO_3 (0.5 M)	50	30
4	60 °C, 24 h, NaOH (1 M)	55	25
5	60 °C, 24 h, NaOH (1 M), slow addition of **1** over 9 h	68[c]	15[c]

[a]Standard conditions: 4-chlorophenylhydrazine hydrochloride (**1** × HCl) (1 mmol), 4-fluoroaniline (**2**) (20 mmol), H_2O (1 mL) under air. [b]Yield determined by ^{1}H NMR referenced to 4-fluoroaniline. [c]Yield determined by ^{1}H NMR using dimethyl terephthalate as internal standard.

synthetic access to biphenyls. In a first row of experiments a variety of substituted arylhydrazine hydrochlorides (**1**, **5**–**10**) was reacted with 4-fluoroaniline (**2**) (Table 3, entries 1–7).

Table 3. Oxidative Arylation: Scope and Limitations



entry	hydrazine: R^1 =	aniline: R^2 =	aminobiphenyl[a,b] (%)
1	**1**: 4-Cl	**2**: F	**3** (55)
2	**5**: H	**2**: F	**17** (48)
3	**6**: 4-F	**2**: F	**18** (53)
4	**7**: 3,4,5-F_3	**2**: F	**19** (24)
5	**8**: 3,4-Cl_2	**2**: F	**20** (44)
6	**9**: 4-CN	**2**: F	**21** (49)
7	**10**: 4-OMe	**2**: F	**22** (35)
8	**1**: 4-Cl	**11**: H	**23** (60, *o*:*p* = 51:9)
9	**1**: 4-Cl	**12**: Cl	**24** (47)
10	**1**: 4-Cl	**13**: Br	**25** (57)
11	**1**: 4-Cl	**14**: CN	**26** (27)
12	**1**: 4-Cl	**15**: OMe	**27** (42)
13	**1**: 4-Cl	**16**: OEt	**28** (30)

[a]Standard conditions: hydrazine hydrochloride **1**, **5**–**10** (1 mmol, slowly added to the reaction mixture in 10 batches over 9 h), aniline **2**, **11**–**16** (20 mmol), NaOH (1M, 1 mL). [b]Isolated yields after purification by column chromatography.

Moderate to good yields were obtained for most substitution patterns on the arylhydrazine with two exceptions. The aromatic core of 3,4,5-trifluorophenylhydrazine (**7**) is probably too strongly activated toward nucleophilic substitution so that homocoupling of **7** (e.g., via the hydrazine unit acting as nucleophile) competes with the desired, but not too rapid, oxidation of the hydrazine. The fact that anisole was observed as the major product (60% yield) in the reaction of the electron-rich 4-methoxyphenylhydrazine (**10**) points to the

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increased tendency of *para*-donor-substituted aryl radicals to stabilize themselves via hydrogen abstraction (entry 7). This effect was somehow unexpected since only methoxy groups in the *ortho* position were so far known to modify the reactivity of an aryl radical through their negative inductive effect on the carbon sceleton.[32] Substituents in the *para*-position, even with strong mesomeric effects, usually do not significantly change the reactivity of the aryl radical since it is located in an sp^2 orbital which shows no major overlap with the conjugated π system.

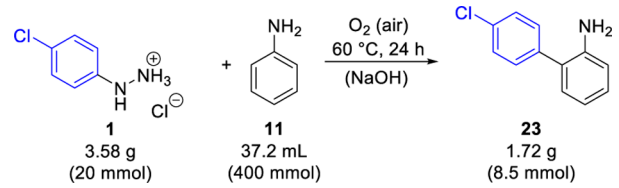
In a second row of experiments, 4-chlorophenylhydrazine (**1**) was reacted with six different anilines (Table 3, entries 8–13). The results clearly indicate that halogen-substituted unpolar anilines, including nonfunctionalized aniline (**11**), are the preferred substrates for the oxidative arylation reaction (entries 8–10). Two repetitions of the experiment leading to aminobiphenyl **23** (entry 8) gave yields of 57% (*o*:*p* = 44:13) and 68% (*o*:*p* = 55:13), thus demonstrating a reasonable reproducibility. Lower yields were obtained with the 4-cyano, 4-methoxy, and 4-ethoxy derivatives **14**–**16** (entries 11–13). Since no major products other than the desired 2-aminobiphenyls **26**–**28** could be detected after recovery of the excess of aniline by Kugelrohr distillation and only volatile side products had thus been formed, the nitrile or alkoxy groups apparently led to increased hydrogen abstraction by the aryl radical. This could to a certain degree be due to a simple polarity effect in the sense that there is a less distinct phase separation which in turn makes the reaction conditions more comparable to the homogeneous variant (Table 1). These conditions had previously led to increased hydrogen abstraction. The explanation that a radical-stabilizing substituent in the *para*-position of the aniline, such as alkoxy or cyano, could increase the hydrogen atom donor capabilities of the amino group due to the formation of a related nitrogen-centered "benzylic" radical[33] appears less probable since nonvolatile products should arise from that side reaction.

Remarkably, no regioisomers resulting from an attack of the aryl radical in 3-position of aniline could be detected in the reaction mixtures by ^{1}H NMR analysis. We therefore estimate the *ortho*:*meta* regioselectivity of the aniline arylation to be at least 20:1. Such high regioselectivities were especially surprising for 4-anisidine (**15**) and 4-phenetidine (**16**), since previous studies with these substrates had shown that an additional donor substitutent on the aniline can significantly decrease the *ortho*:*meta* regioselectivity to ratios of only 3.5:1.[17]

The strong directing effect of the amino group in anilines, which is probably further supported by a stabilizing effect of the amino group on the intermediate cyclohexadienyl radical (cf. **37**, Scheme 2), is currently our only explanation for the high regioselectivity. The magnitude of these effects also became apparent in a comparative experiment with 4-fluoroanisole (**29**). Under otherwise identical conditions, and with 4-chlorophenylhydrazine (**1**) as aryl radical source, the *ortho* and *meta* arylation products **30** and **30′** were formed in yields of 36% and 9%, respectively, and thus with much less regioselectivity.

