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# Radical Arylation of Phenols, Phenyl Ethers, and Furans

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**Abstract:** Radical arylations of *para*-substituted phenols and phenyl ethers proceeded with good regioselectivity at the *ortho* position with respect to the hydroxy or alkoxy group. The reactions were conducted with arenediazonium salts as the aryl radical source, titanium(III) chloride as the reductant, and diluted hydrochloric acid as the solvent. Substituted biaryls were obtained from hydroxy- and alkoxy-substituted benzylamines, phenethylamines, and aromatic amino acids. The methodology described offers a fast, efficient, and cost-effective new access to diversely functionalized biphenyl alcohols and ethers. Free phenolic hydroxy groups, aromatic and aliphatic amines, as well as amino acid substructures, are well tolerated. Two examples for the applicability of the methodology are the partial synthesis of a β-secretase inhibitor and the synthesis of a calcium-channel modulator.

**Keywords:** diazonium salts · biaryls · phenols · phenyl ethers · radical reactions

## Introduction

Organometallic cross-coupling reactions are currently popular strategies for biaryl synthesis.[1] In the widely applied Suzuki, Stille, Negishi, and Kumada reactions, aromatic boronic acids, aryl tin, aryl zinc, and aryl magnesium compounds are treated with aryl halides, aryl tosylates, or aryl diazonium salts to give biaryl compounds.[2] Recent studies revealed that, besides the well-known palladium- or nickel-based catalysts, cobalt- or iron-containing compounds can be a useful alternative.[3,4] The newly developed decarboxylative cross-coupling reactions of aryl carboxylic acids and aryl carboxylates in the presence of copper, nickel, and palladium catalysts represent another valuable extension of the synthetic routes towards biaryls.[5] Substrates that are suitable precursors for the formation of biaryls, based on carbon-centered leaving groups, are benzonitriles and arylcarbinoles.[6] Major advantages of the established organometallic reactions certainly are the broad substrate tolerance and the unambiguous regioselectivity. Disadvantages can arise from the need for protecting groups, difficult optimization, challenging reaction conditions, as well as the limited commercial availability of substrates.

Biaryl synthesis based on the activation of C–H bonds is currently an intensively investigated field of research.[7–9] In contrast to the classical cross-coupling methods, reactions of this type often only require easily accessible starting materials, although lower regioselectivity and double arylation are still potential risks.

Very recently, reactions with combined radical and organometallic mechanisms were shown to be highly efficient with respect to increased reactivity and selectivity.[10,11]

The classical radical methods for biaryl synthesis are known as the Gomberg–Bachmann and Pschorr reactions,[12,13] in which aryl diazonium salts serve as precursors for aryl radicals. New developments in this area include the use of aryl halides in the presence of organotin, organosilicon, or samarium compounds.[14] The low regioselectivity of radical arylations has certainly impeded the broad use of these reactions in synthetic organic chemistry. Moreover, the slow addition of aryl radicals to substituted benzenes often requires the use of the substrates in great excess or even as solvents, therefore, usually only cheap, easily accessible, and conveniently separable arenes are employed.[15] For the same reason, intramolecular radical arylation reactions are frequently employed.[16] Improvements and recent reports on Gomberg–Bachmann-type reactions include

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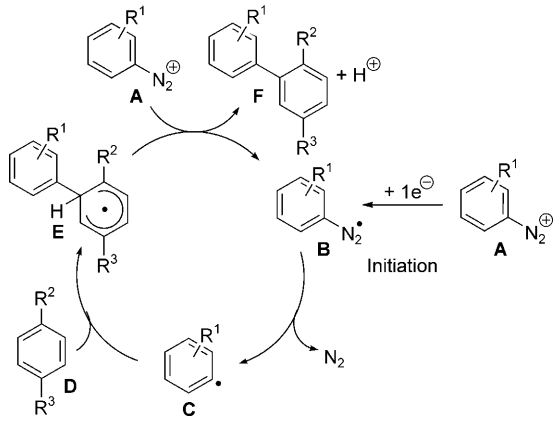
phase-transfer variants,[17] the application of oxygen as reoxidant in tin-mediated radical biaryl syntheses,[18] and the application of arylhydrazines and Grignard reagents[19,20] as aryl radical precursors. Biaryl compounds can also be obtained by radical addition to a nonaromatic precursor and subsequent aromatization.[21]

Radical biaryl syntheses that rely on a chain mechanism, in the sense of an $S_{RN}1$-reaction,[22] have, so far, only been described for a few substrates.[23] In this reaction type the diazonium salt **A** serves as both the aryl radical source and the oxidizing agent (Scheme 1). Therefore, the rearomatization step leads from **E** to the product **F**, as well as to a new aryl diazenyl radical **B**, which, after loss of nitrogen to aryl radical **C**, enters the cycle again. Aryl radical **C** is captured by the substrate **D** to give the cyclohexadienyl intermediate **E**.



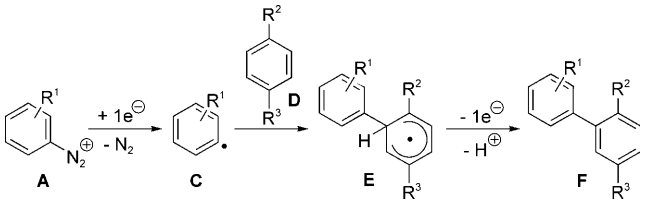

Scheme 1. Radical biaryl coupling by an $S_{RN}1$-type chain reaction.

Phenolates, as electron-rich substrates, are adequate reaction partners for aryl radicals, but the undesired azo-coupling reaction requires the use of azo sulfides instead of aryl diazonium salts.[24] The chain reaction can also be put into effect by the combination of electron-poor aryl diazonium salts and nonactivated substrates, such as benzene. Several examples have been described with pentafluorophenyl diazonium salts.[25] The perfluorinated diazonium salt, moreover, had the advantage that no attack of the aryl radical on the diazonium salt itself, either in the sense of a biaryl coupling or in the sense of an azo coupling, was observed.

## Results and Discussion

The main goal of our work is the development of radical arylation methods for electron-rich aromatics, including anilines and phenols,[26] based on the use of arene diazonium salts[27] (Scheme 2).

To allow the use of free diazonium salts **A** as radical precursors, in combination with anilines and phenols **D**, the undesired azo coupling and triazene formation needs to be




Scheme 2. Radical arylation of anilines and phenols.

suppressed by low concentrations of the diazonium salt and a fast reductive step from **A** to **C**. In addition to this challenging aspect, radical arylations of anilines and phenols are likely to imply the following advantages: 1) effective aryl radical addition to electron-rich substrates **D**; 2) increased regioselectivity; 3) the possibility to use water as a solvent; 4) facilitated reoxidation of the cyclohexadienyl intermediate **E**.

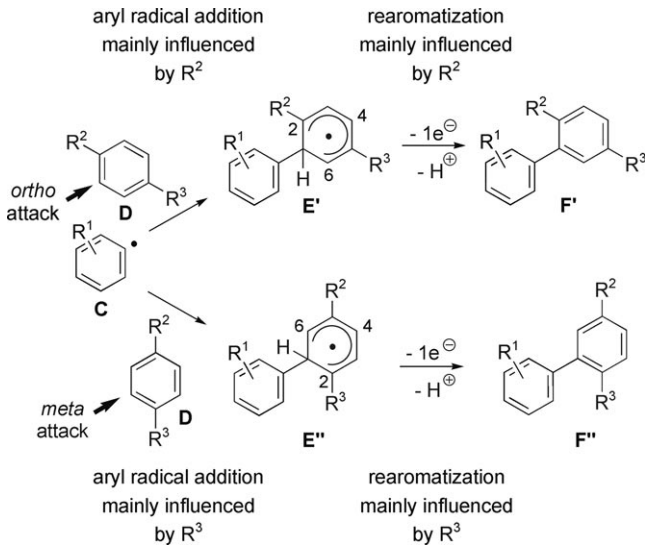
The aryl radical addition to electron-rich substrates **D** can be considered as more effective than to unsubstituted benzene ($k = 10^6\,M^{-1}s^{-1}$) due to the electrophilic character of the aryl radical **C**. Moreover, hydroxy and amino substituents attached to an aromatic core exert decisive effects on the electron density of the positions of the benzene ring of **D**, as well as on the stabilization of the resulting cyclohexadienyl intermediate **E**, which should lead to good regioselectivity. The use of water as the solvent can be beneficial in several ways. First, the aromatic hydroxy and amino groups are much less prone to hydrogen abstraction by the aryl radical due to hydrogen bonding.[28] The aryl radical is also practically unable to abstract hydrogen from water, which is not true for most common organic solvents.[29] Due to the insolubility of the biaryl products **F**, the solvent water is, indirectly, useful to prevent double arylation even when only a comparatively low excess of substrate **D** is applied.[30] Finally, electron-donating substituents facilitate the reoxidation of the cyclohexadienyl intermediate **E** and can enable the reaction to run as a radical chain, in which the diazonium salt **A** acts as an oxidant for **E**.

A closer look at the factors influencing regioselectivity reveals that one suitable substituent in a *para*-substituted aromatic substrate should be sufficient for successful radical arylation reactions (Scheme 3).

When the $R^2$ substituent is an electron-donating and radical-stabilizing substituent (such as hydroxyl), the relative rate of the *ortho* attack of radical **C** on substrate **D** is increased by the additional stability of intermediate **E′**. Since the SOMO energy level of the resulting cyclohexadienyl intermediate **E′** is much more dependent on the nature of $R^2$ (compare resonance structures of radical **E′**), reoxidation of **E′** to **F′** will be facilitated by electron-donating $R^2$ substituents, which raise the SOMO energy level.[31] Low regioselectivities, however, must be expected if both $R^2$ and $R^3$ are competing electron-donating substituents because both pathways leading to **F′** and **F″** are then equally favored.

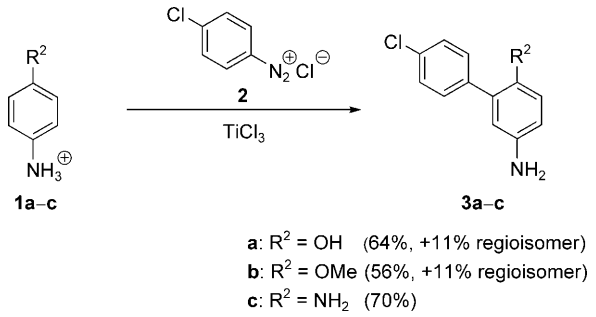
In our first report on radical arylation, we demonstrated that the considerations shown above can indeed be put into




Scheme 3. Substituent effects on regioselectivity.

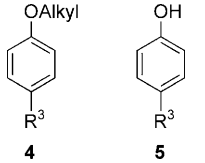
practice (Scheme 4).[32] With suitable $R^2$ groups, such as amino, hydroxy, and alkoxy, the radical arylation of anilinium salts **1** ($R^3 = NH_3^+$) to biaryls **3** proceeded with good yields and acceptable regioselectivities. The ammonium group as the *para* substituent nicely fulfils the requirements for $R^3$, in the sense that $R^3$ is a non-electron-donating substituent with sufficient polarity to achieve water solubility.

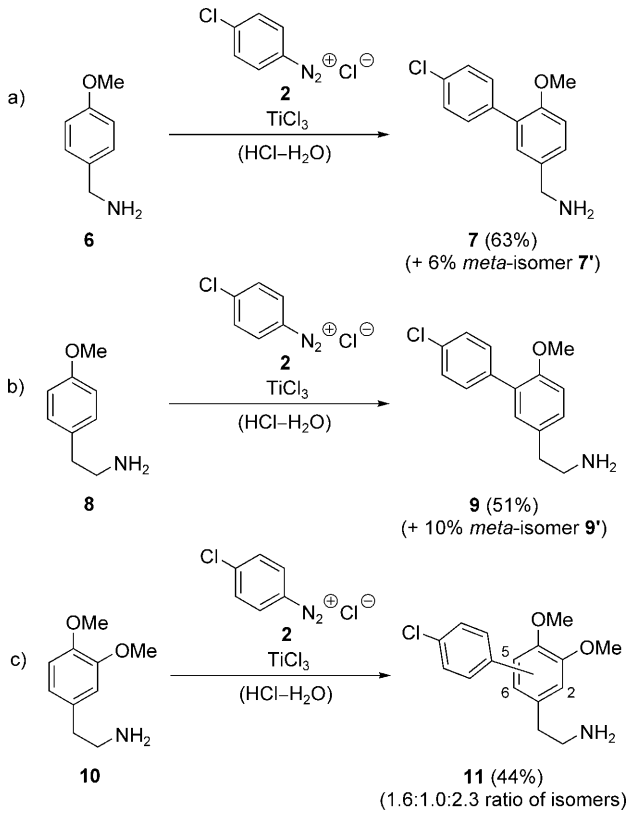



Scheme 4. Radical arylation of (mono)protonated 4-aminophenol (**1a**), *p*-anisidine (**1b**), and 1,4-phenylene diamine (**1c**).