We further investigated the feasibility of the metal-free radical arylation on a larger, 20-fold scale. Starting from 4-chlorophenylhydrazine hydrochloride **1** (×HCl) and aniline (**11**), the desired 4′-chlorobiphenyl-2-amine (**23**) was obtained in a yield of 43% (cf. 51% in Table 3, entry 8) along with 9% of its regioisomer 4′-chlorobiphenyl-4-amine after distillative recovery of aniline (**11**) and column chromatography (Scheme 1). Aminobiphenyl **23** represents a key buildling block for the fungicide boscalid and is currently produced through

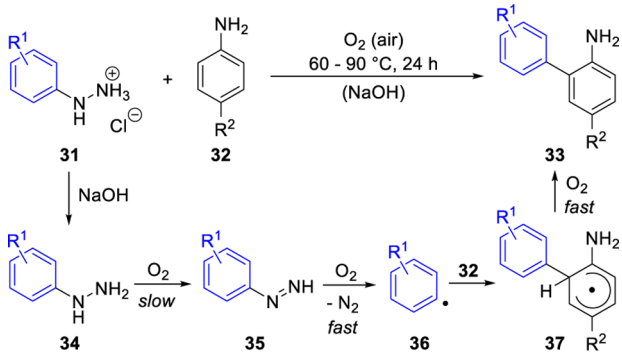
Scheme 1. Synthesis of 2-Aminobiphenyl 23 on a Larger Scale



palladium-catalyzed cross-coupling of 2-chloronitrobenzene and 4-chlorophenylboronic acid.[7]

A plausible reaction mechanism for all arylations described above is depicted in Scheme 2. After a rapid formation of the

Scheme 2. Plausible Reaction Mechanism for the Formation of 2-Aminobiphenyls



free phenylhydrazine **34** from its hydrochloride salt **31** a slow oxidation to a phenyldiazene **35** occurs. The diazene **35** is then rapidly converted to an aryl radical **36** in the presence of oxygen,[28] and its addition to an aniline **32** provides the cyclohexadienyl intermediate **37**. Final oxidation of **37**, which is again known to be fast in presence of oxygen,[34] leads to 2-aminobiphenyls **33**. Representing a key element of the process, the only slow step from hydrazine **34** to diazene **35** requires a slow addition of the hydrochloride **31** to the reaction mixture to minimize hydrogen abstraction from **34** by the aryl radical **36**.

In summary, we have described an improved, now metal-free access to 2-aminobiphenyls using anilines, arylhydrazines, and air as oxidant. The directing effect of the unprotonated amino functionality leads to product formation with high regioselectivity. From a synthetic standpoint, advantages of the new methodology result from the use of cheap and readily available starting materials as well as sustainable and mild conditions. Since the arylation reactions are particularly well suited for arylhydrazines and anilines bearing halogen atoms, they are moreover a valuable extension to known palladium-catalyzed cross-coupling reactions.

EXPERIMENTAL SECTION

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. Chemical shifts are given in parts per million (ppm). ^{19}F NMR spectra were recorded at 338.8 MHz using $CFCl_3$ (0

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ppm) or C_6F_6 (−164.9 ppm) as standard. Chemical shifts are reported in parts per million (ppm). Coupling constants are in reported 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 electron impact (EI). A sector field mass analyzer was used for HRMS measurements. Analytical TLC was carried out on Merck silica gel plates using short wave (254 nm) UV light and $KMnO_4$ to visualize components. Silica gel (Kieselgel 60, 40−63 μm, Merck) was used for flash column chromatography.

Starting materials: hydrazine hydrochlorides **1**, **5**, **9**, and **10** and all anilines **2** and **11**−**16** were commercially available.

General Procedure for the Synthesis of Arylhydrazine Hydrochlorides.[23] To a solution of the aniline (10.0 mmol) in acetic acid (5.0 mL) was added concentrated hydrochloric acid (10 mL) at room temperature. After cooling to 0 °C, a solution of $NaNO_2$ (830 mg, 12.0 mmol) in water (3.0 mL) was added dropwise over a period of 20 min, and stirring at 0 °C was continued for further 30 min. A precooled solution of tin(II) chloride dihydrate (5.00 g, 22.0 mmol) in concentrated hydrochloric acid (10 mL) was added dropwise over a period of 10 min. After 1 h of stirring at 0 °C, the formed precipitate was collected by filtration, washed with water, and dried in vacuo. The hydrazine hydrochloride was used without further purification.

General Procedure for the Synthesis of 2-Aminobiphenyls from Arylhydrazine Hydrochlorides. A mixture of the aniline (20.0 mmol) and aqueous sodium hydroxide (1 M, 1.0 mL) was heated to 60−90 °C, and the arylhydrazine hydrochloride was added portionwise in 10 batches over a period of 9 h. The reactions were 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 2-aminobiphenyls were purified by column chromatography on silica gel (hexane/EtOAc = 8:1) unless otherwise noted.