Herein, we would like to demonstrate that the radical *ortho*-arylation of phenyl ethers **4** and phenols **5** with arenediazonium salts is a more generally applicable method with the partial limitations that the *para*-substituent $R^3$ is neither strongly electron donating nor too lipophilic.

The *ortho*-arylation of phenyl ethers **4** was first investigated with 4′-methoxybenzylamine (**6**) as a substrate (Scheme 5a). The addition of 4-chlorophenyldiazonium chloride (**2**) to a fivefold excess of **6** and titanium(III) chloride in dilute hydrochloric acid led to the desired biarylamine (**7**) in 63% yield accompanied by 6% of the *meta*-isomer (Scheme 5a).




Scheme 5. Radical arylation of *para*-substituted phenyl ethers.

Variation of the reaction temperature had shown that room temperature and 40°C gave similar results, but running the reaction at 0°C proved less favorable. The relatively slow (10 to 15 min) and controlled addition of the solution of diazonium salt to the reaction mixture by syringe pump was beneficial in the sense that homocoupling reactions (addition of the aryl radical to the diazonium ion) were largely suppressed.[33] Under the improved conditions, biarylamine **9** was obtained from 4-methoxyphenethylamine (**8**) in 51% yield along with 10% of the *meta*-product (Scheme 5b). The arylation of 3,4-dimethoxyphenethylamine (**10**) proceeded with only low regioselectivity and an inseparable mixture of regioisomers was isolated (Scheme 5c). Analysis of the product distribution by proton NMR spectroscopy suggested a ratio of the 2′-, 5′- and 6′-isomers of 1.6:1.0:2.3, respectively, with the 6′-isomer as the major product.

The results obtained in the arylation reactions are remarkable because the structures of all substrates possess benzylic hydrogen atoms, which are known to be labile in the presence of aryl radicals. Given the reported rate constants for the aryl radical induced abstraction of hydrogen from toluene ($k \approx 10^6\,M^{-1}s^{-1}$)[34] and for aryl radical additions to benzene ($k \approx 10^6\,M^{-1}s^{-1}$),[35] the results shown above clearly indicate that electron-rich aromatic compounds are well-suited substrates to which aryl radicals add significantly faster than to benzene. Otherwise, the competing abstrac-

tion reactions could not be successfully overcome. The slightly better yield that was obtained in the arylation of **6** compared with that of **8** might also be explained by the different electronic properties of the benzylic C–H bonds. Although the proximity of the protonated (under the reaction conditions) amine in **6** renders the benzylic C–H bonds less electron rich and, therefore, more stable towards hydrogen abstraction, the properties of the benzylic C–H bonds of **8**, in contrast, remain more or less unaffected by the inductive effect of the ammonium group and are more easily attacked.

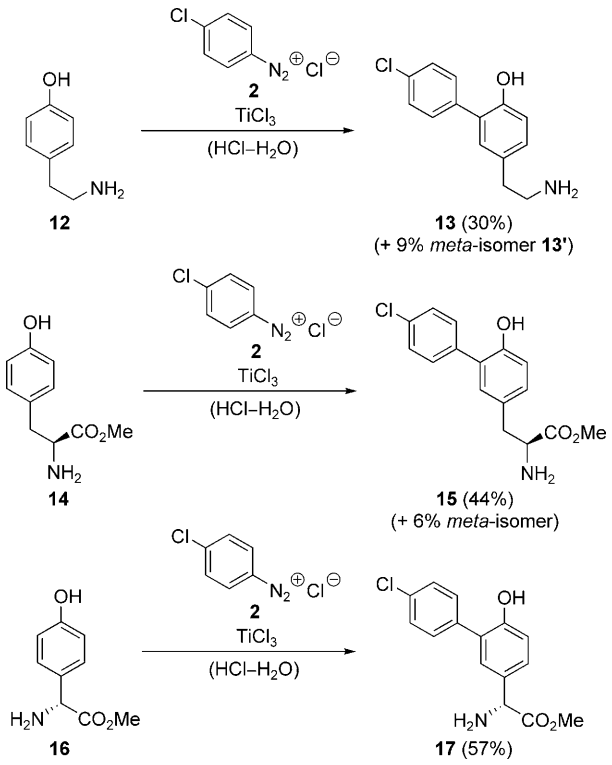
Radical arylations of phenols benefit from the use of aqueous solvents. Although phenols are efficient hydrogen donors when employed in nonpolar solvents, as exemplified by the antioxidant vitamin tocopherol,[36] hydrogen bonding to the phenolic hydroxy group significantly reduces its hydrogen atom donor capabilities.

The substrates for the following series of experiments were chosen to investigate which, potentially even more labile, C–H bonds would be tolerated by the radical arylation. To enable comparison with the previous experiments, compound **2** was again used as the aryl radical source. With respect to the general applicability, several previous studies have led to the conclusion that the outcome of radical arylation reactions is, in most cases, only slightly dependent on the nature of the ring substituents of the aryl radical.[37] An exchange of the chloro substituent for a multitude of other functional groups should, therefore, be possible.

The 39% overall yield with 3:1 regioselectivity obtained from the arylation of tyramine (**12**; Scheme 6) shows, in comparison with **8** (Scheme 5), that the phenolic hydroxy group is indeed not a prohibitive structural element.[38] Due to the polarity of biarylamine **13**, quantitative extraction from the aqueous phase turned out to be difficult and may be a reason for the slightly lower yields obtained in these experiments. Moreover, the usual purification by column chromatography failed. Instead, compound **13** was purified by sublimation and preparative HPLC.

The successful arylation of methyl L-tyrosinate (**14**) demonstrates that amino acids can be functionalized in this way.[39] The free amino group in **14** is a crucial structural element, since formation of the ammonium salt under the acidic reaction conditions successfully suppresses hydrogen abstraction from the CH unit, which would otherwise lead to a radical stabilized by the captodative effect.[40] Even the rate of hydrogen abstraction from methyl D-4-hydroxyphenyl glycinate (**16**) can be sufficiently reduced by protonation such that the desired radical arylation of the phenol core occurs as the main reaction pathway. In the case of **17**, we were unable to detect the *meta*-regioisomer in the crude product mixture.

The observation that C–H bonds, which are usually labile with respect to hydrogen abstraction, become significantly more stable by protonation of an adjacent amine can also be rationalized by the fact that electrophilic aryl radicals are less likely to attack electron-deficient than -rich bonds. Comparable results have been obtained in earlier studies of




Scheme 6. Radical arylation of *para*-substituted phenols.