*4′-Chloro-5-fluorobiphenyl-2-amine (**3**).* Compound **3** was prepared from 4-fluoroaniline (1.92 mL, 20.0 mmol) and 4-chlorophenylhydrazine hydrochloride (179 mg, 1.00 mmol) according to the general procedure at 60 °C. The excess of 4-fluoroaniline was removed by Kugelrohr distillation in vacuo at 80 °C. Purification by column chromatography gave **3** (121 mg, 0.55 mmol, 55%): dark brown oil; R_f = 0.4 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.70 (dd, J_{HF} = 4.8 Hz, *J* = 8.7 Hz, 1 H), 6.83 (dd, *J* = 3.0 Hz, J_{HF} = 9.2 Hz, 1 H), 6.85 (ddd, *J* = 3.0 Hz, J_{HF} = 8.2 Hz, *J* = 8.3 Hz, 1 H), 7.38 (d, *J* = 8.8 Hz, 2 H), 7.43 (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 115.2 (d, J_{CF} = 22.2 Hz, CH), 116.5 (d, J_{CF} = 22.6 Hz, CH), 116.8 (d, J_{CF} = 7.8 Hz, CH), 127.5 (d, J_{CF} = 7.3 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), 139.2 (d, J_{CF} = 2.2 Hz, Cq), 155.1 (d, J_{CF} = 243.9 Hz, C_q). The analytical data obtained are in agreement with those reported in ref 17.

*5-Fluorobiphenyl-2-amine (**17**).* Compound **17** was prepared from 4-fluoroaniline (1.92 mL, 20.0 mmol) and phenylhydrazine hydrochloride (99.0 μL, 1.00 mmol) according to the general procedure at 60 °C. The excess of 4-fluoroaniline was removed by Kugelrohr distillation in vacuo at 80 °C. Purification by column chromatography gave **17** (99.0 mg, 0.48 mmol, 48%): brown oil; R_f = 0.3 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.72 (dd, J_{HF} = 4.9 Hz, *J* = 9.6 Hz, 1 H), 6.85 - 6.90 (m, 2 H), 7.34−7.38 (m, 1 H), 7.42−7.47 (m, 4 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 114.8 (d, J_{CF} = 22.3 Hz, CH), 116.5 (d, J_{CF} = 22.4 Hz, CH), 116.7 (d, J_{CF} = 7.9 Hz, CH), 127.6 (CH), 128.7 (d, J_{CF} = 7.2 Hz, C_q), 128.9 (4 × CH), 138.5 (d, J_{CF} = 1.3 Hz, C_q), 139.1 (d, J_{CF} = 2.3 Hz, C_q), 156.4 (d, J_{CF} = 235.4 Hz, C_q). The analytical data obtained are in agreement with those reported in ref 17.

*4′,5-Difluorobiphenyl-2-amine (**18**).* Compound **18** was prepared from 4-fluoroaniline (1.92 mL, 20.0 mmol) and 4-fluorophenylhydrazine hydrochloride (163 mg, 1.00 mmol) according to the general procedure at 60 °C. The excess of 4-fluoroaniline was removed by Kugelrohr distillation in vacuo at 80 °C. Purification by column chromatography gave **18** (108 mg, 0.53 mmol, 53%): black crystalline solid; mp 88−94 °C; R_f = 0.4 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.69 (dd, J_{HF} = 4.8 Hz, *J* = 8.7 Hz, 1 H), 6.83 (dd, *J* = 3.0 Hz, J_{HF} = 9.2 Hz, 1 H), 6.84−6.89 (m, 1 H), 7.13 (t, *J* = 8.7 Hz, J_{HF} = 8.7 Hz, 2 H), 7.40 (dd, J_{HF} = 5.4 Hz, *J* = 8.8 Hz, 2 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 115.0 (d, J_{CF} = 22.3 Hz, CH), 115.8 (d, J_{CF} = 21.4 Hz, 2 × CH), 116.6 (d, J_{CF} = 7.7 Hz, CH), 116.7 (d, J_{CF} = 22.5 Hz, CH), 127.7 (d, J_{CF} = 7.2 Hz, C_q), 130.6 (d, J_{CF} = 8.0 Hz, 2 × CH), 134.4 (dd, J_{CF} = 1.6 Hz, J_{CF} = 3.3 Hz, C_q), 139.4 (d, J_{CF} = 2.3 Hz, C_q), 156.3 (d, J_{CF} = 237.5 Hz, C_q), 162.3 (d, J_{CF} = 247.2 Hz, C_q). The analytical data obtained are in agreement with those reported in ref 17.

*3′,4′,5′,5-Tetrafluorobiphenyl-2-amine (**19**).* Compound **19** was prepared from 4-fluoroaniline (1.92 mL, 20.0 mmol) and 3,4,5-trifluorophenylhydrazine hydrochloride (199 mg, 1.00 mmol) according to the general procedure at 60 °C. The excess of 4-fluoroaniline was removed by Kugelrohr distillation in vacuo at 80 °C. Purification by column chromatography gave **19** (57.0 mg, 0.24 mmol, 24%): dark red oil; R_f = 0.6 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.71 (dd, J_{HF} = 4.8 Hz, *J* = 8.8 Hz, 1 H), 6.80 (dd, *J* = 3.0 Hz, J_{HF} = 9.0 Hz, 1 H), 6.90 (ddd, *J* = 3.0 Hz, J_{HF} = 8.1 Hz, *J* = 8.8 Hz, 1 H), 7.06−7.13 (m, 2 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 113.1 (dd, J_{CF} = 8.9 Hz, J_{CF} = 22.0 Hz, 2 × CH), 116.0 (d, J_{CF} = 22.2 Hz, CH), 118.9 (d, J_{CF} = 23.9 Hz, CH), 124.4 (d, J_{CF} = 8.9 Hz, C_q), 129.9 (d, J_{CF} = 7.7 Hz, CH), 130.1 (d, J_{CF} = 1.9 Hz, C_q), 135.4 (dt, J_{CF} = 4.9 Hz, J_{CF} = 7.9 Hz, C_q), 138.9 (dt, J_{CF} = 15.2 Hz, J_{CF} = 251.9 Hz, C_q), 143.1 (d, J_{CF} = 252.0 Hz, C_q), 151.6 (ddd, J_{CF} = 4.4 Hz, J_{CF} = 9.7 Hz, J_{CF} = 256.1 Hz, 2 × C_q); MS (EI) *m*/*z* 241 [M^+] (100), 242 (36), 240 (46), 239 (29), 222 (26), 221 (46), 220 (31), 193 (13), 120 (11), 110 (11), 18 (30); HRMS (EI) calcd for $C_{12}H_7F_4N$ [M^+] 241.0515, found 241.0515.