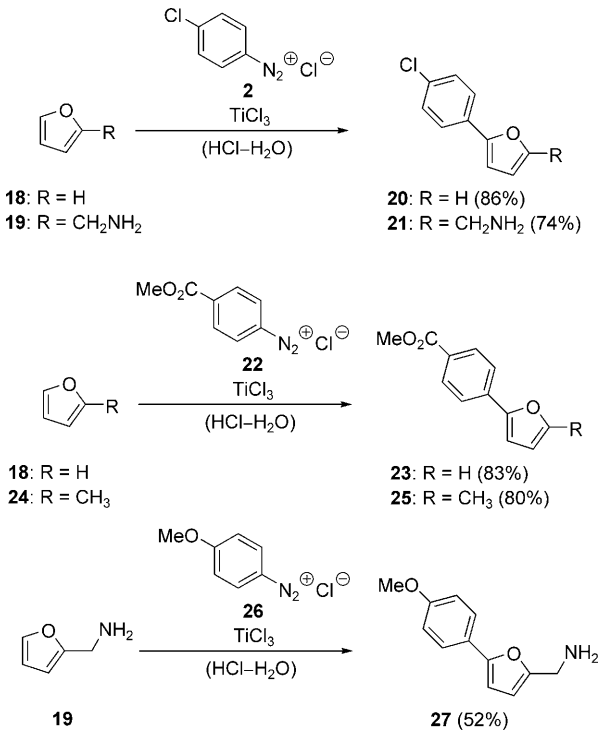
aryl radical based olefin functionalization reactions. Although nonprotonated allylic amines are not suitable substrates due to extensive hydrogen abstraction from the allylic position, the protonated ammonium salts of these substrates react without difficulties.[41]

The best results from the arylation of heterocycles were obtained with furan (**18**),[42] furfurylamine (**19**), and 2-methylfuran (**24**). All three substrates gave the desired biaryls in good yields and with high regioselectivity (Scheme 7).[43] Among the diazonium salts used for the arylation of the furan derivatives, the "electron-neutral" and the acceptor-substituted salts **2** and **22** led to a more efficient product formation than the donor-substituted diazonium salt **26**. Diazonium salt **26** is not as easily reduced as **2** and **22** and the reaction was, therefore, carried out at 40°C instead of room temperature.

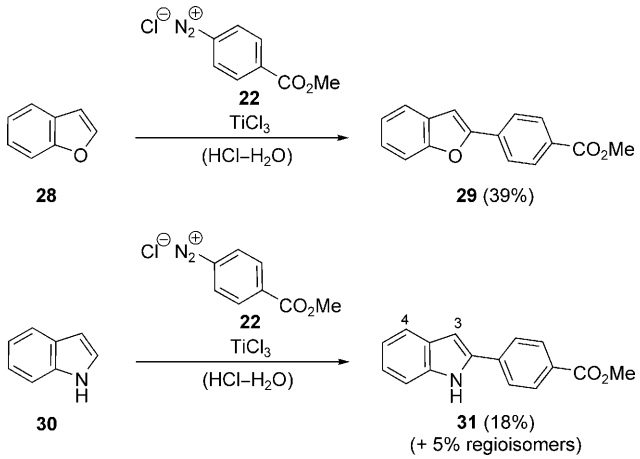
Arylation products could also be obtained from the heterocycles benzofuran (**28**) and indole (**30**) (Scheme 8). Due to the additional benzene core in the substrate, small amounts of the corresponding regioisomers were isolated along with the desired products **29** and **31**, which were only accessible in moderate to low yields. In contrast to **28**, the arylation of **30** is significantly complicated by the azo coupling of **22** to the 3-position of indole.[44a,b] Further attempts with pyrrol and N-alkylated pyrrols have, so far, failed due to the instability of these compounds under strongly acidic conditions (Fichtenspan reaction).[44c]

Although several advantages arise from the fact that water and hydrochloric acid are used as solvents for aryla-



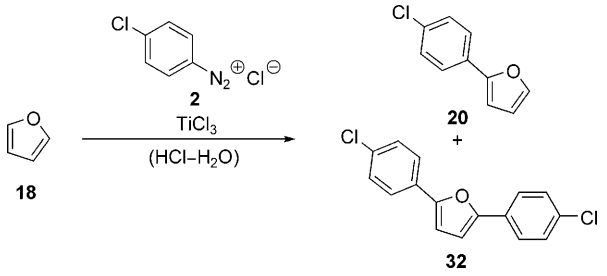

Scheme 7. Radical arylation of **18**, **19**, and **24**.




Scheme 8. Radical arylation of **28** and **30**.

tion, this also has to be considered as a significant drawback because the large group of potential nonpolar substrates is excluded by this choice of conditions. We therefore examined a series of organic solvents with respect to their applicability in the arylation procedure. For this purpose, the functionalization of **18** with **2** (Scheme 7) was carried out in 2.5:1 mixtures of an organic solvent and the original aqueous titanium(III) chloride solution (Scheme 9 and Table 1). The dominant fraction (>70 vol%) of the organic solvent was chosen to extend the substrate range significantly towards more lipophilic reactants.

Three conclusions can be drawn from the results shown in Table 1. First, the organic solvent leads to double arylation.




Scheme 9. Single and double arylation of **18**.

Table 1. Solvent effects on the arylation of **18**.

| Solvent | Yield **20** [%][a] | Yield **32** [%][a] | Product ratio **20**/**32** |
|---|---|---|---|
| no additive | 86 | <2 | >40:1 |
| 2,2,2-trifluoroethanol | 55 | 24 | 4:1 |
| acetonitrile | 58 | 12 | 10:1 |
| acetic acid | 59 | 18 | 6:1 |
| acetone | 50 | 14 | 7:1 |

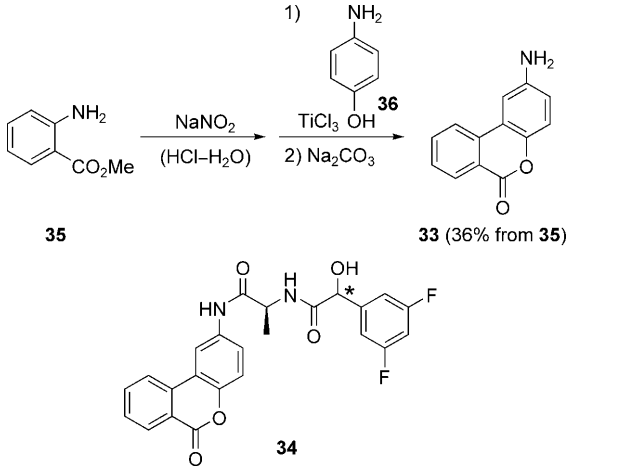
[a] Yields based on the diazonium salt **2**.

The monoarylated furan **20**, which is usually not attacked by a second 4-chlorophenyl radical due to its low solubility, is now partially converted to **32**. This observation in turn proves that under the modified conditions rather lipophilic substrates, such as **20**, can be used as reactants. Second, the total recovery of the 4-chlorophenyl group decreases in the presence of organic solvents in the following order: water > trifluoroethanol, acetic acid > acetonitrile > acetone. The loss of the chlorophenyl radicals is most probably due to hydrogen abstraction, which occurs most easily from acetone, and leads to the formation of volatile chlorobenzene. Finally, among the organic additives, acetonitrile was shown to give the most favorable ratio of mono- versus doubly arylated product.

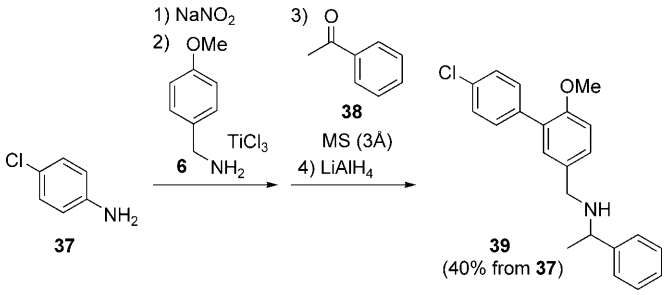
The radical arylation was finally applied to the synthesis of bioactive substructures and compounds. Aminobenzocoumarin **33** has been reported as a substructure of the β-secretase (BACE-1) inhibitor **34** (Scheme 10).[45] β-Secretase represents a target enzyme for the treatment of Alzheimer's disease. By using a radical biaryl coupling, fragment **33** is now conveniently accessible in three steps from methyl anthranilate (**35**) and 4-aminophenol (**36**).

Benzylamine **39** has been examined with respect to biological activity against the human parathyroid cell $Ca^{2+}$ receptor (hPCaR).[46] Pharmaceutical compositions of **39** and its derivatives should, therefore, be useful for the treatment or prophylaxis of diseases associated with bone disorders, such as osteoporosis. Racemic **39** can be obtained from 4-chloroaniline (**37**) by diazotization, biaryl coupling with 4′-methoxybenzylamine (**6**) (see compound **7**, Scheme 5), condensation with acetophenone (**38**), and lithium aluminum hydride reduction. The simple four-step protocol gave **39** in 40% overall yield without intermediate purification (Scheme 11).




Scheme 10. Synthesis of aminobenzocoumarin **33**.




Scheme 11. Synthesis of the calcium receptor ligand **39** (MS = molecular sieves).

## Conclusion

Biaryl syntheses, which proceed by the addition of aryl radicals to phenols and phenyl ethers, provided a fast, efficient, cost-effective, and, so far, unexploited access to functionalized biphenyls. Side reactions of the aryl radicals were minimized by the controlled addition of arenediazonium salts to a solution of the phenolic substrate and titanium(III) chloride in diluted hydrochloric acid. All of the *para*-substituted phenols and phenyl ethers included in our study were converted to biphenyls with synthetically useful yields and regioselectivities. Only small amounts of doubly arylated products were observed. An adjustment of the general procedure to specific substrates was not necessary. Successful coupling reactions with tyrosine and phenylglycine showed that the aryl radical addition step was effective enough so that the reaction was not significantly impeded by hydrogen abstraction from benzylic positions. For the conversion of more lipophilic substrates, organic cosolvents, such as acetonitrile, can be added to the reaction mixture without a major decrease in product yield. Purification of the polar products was often difficult by column chromatography, but could, in most cases, be achieved by distillation, sublimation, or extraction. Not surprisingly, the best results in purification were obtained by employing preparative HPLC on reversed-phase columns. Since functionalized arylalkylamines and amino acids often appear as substructures in compounds possessing significant biological activity, our ongoing studies on radical arylation reactions focus on the application and establishment of this reliable methodology as a new tool for the synthesis of compound libraries for biological screening.[47]

## Experimental Section

**General**: Solvents and reagents were degassed with argon prior to use in radical reactions. $^1$H NMR spectra were recorded on 250, 360, and 600 MHz spectrometers with $CDCl_3$ and $CD_3OD$ as solvents referenced to $CHCl_3$ ($\delta = 7.26$ ppm) and $CHD_2OD$ ($\delta = 3.31$ ppm), respectively. Chemical shifts are reported in parts per million (ppm). Coupling constants ($J$) are in hertz. The following abbreviations are used for the description of signals: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quadruplet), and m (multiplet). $^{13}$C NMR spectra were recorded at 63, 91, and 151 MHz in $CDCl_3$ and $CD_3OD$ with the residual solvent $CHCl_3$ ($\delta = 77.0$ ppm) and $CHD_2OD$ ($\delta = 49.5$ ppm) as internal standards. Chemical shifts are given in parts per million (ppm). Analytical TLC was carried out on Merck silica-gel plates by using short wave (254 nm) UV light to visualize components. Silica gel (Kieselgel 60, 40–63 μm, Merck) was used for flash column chromatography. Purification by preparative HPLC was carried out by using a YMC ODS-A column (RP-18, 250 × 20 mm, 5 μm particle size, 12 nm pore size) and UV detection (Dionex P580, UVD-170U).

**General procedure for the radical arylation**

*Preparation of the arenediazonium chloride*: A degassed solution of sodium nitrite (1.38 g, 20.0 mmol) in water (10 mL) was added dropwise over a period of 10 min to an ice-cooled degassed solution of the aniline (20.0 mmol) in 3 N hydrochloric acid (20 mL) and water (20 mL). After stirring for a further 20 min at 0 °C, the clear solution was used for the biaryl coupling reactions (20 mmol/50 mL = 0.4 M).

*Biaryl coupling*: A 5 mL aliquot of the 0.4 M arenediazonium chloride solution (2 mmol) was added dropwise by using a syringe pump to a vigorously stirred solution of the substrate (10.0 mmol) in water (6 mL) and titanium(III) chloride (4 mL, approximately 1 M solution in 3 N hydrochloric acid, 4 mmol) under an argon atmosphere within 10–15 min. After the addition was complete, the mixture was left to stir for a further 10 min and a solution of sodium hydroxide (2.0 g) and sodium sulfite (2.0 g) in water (20 mL) was added. After extraction with diethyl ether or ethyl acetate (3 × 50 mL), the combined organic phases were washed with saturated aqueous sodium chloride and dried over sodium sulfate. Concentration in vacuo and purification by various methods (as described with each product) gave the desired biaryls.