*3′,4′-Dichloro-5-fluorobiphenyl-2-amine (**20**).* Compound **20** was prepared from 4-fluoroaniline (1.92 mL, 20.0 mmol) and 3′,4′-dichlorophenylhydrazine hydrochloride (214 mg, 1.00 mmol) according to the general procedure at 60 °C. The excess of 4-fluoroaniline was removed by Kugelrohr distillation in vacuo at 80 °C. Purification by column chromatography gave **20** (100 mg, 0.39 mmol, 39%): brown oil; R_f = 0.3 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.69 (dd, J_{HF} = 4.8 Hz, *J* = 8.8 Hz, 1 H), 6.81 (dd, *J* = 3.0 Hz, J_{HF} = 9.0 Hz, 1 H), 6.89 (ddd, *J* = 3.0 Hz, J_{HF} = 8.1 Hz, *J* = 8.8 Hz, 1 H), 7.29 (dd, *J* = 2.0 Hz *J* = 8.3 Hz, 1 H), 7.52 (d, *J* = 8.2 Hz, 1 H), 7.55 (d, *J* = 2.1 Hz, 1 H); ^{13}C NMR (91 MHz, $CDCl_3$): δ 115.8 (d, J_{CF} = 22.3 Hz, CH), 116.4 (d, J_{CF} = 22.8 Hz, CH), 116.9 (d, J_{CF} = 7.7 Hz, CH), 125.7 (d, J_{CF} = 7.3 Hz, C_q), 128.9 (CH), 130.8 (2 × CH), 132.1 (C_q), 133.2 (C_q), 138.4 (d, J_{CF} = 2.5 Hz, C_q), 139.4 (d, J_{CF} = 2.1 Hz, C_q), 156.3 (d, J_{CF} = 237.2 Hz, C_q). The analytical data obtained are in agreement with those reported in ref 17.

*4′-Cyano-5-fluorobiphenyl-2-amine (**21**).* Compound **21** was prepared from 4-fluoroaniline (1.92 mL, 20.0 mmol) and 4-cyanophenylhydrazine hydrochloride (169 mg, 1.00 mmol) according to the general procedure at 60 °C. The excess of 4-fluoroaniline was removed by Kugelrohr distillation in vacuo at 80 °C. Purification by column chromatography gave **21** (103 mg, 0.49 mmol, 49%): brown crystals; mp 163−165 °C; R_f = 0.2 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.73 (dd, J_{HF} = 4.7 Hz, *J* = 8.7 Hz, 1 H), 6.83 (dd, *J* = 3.0 Hz, J_{HF} = 9.1 Hz, 1 H), 6.95 (dt, *J* = 3.0 Hz, J_{HF} = 8.1 Hz, 1 H), 7.59 (d, *J* = 8.2 Hz, 2 H), 7.75 (d, *J* = 8.3 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 111.4 (C_q), 116.3 (d, J_{CF} = 18.3 Hz, CH), 116.6 (d, J_{CF} = 18.9 Hz, CH), 117.2 (d, J_{CF} = 7.5 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), 143.1 (d, J_{CF} = 2.0 Hz, C_q), 156.4 (d, J_{CF} = 237.4 Hz, C_q). The analytical data obtained are in agreement with those reported in ref 23.

*5-Fluoro-4′-methoxybiphenyl-2-amine (**22**).* Compound **22** was prepared from 4-fluoroaniline (1.92 mL, 20.0 mmol) and 4-methoxyphenylhydrazine hydrochloride (175 mg, 1.00 mmol) according to the general procedure at 60 °C. The excess of 4-fluoroaniline was removed by Kugelrohr distillation in vacuo at 80 °C. Purification by column chromatography gave **22** (76.0 mg, 0.35 mmol, 35%): dark brown oil; R_f = 0.3 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.85 (s, 3 H), 6.68 (dd, J_{HF} = 4.9 Hz, *J* = 9.2 Hz, 1 H), 6.80−6.70 (m, 2 H), 6.99 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 8.9

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Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.3 (CH_3), 114.4 (2 × CH), 114.6 (d, J_{CF} = 22.3 Hz, CH), 116.2 (d, J_{CF} = 22.3 Hz, CH), 116.6 (d, J_{CF} = 7.8 Hz, CH), 128.2 (d, J_{CF} = 7.5 Hz, C_q), 130.0 (2 × CH), 130.3 (C_q), 139.7 (d, J_{CF} = 2.0 Hz, C_q), 156.7 (d, J_{CF} = 236.0 Hz, C_q), 159.4 (C_q). The analytical data obtained are in agreement with those reported in ref 23.