***C*-(4′-Chloro-6-methoxybiphen-3-yl)methylamine (7)**: Compound **7** was prepared from **37** and **6** according to the general procedure described above. Purification by distillation in vacuo (approximately 0.03 mbar) at 120 °C gave **7** as an orange oil (312 mg, 1.26 mmol, 63 %) and unreacted **6** (875 mg, 6.38 mmol, 74 % of unconverted starting material). $R_f = 0.5$ ($CH_2Cl_2$/MeOH = 10:3 + 10 % AcOH); $^1$H NMR (250 MHz, $CDCl_3$): $\delta =$ 1.42 (s, 2H), 3.71 (s, 3H), 3.77 (s, 2H), 6.86 (d, $J = 8.3$ Hz, 1H), 7.14–7.22 (m, 2H), 7.28 (d, $J = 8.7$ Hz, 2H), 7.38 ppm (d, $J = 8.7$ Hz, 2H); $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta = 45.8$ ($CH_2$), 55.7 ($CH_3$), 111.3 (CH), 127.5 (CH), 128.1 (2 × CH), 129.4 ($C_q$), 129.6 (CH), 130.7 (2 × CH), 132.8 ($C_q$), 135.7 ($C_q$), 136.8 ($C_q$), 155.2 ppm ($C_q$); MS (EI): $m/z$ (%): 249 (32) [$^{37}$Cl–$M^+$], 248 (42), 247 (100) [$M^+$], 246 (73), 230 (18), 216 (55), 205 (55), 184 (9), 181 (12), 168 (16), 152 (23), 136 (41), 122 (14), 105 (13), 98 (17), 78 (27), 63 (27), 44 (56); HRMS (EI): $m/z$: calcd for $C_{14}H_{14}NO^{35}Cl$: 247.0764 [$M^+$]; found: 247.0758; calcd for $C_{14}H_{13}NO^{35}Cl$: 246.0686 [$M^+ - H$]; found: 246.0682.

**2-(4′-Chloro-6-methoxybiphen-3-yl)ethylamine (9)**: Compound **9** was prepared from **37** and **8** according to the general procedure described above. Purification by column chromatography (silica gel, $CH_2Cl_2$/MeOH/AcOH = 10:1:1) gave **9** as a colorless oil (267 mg, 1.02 mmol, 51 %). $R_f =$

0.3 ($CH_2Cl_2$/MeOH = 20:1 + 10% AcOH); $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 1.78 (s, 2H), 2.75 (t, $J$ = 6.8 Hz, 2H), 2.98 (t, $J$ = 6.8 Hz, 2H), 3.79 (s, 3H), 6.92 (d, $J$ = 8.2 Hz, 1H), 7.15–7.23 (m, 2H), 7.36 (d, $J$ = 7.8 Hz, 2H), 7.46 ppm (d, $J$ = 7.8 Hz, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$): $\delta$ = 38.9 ($CH_2$), 43.6 ($CH_2$), 55.7 ($CH_3$), 111.5 (CH), 128.1 (2×CH), 129.1 (CH), 129.4 ($C_q$), 130.8 (2×CH), 131.0 (CH), 132.0 ($C_q$), 132.9 ($C_q$), 136.9 ($C_q$), 154.9 ppm ($C_q$); MS (EI): $m/z$ (%): 263 (4) [$^{37}$Cl−$M^+$], 261 (9) [$^{35}$Cl−$M^+$], 234 (22), 233 (15), 232 (67), 220 (32), 206 (22), 205 (100), 181 (13), 145 (9), 83 (17), 57 (39), 43 (15); HRMS (EI): $m/z$: calcd for $C_{15}H_{16}{}^{35}ClNO$: 261.0920 [$M^+$]; found: 261.0915.

**2-(4′-Chloro-5-methoxybiphen-2-yl)ethylamine (9′)**: Colorless oil; $R_f$ = 0.4 ($CH_2Cl_2$/MeOH = 20:1 + 10% AcOH); $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 2.62–2.67 (m, 2H), 2.70–2.75 (m, 2H), 3.80 (s, 1H), 6.73 (d, $J$ = 2.7 Hz, 1H), 6.87 (dd, $J$ = 2.7, 8.4 Hz, 1H), 7.20 (d, $J$ = 8.4 Hz, 1H), 7.24 (d, $J$ = 8.4, 2H), 7.38 ppm (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (91 MHz, $CDCl_3$): $\delta$ = 36.4 ($CH_2$), 43.4 ($CH_2$), 55.3 ($CH_3$), 113.4 (CH), 115.4 (CH), 128.3 (2× CH), 129.2 ($C_q$), 130.4 (2×CH), 130.7 (CH), 133.0 ($C_q$), 140.1 ($C_q$), 142.0 ($C_q$), 157.7 ppm ($C_q$); MS (EI): $m/z$ (%): 261 (1) [$M^+$], 234 (32), 233 (21), 232 (100), 231 (18), 196 (28), 181 (12), 165 (18), 152 (24).

**2-(4,4″-Dichloro-5′-methoxy[1,1′;4′,1″]terphen-2′-yl)ethylamine (double arylation product of 8)**: Colorless oil; $R_f$ = 0.5 ($CH_2Cl_2$/MeOH = 20:1 + 10% AcOH); $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 2.66–2.80 (m, 4H), 3.79 (s, 3H), 6.79 (s, 1H), 7.21 (s, 1H), 7.30 (d, $J$ = 8.4 Hz, 2H), 7.39 (d, $J$ = 8.5 Hz, 2H), 7.41 (d, $J$ = 8.4 Hz, 2H), 7.50 ppm (d, $J$ = 8.5 Hz, 2H); MS (ESI) $m/z$: 374 [$^{37}$Cl$^{35}$Cl−$M^+$+H], 372 [$^{35}Cl_2$−$M^+$+H].

**2-(4′-Chloro-6-hydroxybiphen-3-yl)ethylamine (13)**: Compound **13** was prepared from **37** and **12** according to the general procedure described above. Excess **12** was removed by sublimation. The residue was dissolved in diluted hydrochloric acid, extracted twice with $Et_2O$, and basified to pH 10 with sodium carbonate. Extraction with EtOAc gave **13** along with the regioisomer **13′** (193 mg, 0.78 mmol, 39%). Separation of the regioisomers was achieved by preparative HPLC (MeOH/($H_2O$+0.1% $CF_3COOH$) = 50:50). Colorless oil; $R_f$ = 0.2 ($CH_2Cl_2$/MeOH/AcOH = 10:1:1); $^1$H NMR (360 MHz, $CD_3OD$): $\delta$ = 2.68 (t, $J$ = 6.9 Hz, 2H), 2.84 (t, $J$ = 6.3 Hz, 2H), 6.84 (d, $J$ = 8.1 Hz, 1H), 7.00 (dd, $J$ = 2.0, 8.1 Hz, 1H), 7.08 (brs, 1H), 7.34 (d, $J$ = 8.5 Hz, 2H), 7.54 ppm (d, $J$ = 8.5 Hz, 2H); $^1$H NMR (360 MHz, $CD_3OD$, regioisomer **13′**): $\delta$ = 2.60 (brs, 4H), 6.60 (d, $J$ = 2.5 Hz, 1H), 6.73 (dd, $J$ = 2.5, 8.6 Hz, 1H), 6.94 (d, $J$ = 8.6 Hz, 1H), 7.24 (d, $J$ = 8.4 Hz, 2H), 7.38 ppm (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (91 MHz, $CD_3OD$, mixture of regioisomers **13** and **13′**): $\delta$ = 36.5 ($CH_2$), 39.2 ($CH_2$), 43.9 ($CH_2$), 44.3 ($CH_2$), 116.4 (CH), 117.4 (CH), 118.3 (CH), 128.6 ($C_q$), 129.0 (CH), 129.3 (CH), 130.1 (CH), 131.7 (CH), 131.8 (CH), 131.9 (CH), 132.0 (CH), 133.4 ($C_q$), 133.9 ($C_q$), 139.1 ($C_q$), 142.1 ($C_q$), 143.2 ($C_q$), 154.3 ($C_q$), 157.9 ppm ($C_q$), (two $C_q$ signals missing due to overlap); MS (ESI): $m/z$: 248 [$M^+$+H]; HRMS (ESI): $m/z$: calcd for $C_{14}H_{15}{}^{35}ClNO$: 248.0837 [$M^+$+H]; found: 248.0830.

**5′-(2-Aminoethyl)-4,4″-dichloro-[1,1′;3′,1″]terphenyl-2′-ol (double arylation product of 12)**: Yellow oil; $R_f$ = 0.6 ($CH_2Cl_2$/MeOH/AcOH = 10:1:1); $^1$H NMR (360 MHz, $CD_3OD$): $\delta$ = 2.94 (t, $J$ = 7.5 Hz, 2H), 3.17 (t, $J$ = 7.5 Hz, 2H), 7.15 (s, 2H), 7.42 (d, $J$ = 8.3 Hz, 4H), 7.53 ppm (d, $J$ = 8.3 Hz, 4H); $^{13}$C NMR (91 MHz, $CD_3OD$): 34.1 ($CH_2$), 42.2 ($CH_2$), 129.5 (CH), 131.5 ($C_q$), 131.6 (CH), 132.2 (CH), 134.2 ($C_q$), 138.6 ($C_q$), 150.9 ppm ($C_q$) (one $C_q$ signal missing); MS (ESI): $m/z$: 360 [$^{37}$Cl$^{35}$Cl−$M^+$ +H], 358 [$^{35}Cl_2$−$M^+$+H].

**Methyl 2-amino-3-(4′-chloro-6-hydroxybiphen-3-yl)propanoate (15)**: Compound **15** was prepared from **37** and **14** according to the general procedure described above. Before threefold extraction with ethyl acetate, saturated aqueous sodium carbonate was used to adjust the pH of the crude mixture to a value of 9–10. After concentration in vacuo, the crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH = 10:1) to give **15** as a white solid (269 mg, 0.88 mmol, 44%) along with minor amount of its regioisomer. Separation of the regioisomers was achieved by preparative HPLC (MeOH/($H_2O$+0.1% $CF_3COOH$) = 50:50). $R_f$ = 0.4 ($CH_2Cl_2$/MeOH = 10:1); $^1$H NMR (360 MHz, $CD_3OD$): $\delta$ = 2.94 (dd, $J$ = 6.0, 13.9 Hz, 1H), 3.02 (dd, $J$ = 7.0, 13.9 Hz, 1H), 3.71 (s, 3H), 3.83 (dd, $J$ = 6.0, 7.0 Hz, 1H), 6.85 (d, $J$ = 8.3 Hz, 1H), 7.01 (dd, $J$ = 2.2, 8.6 Hz, 1H), 7.09 (d, $J$ = 2.2 Hz, 1H), 7.37 (d, $J$ = 8.6 Hz, 2H), 7.54 ppm (d, $J$ = 8.6 Hz, 2H); $^{13}$C NMR (91 MHz, $CD_3OD$): $\delta$ = 39.9 ($CH_2$), 49.9 ($CH_3$), 56.4 (CH), 117.3 (CH), 128.6 ($C_q$), 128.7 ($C_q$), 129.0 (CH), 130.7 (CH), 131.9 (CH), 132.4 (CH), 133.6 ($C_q$), 138.7 ($C_q$), 154.6 ($C_q$), 175.3 ppm ($C_q$); MS (ESI): $m/z$: 306 [$^{35}$Cl−$M^+$ +H]; MS (EI): $m/z$ (%): 307 (3) [$^{37}$Cl−$M^+$], 305 (8) [$^{35}$Cl−$M^+$], 248 (4) [$^{37}$Cl−$M^+$−59], 246 (10) [$^{35}$Cl−$M^+$−59], 219 (42) [$^{37}$Cl−$M^+$−88], 217 (100) [$^{35}$Cl−$M^+$−88], 181 (15), 152 (10), 136 (10), 107 (58), 88 (58), 70 (9), 57 (21), 43 (60); HRMS (EI): $m/z$: calcd for $C_{16}H_{16}NO_3{}^{35}Cl$: 305.0819 [$M^+$]; found: 305.0806.