*4′-Chlorobiphenyl-2-amine (**23**) and 4′-Chlorobiphenyl-4-amine (**23′**).* Compounds **23** and **23′** were prepared from aniline (1.82 mL, 20.0 mmol) and 4-chlorophenylhydrazine hydrochloride (179 mg, 1.00 mmol) according to the general procedure at 60 °C. The excess of aniline was removed by Kugelrohr distillation in vacuo at 75 °C. Purification by column chromatography gave **23** (104 mg, 0.51 mmol, 51%) as a black solid, mp 65−67 °C, and **23′** (18.0 mg, 0.09 mmol, 9%) as a brown solid, mp 118 °C−120 °C. 4′-Chlorobiphenyl-2-amine (**23**): R_f = 0.6 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.76 (dd, J = 1.2 Hz, J = 8.6 Hz, 1 H), 6.86 (dt, J = 1.2 Hz, J = 7.5 Hz, 1 H), 7.08 (dd, J = 1.6 Hz, J = 7.6 Hz, 1 H), 7.16 (ddd, J = 1.6 Hz, J = 7.4 Hz, J = 8.0 Hz, 1 H), 7.38−7.42 (m, 4 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 115.6 (CH), 118.4 (CH), 126.3 (C_q), 128.7 (CH), 129.1 (2 × CH), 130.3 (CH), 130.5 (2 × CH), 133.6 (C_q), 136.9 (C_q), 143.2 (C_q). 4′-Chlorobiphenyl-4-amine (**23′**): R_f = 0.3 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.76 (d, J = 8.6 Hz, 2 H), 7.35 (d, J = 8.6 Hz, 2 H), 7.38 (d, J = 8.6 Hz, 2 H), 7.46 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 115.4 (2 × CH), 127.4 (2 × CH), 127.9 (2 × CH), 128.7 (2 × CH), 130.2 (C_q), 132.5 (C_q), 139.8 (C_q), 146.7 (C_q). The analytical data obtained are in agreement with those reported in ref 17.

*4′,5-Dichlorobiphenyl-2-amine (**24**).* Compound **24** was prepared from 4-chloroaniline (2.55 g, 20.0 mmol) and 4-chlorophenylhydrazine hydrochloride (179 mg, 1.00 mmol) according to the general procedure at 80 °C. The excess of 4-chloroaniline was removed by Kugelrohr distillation in vacuo at 120 °C. Purification by column chromatography gave **24** (140 mg, 0.47 mmol, 47%): dark brown oil; R_f = 0.5 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.69 (d, J = 8.2 Hz, 1 H), 7.07 (d, J = 2.5 Hz, 1 H), 7.11 (dd, J = 2.5 Hz, J = 8.5 Hz, 1 H), 7.36 (d, J = 8.7 Hz, 2 H), 7.41 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 116.9 (CH), 124.0 (C_q), 128.3 (CH), 129.1 (2 × CH), 130.0 (2 × CH), 130.6 (CH), 131.6 (C_q), 133.5 (C_q), 136.1 (C_q), 141.8 (C_q). The analytical data obtained are in agreement with those reported in ref 17.

*5-Bromo-4′-chlorobiphenyl-2-amine (**25**).* Compound **25** was prepared from 4-bromoaniline (3.44 g, 20.0 mmol) and 4-chlorophenylhydrazine hydrochloride (179 mg, 1.00 mmol) according to the general procedure at 70 °C. The excess of 4-bromoaniline was removed by Kugelrohr distillation in vacuo at 105 °C. Purification by column chromatography gave **25** (160 mg, 0.57 mmol, 57%): dark brown oil; R_f = 0.6 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.76 (d, J = 8.5 Hz, 1 H), 7.25 (d, J = 2.3 Hz, 1 H), 7.30 (dd, J = 2.3 Hz, J = 8.5 Hz, 1 H), 7.36 (d, J = 8.4 Hz, 2 H), 7.40 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 110.6 (C_q), 118.4 (CH), 129.1 (2 × CH), 130.3 (2 × CH), 130.6 (C_q), 131.5 (CH), 132.1 (C_q), 132.8 (CH), 133.9 (C_q), 135.9 (C_q). The analytical data obtained are in agreement with those reported in ref 17.

*4′-Chloro-5-cyanobiphenyl-2-amine (**26**).* Compound **26** was prepared from 4-aminobenzonitrile (2.36 g, 20.0 mmol) and 4-chlorophenylhydrazine hydrochloride (179 mg, 1.00 mmol) according to the general procedure at 90 °C. The excess of 4-aminobenzonitrile was removed by Kugelrohr distillation in vacuo at 130 °C. Purification by column chromatography gave **26** (61.0 mg, 0.27 mmol, 27%): red oil; R_f = 0.7 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.74 (d, J = 8.4 Hz, 1 H), 7.33−7.37 (m, 3 H), 7.42 (dd, J = 2.0 Hz, J = 8.4 Hz, 1 H), 7.46 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 100.7 (C_q), 115.4 (CH), 119.5 (C_q), 126.1 (C_q), 129.0 (2 × CH), 130.4 (2 × CH), 132.9 (CH), 134.2 (C_q), 134.4 (CH), 135.5 (C_q), 147.6 (C_q). The analytical data obtained are in agreement with those reported in ref 17.

*4′-Chloro-5-methoxybiphenyl-2-amine (**27**).* Compound **27** was prepared from 4-methoxyaniline (2.46 g, 20.0 mmol) and 4-chlorophenylhydrazine hydrochloride (179 mg, 1.00 mmol) according to the general procedure at 60 °C. The excess of 4-methoxyaniline was removed by Kugelrohr distillation in vacuo at 120 °C. The crude product was purified by column chromatography (hexane/EtOAc = 6:1) to give **27** (99.0 mg, 0.42 mmol, 42%): black crystalline solid; mp 88−92 °C; R_f = 0.6 (CH_2Cl_2/EtOAc = 50:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.77 (s, 3 H), 6.70 (d, J = 2.8 Hz, 1 H), 6.76 (d, J = 8.6 Hz, 1 H), 6.80 (dd, J = 2.8 Hz, J = 8.1 Hz, 1 H), 7.39−7.44 (m, 4 H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 55.8 (CH_3), 114.7 (C_q), 115.7 (CH), 117.1 (CH), 127.5 (CH), 129.0 (2 × CH), 130.4 (2 × CH), 133.2 (C_q), 136.9 (Cq), 137.9 (C_q), 152.9 (C_q). The analytical data obtained are in agreement with those reported in ref 17.

*4′-Chloro-5-ethoxybiphenyl-2-amine (**28**).* Compound **28** was prepared from 4-ethoxyaniline (2.59 g, 20.0 mmol) and 4-chlorophenylhydrazine hydrochloride (179 mg, 1.00 mmol) according to the general procedure at 60 °C. The excess of 4-ethoxyaniline was removed by Kugelrohr distillation in vacuo at 130 °C. The crude product was purified by column chromatography (hexane/EtOAc = 6:1) to give **28** (80.0 mg, 0.30 mmol, 30%): black oil; R_f = 0.4 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.38 (t, J = 7.0 Hz, 3 H), 3.98 (q, J = 7.0 Hz, 2 H), 6.70 (d, J = 2.8 Hz, 1 H), 6.74 (d, J = 8.6 Hz, 1 H), 6.80 (dd, J = 2.8 Hz, J = 8.1 Hz, 1 H), 7.40 (s, 4 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 15.0 (CH_3), 64.8 (CH_2), 115.7 (CH), 116.7 (CH), 117.5 (CH), 127.9 (C_q), 129.0 (2 × CH), 130.4 (2 × CH), 133.2 (C_q), 136.9 (Cq), 137.9 (C_q), 152.9 (C_q). The analytical data obtained are in agreement with those reported in ref 17.

*4′-Chloro-5-fluoro-2-methoxybiphenyl (**30**) and 4′-chloro-6-fluoro-3-methoxybiphenyl (**30′**).* Compounds **30** and **30′** were prepared from 4-fluoroanisole (2.26 mL, 2.59 g, 20.0 mmol) and 4-chlorophenylhydrazine hydrochloride (179 mg, 1.00 mmol) according to the general procedure at 60 °C. The excess of 4-fluoroanisole was removed by Kugelrohr distillation in vacuo at 110 °C. The crude products were purified by column chromatography (silica gel, hexane/EtOAc = 8:1) to give the regioisomers 4′-chloro-5-fluoro-2-methoxybiphenyl (**30**) (86.0 mg, 0.36 mmol, 36%) as a brown oil and 4′-chloro-6-fluoro-3-methoxybiphenyl (**30′**) as a brown oil (22.0 mg, 0.09 mmol, 9%). 4′-Chloro-5-fluoro-2-methoxybiphenyl (**30**): R_f = 0.7 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.76 (s, 3 H), 6.89 (dd, J_{HF} = 4.9 Hz, J = 8.7 Hz, 1 H), 6.97−7.03 (m, 2 H), 7.37 (d, J = 8.8 Hz, 2 H), 7.44 (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 238 (30) [^{37}Cl-M$^+$], 237 (14), 236 (100) [^{35}Cl-M$^+$], 221 (19), 186 (98), 157 (24); HRMS (EI) calcd for $C_{13}H_{10}{}^{35}ClFO$ [M$^+$] 236.0404, found 236.0404. 4′-Chloro-6-fluoro-3-methoxybiphenyl (**30′**): R_f = 0.3 (hexane/EtOAc = 4:1) (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.79 (s, 3 H), 6.78 (d, J_{HF} = 4.9 Hz, 1 H), 6.82 (dd, J_{HF} = 4.0 Hz, J = 8.8 Hz, 1 H), 6.89 (dd, J_{HF} = 8.8 Hz, 1 H), 7.41−7.48 (m, 4 H); ^{13}C NMR (151 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.

*Experiment on a Larger Scale: 4′-Chlorobiphenyl-2-amine (**23**).* Compound **23** was prepared from aniline (37.2 mL, 400 mmol) and 4-chlorophenylhydrazine hydrochloride (3.58 g, 20.0 mmol) in the presence of aqueous sodium hydroxide (1M, 20.0 mL) according to the general procedure at 60 °C. After phase separation and 3-fold extraction of the aqueous phase with CH_2Cl_2 (3 × 20 mL), the excess of aniline could be recovered in high purity by distillation in vacuo at 80 °C. Purification by column chromatography gave **23** (1.72 g, 8.48 mmol, 43%) and **23′** (357 mg, 1.76 mmol, 9%). The analytical data obtained are in agreement with those reported in ref 17.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all 2-aminobiphenyls **3** and **17**−**28** and biphenyl ethers **30** and **30′**. 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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■ REFERENCES

(1) (a) Costantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65. (b) Jiang, H.; Sun, J.; Zhang, J. *Curr. Org. Chem.* **2012**, *16*, 2014. (c) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447.

(2) (a) Matsubara, S.; Asano, K.; Kajita, Y.; Yamamoto, M. *Synthesis* **2007**, 2055. (b) Price, J. R.; Lan, Y.; Brooker, S. *J. Chem. Soc., Dalton Trans.* **2007**, 1807. (c) Fliedel, C.; Maisse-Francois, A.; Bellemin-Laponnaz, S. *Inorg. Chim. Acta* **2007**, *360*, 143. (d) Fedushkin, I. L.; Chudakova, V. A.; Skatova, A. A.; Khvoinova, N. M.; Kurskii, Y. A.; Glukhova, T. A.; Fukin, G. K.; Dechert, S.; Hummert, M.; Schumann, H. *Z. Anorg. Allg. Chem.* **2004**, *630*, 501. (e) Pan, X.; Wilcox, C. S. *J. Org. Chem.* **2010**, *75*, 6445. (f) Hoffmann-Emery, F.; Jakob-Roetne, R.; Flohr, A.; Bliss, F.; Reents, R. *Tetrahedron Lett.* **2009**, *50*, 6380.

(3) (a) Eicken, K.; Rack, M.; Wetterich, F.; Ammermann, E.; Lorenz, G.; Strathmann, S. (BASF SE) DE19735224, 1999; *Chem. Abstr.* **1999**, *130*, 182464. (b) Eicken, K.; Rang, H.; Harreus, A.; Goetz, N.; Ammermann, E.; Lorenz, G.; Strathmann, S. (BASF SE) DE19531813, 1997; *Chem. Abstr.* **1997**, *126*, 264007.

(4) Jörges, W.; Heinrich, J.-D.; Lantzsch, R. (Bayer Cropscience) WO2006024388, 2006; *Chem. Abstr.* **2006**, *144*, 253890.

(5) Dietz, J.; Strathmann, S.; Stierl, R.; Montag, J. (BASF SE) WO 2007128756, 2007; *Chem. Abstr.* **2007**, *147*, 516420.

(6) (a) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*, 2nd ed.;Wiley-VCH: Weinheim, 2004. (b) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004. (c) Bonin, H.; Fouquet, E.; Felpin, F.-X. *Adv. Synth. Catal.* **2011**, *353*, 3063.

(7) Rouhi, A. M. *Chem. Eng. News* **2004**, *82*, 49.

(8) For recently developed alternative synthetic strategies toward boscalid, see: (a) Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (b) Glasnov, T. N.; Kappe, C. O. *Adv. Synth. Catal.* **2010**, *352*, 3089. (c) Caron, L.; Campeau, L.-C.; Fagnou, K. *Org. Lett.* **2008**, *10*, 4533. (d) Felpin, F.-X.; Fouquet, E.; Zakri, C. *Adv. Synth. Catal.* **2009**, *351*, 649. (e) Spivey, A. C.; Tseng, C.-C.; Hannah, J. P.; Gripton, C. J. G.; de Fraine, P.; Parr, N. J.; Scicinski, J. J. *Chem. Commun.* **2007**, 2926.

(9) For review articles on the homolytic aromatic substitution, see: (a) Bolton, R.; Williams, G. H. *Chem. Soc. Rev.* **1986**, *15*, 261. (b) Studer, A. In *Radicals in Organic Synthesis*, 1st ed.; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; p 44. (c) Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**, *36*, 1803. (d) Vaillard, S. E.; Schulte, B.; Studer, A. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, 2009; p 475.

(10) For review articles on C−H activation, see: (a) Dyker, G. *Handbook of C−H Transformations*; Wiley-VCH: Weinheim, 2005. (b) Ackermann, L. *Top. Organomet. Chem.* **2008**, *24*, 35. (c) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (d) Lersch, M.; Tilset, M. *Chem. Rev.* **2005**, *105*, 2471.

(11) For recent articles on C−H activation, see: (a) Ishikawa, A.; Nakao, Y.; Sato, H.; Sakaki, S. *Dalton Trans.* **2010**, *39*, 3279. (b) Foley, N. A.; Ke, Z.; Gunnoe, T. B.; Cundari, T. R.; Petersen, J. L. *Organometallics* **2008**, *27*, 3007. (c) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 458. (d) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305. (e) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (f) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (g) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (h) Vallée, F.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 1514. (i) Liu, W.; Cao, H.; Lei, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 2004. (j) Pirali, T.; Zhang, F.; Miller, A. H.; Head, J. L.; McAusland, D.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 1006.

(12) (a) Gomberg, M.; Bachmann, W. E. *J. Am. Chem. Soc.* **1924**, *46*, 2339. (b) Dermer, O. C.; Edmison, M. T. *Chem. Rev.* **1957**, *57*, 77.

(13) Beadle, J. R.; Korzeniowski, S. H.; Rosenberg, D. E.; Garcia-Slanga, B. J.; Gokel, G. W. *J. Org. Chem.* **1984**, *49*, 1594.

(14) For the rate of addition of aryl radicals to benzene, see: Scaiano, J. C.; Stewart, L. C *J. Am. Chem. Soc.* **1983**, *105*, 3609.

(15) Galli, C. *Chem. Rev.* **1988**, *88*, 765.

(16) (a) Kosynkin, D.; Bockman, T. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 4846. (b) Hari, D. P.; Schroll, P.; König, B. *J. Am. Chem. Soc.* **2012**, *134*, 2958. (c) Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18566.

(17) Pratsch, G.; Wallaschkowski, T.; Heinrich, M. R. *Chem.—Eur. J.* **2012**, *18*, 11555.

(18) For reviews, see: (a) Vaillard, S. E.; Studer, A. Radical Arylations. In *Encyclopedia of Radicals in Chemistry, Biology, and Materials*; Chatgilialoglu, C., Studer, A., Ed.; Wiley: New York, 2012; Vol. 2. (b) Jasch, H.; Heinrich, M. R. Tin Hydrides and Functional Group Transformations. In *Encyclopedia of Radicals in Chemistry, Biology, and Materials*; eds. Chatgilialoglu, C., Studer, A., Eds.; Wiley: New York, 2012; Vol. 2. (c) Pratsch, G.; Heinrich, M. R. In *Topics in Current Chemistry*; Heinrich, M. R., Gansäuer, A., Eds.; Springer: New York, 2012 ;Vol. *320*.

(19) (a) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673. (b) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044. (c) Shirakawa, E.; Itoh, K.-I.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537. (d) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737.

(20) For possible reaction mechanisms, see: Studer, A.; Curran, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018.

(21) (a) Chaturbhuj, G. U.; Akamanchi, K. G. *Tetrahedron Lett.* **2011**, *52*, 4950. (b) Curran, D. P.; Keller, A. I. *J. Am. Chem. Soc.* **2006**, *128*, 13706. (c) Demir, A. S.; Reis, Ö.; Emrullahoglu, M. *J. Org. Chem.* **2003**, *68*, 578.

(22) (a) Wetzel, A.; Ehrhardt, V.; Heinrich, M. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 9130. (b) Wetzel, A.; Pratsch, G.; Kolb, R.; Heinrich, M. R. *Chem.—Eur. J.* **2010**, *16*, 2547.

(23) Jasch, H.; Scheumann, J.; Heinrich, M. R. *J. Org. Chem.* **2012**, *77*, 10699.

(24) (a) Taniguchi, T.; Sugiura, Y.; Zaimoku, H.; Ishibashi, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 10154. (b) Taniguchi, T.; Zaimoku, H.; Ishibashi, H. *Chem.—Eur. J.* **2011**, *17*, 4307.

(25) (a) Demir, A. S.; Reis, Ö.; Özgül-Karaaslan, E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3042. (b) Demir, A. S.; Findik, H. *Tetrahedron* **2008**, *64*, 6196. (c) Demir, A. S.; Reis, Ö.; Emrullahoğlu, M. *Tetrahedron* **2002**, *58*, 8055. (d) Mohammadpoor-Baltork, I.; Hajipour, A. R.; Mohammadi, H. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1649. (e) Johnson, M. D.; Hornstein, B. J. *J. Chem. Soc., Chem. Commun.* **1996**, 965. (f) Firouzabadi, H.; Mohajer, D.; Entezari-Moghadam, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2185. (g) Zhang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 6174. (h) Hu, Z.; Kerton, F. M. *Org. Biomol. Chem.* **2012**, *10*, 1618. (i) Hadjiarapoglou, L.;

Spyroudis, S.; Varvoglis, A. *Synthesis* **1983**, 207. (j) Shine, H. J.; Zmuda, H.; Kwart, H.; Horgan, A. G.; Breichbiel, M. *J. Am. Chem. Soc.* **1982**, *104*, 5181. (k) Shine, H. J.; Zmuda, H.; Park, K. H.; Kwart, H.; Horgan, A. G.; Brechbiel, M. *J. Am. Chem. Soc.* **1982**, *104*, 2501. (l) Hoogewerff, S.; van Dorp, W. A. *Chem. Ber.* **1877**, *10*, 1936. (m) Bamberger, E.; Tschirner, F. *Chem. Ber.* **1898**, *31*, 1522. (n) Ruether, T.; Jackson, W. R.; Bond, A. M. *Aust. J. Chem.* **2002**, *55*, 691. (o) Patel, S.; Mishra, B. K. *Tetrahedron Lett.* **2004**, *45*, 1371. (p) Zhang, L.; Xia, J.; Li, Q.; Li, X.; Wang, S. *Organometallics* **2011**, *30*, 375.

(26) Chen, Z.-X.; Wang, G.-W. *J. Org. Chem.* **2005**, *70*, 2380.

(27) Coleman, G. H. *Org. Synth.* **1922**, 2.

(28) (a) Huang, P. C.; Kosower, E. M. *J. Am. Chem. Soc.* **1967**, *89*, 3910. (b) Huang, P. C.; Kosower, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 2367. (c) Kosower, E. M.; Huang, P. C.; Tsuji, T. *J. Am. Chem. Soc.* **1969**, *91*, 2325. (d) Myers, A. G.; Movassaghi, M.; Zheng, B. *Tetrahedron Lett.* **1997**, *38*, 6569.

(29) Braslau, R.; Burrill, L. C., II; Mahal, L. K.; Wedeking, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 237.

(30) Amorati, R.; Valgimigli, L. *Org. Biomol. Chem.* **2012**, *10*, 4147.

(31) For recent advances on the development of diarylamine-based antioxidants, see: (a) Hanthorn, J. J.; Valgimigli, L.; Pratt, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 8306. (b) Hanthorn, J. J.; Valgimigli, L.; Pratt, D. A. *J. Org. Chem.* **2012**, *77*, 6908.

(32) Moorthy, J. N.; Samanta, S. *J. Org. Chem.* **2007**, *72*, 9786.

(33) (a) Amorati, R.; Ferroni, F.; Pedulli, G. F.; Valgimigli, L. *J. Org. Chem.* **2003**, *68*, 9654. (b) Amorati, R.; Valgimigli, L.; Panzella, L.; Napolitano, A.; d'Ischia, M. *J. Org. Chem.* **2013**, *78*, 9857.

(34) Curran, D. P.; Keller, A. I. *J. Am. Chem. Soc.* **2006**, *128*, 13706.