**Methyl 2-amino-2-(4′-chloro-6-hydroxybiphen-3-yl)acetate (17)**: Compound **17** was prepared from **37** and **16** according to the general procedure described above. Before threefold extraction with ethyl acetate, saturated aqueous sodium carbonate was used to adjust the pH of the crude mixture to a value of 9–10. After concentration in vacuo the crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH = 10:1) to give **17** as a colorless solid (333 mg, 1.14 mmol, 57%). $R_f$ = 0.4 ($CH_2Cl_2$/MeOH = 10:1); $^1$H NMR (360 MHz, $CD_3OD$): $\delta$ = 3.71 (s, 3H), 4.63 (s, 1H), 6.90 (d, $J$ = 8.4 Hz, 1H), 7.20 (dd, $J$ = 2.4, 8.4 Hz, 1H), 7.29 (d, $J$ = 2.4 Hz, 1H), 7.38 (d, $J$ = 8.7 Hz, 2H), 7.55 ppm (d, $J$ = 8.7 Hz, 2H); $^{13}$C NMR (90.6 MHz, $CD_3OD$): $\delta$ = 53.0 (CH), 58.6 ($CH_3$), 117.4 (CH), 128.8 (CH), 128.9 ($C_q$), 129.1 (2×CH), 130.5 (CH), 131.0 ($C_q$), 131.9 (2×CH), 133.8 ($C_q$), 138.5 ($C_q$), 155.8 ($C_q$), 175.0 ppm ($C_q$); MS (EI): $m/z$ (%): 293 [$^{37}$Cl−$M^+$] (1), 291 [$^{35}$Cl−$M^+$] (2), 234 [$^{37}$Cl−$M^+$ −59] (35), 232 [$^{35}$Cl−$M^+$−59] (100), 205 (6), 187 (3), 170 (9), 152 (13), 141 (6), 122 (11), 116 (5), 98 (11), 43 (16); HRMS (EI): $m/z$: calcd for $C_{13}H_{11}NO^{35}Cl$: 232.0529 [$M^+$−59]; found: 232.0522.

**2-(4-Chlorophenyl)furan (20)**:[48] Compound **20** was prepared from **37** and furan according to the general procedure described above. Purification by distillation in vacuo gave **20** as a light yellow oil (306 mg, 1.72 mmol, 86%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 6.47 (dd, $J$ = 1.8, 3.4 Hz, 1H), 6.64 (dd, $J$ = 0.7, 3.4 Hz, 1H), 7.35 (d, $J$ = 8.8 Hz, 2H), 7.47 (dd, $J$ = 0.7, 1.8 Hz, 1H), 7.60 ppm (d, $J$ = 8.8 Hz, 2H); $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$ = 105.4 (CH), 111.8 (CH), 125.0 (2×CH), 128.9 (2× CH), 129.4 ($C_q$), 133.0 ($C_q$), 142.3 (CH), 152.9 ppm ($C_q$); All analytical data are in agreement with those reported in ref. [48].

***C*-(5-(4-Chlorophenyl)furan-2-yl)methylamine (21)**: Compound **21** was prepared from **37** and **19** according to the general procedure described above. Purification by distillation in vacuo gave **21** as an orange solid (305 mg, 1.47 mmol, 74%). $R_f$ = 0.4 ($CH_2Cl_2$/MeOH/AcOH = 10:1:1); $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 1.56 (s, 2H), 3.88 (s, 2H), 6.22 (d, $J$ = 3.3 Hz, 1H), 6.56 (d, $J$ = 3.3 Hz, 1H), 7.34 (d, $J$ = 8.6 Hz, 2H), 7.57 ppm (d, $J$ = 8.6 Hz, 2H); $^{13}$C NMR (91 MHz, $CDCl_3$): $\delta$ = 39.5 ($CH_2$), 106.1 (CH), 107.4 (CH), 124.8 (2×CH), 128.8 (2×CH), 129.4 ($C_q$), 132.7 ($C_q$), 152.0 ($C_q$), 156.8 ppm ($C_q$); MS (EI): $m/z$ (%): 209 (29) [$^{37}$Cl−$M^+$], 208 (24), 207 (80) [$^{35}$Cl−$M^+$], 206 (47), 193 (18), 192 (38), 191 (58), 190 (100), 149 (12), 139 (18), 128 (24), 111 (16), 96 (42), 78 (8), 68 (80); HRMS (EI): $m/z$: calcd for $C_{11}H_{10}NO^{35}Cl$: 207.0451 [$M^+$]; found: 207.0449.

**Methyl 4-(furan-2-yl)benzoate (23)**[49] was prepared from methyl 4-aminobenzoate and **18** by using the modified procedure described below.

*Preparation of the arenediazonium chloride*: A degassed solution of sodium nitrite (0.69 g, 10.0 mmol) in water (5 mL) was added dropwise over 10 min to an ice-cooled degassed solution of methyl 4-aminobenzoate (1.51 g, 10.0 mmol) in 3 N hydrochloric acid (10 mL), water (10 mL), and acetonitrile (4 mL). After stirring for a further 20 min at 0 °C, the light yellow solution was used for the biaryl coupling reactions (10 mmol/29 mL = 0.35 M).

*Biaryl coupling*: A 5.8 mL aliquot of the arenediazonium chloride solution (0.35 M, 2 mmol) was added dropwise by using a syringe pump to a vigorously stirred solution of **18** (10.0 mmol) in water (6 mL) with titanium(III) chloride (4 mL, of an approximately 1 M solution in 3 N hydrochloric acid, 4 mmol) under argon atmosphere within 10–15 min. After the addition was complete, the mixture was left to stir for a further 10 min and the pH was adjusted to a value of 9–10 with saturated aqueous sodium carbonate. After extraction with diethyl ether (2×50 mL) and ethyl acetate (2×50 mL), the combined organic phases were washed with saturated aqueous sodium chloride and dried over sodium sulfate. Purification by distillation in vacuo gave the light orange solid **23** (336 mg, 1.66 mmol, 83%). Orange solid; $R_f$ = 0.8 (ethyl acetate);

$^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 3.92 (s, 3H), 6.49–6.51 (m, 1H), 6.79 (d, $J$ = 3.3 Hz, 1H), 7.52 (brs, 1H), 7.73 (d, $J$ = 8.7 Hz, 2H), 8.05 ppm (d, $J$ = 8.7 Hz, 2H); $^{13}$C NMR (91 MHz, $CDCl_3$): $\delta$ = 52.1 ($CH_3$), 107.2 (CH), 112.0 (CH), 123.4 (2×CH), 128.5 ($C_q$), 130.1 (2×CH), 134.8 ($C_q$), 143.1 (CH), 152.9 ($C_q$), 166.8 ppm ($C_q$); MS (EI): $m/z$ (%): 203 (11), 202 (78), 172 (12), 171 (100), 143 (15), 115 (33). All analytical data are in agreement with those reported in ref. [49].

**Methyl 4-(5-methylfuran-2-yl)benzoate (25)**:[50] Compound **25** was prepared from methyl 4-aminobenzoate and **24** according to the modified procedure described for the preparation of **23**. To increase the solubility of **24** in the aqueous phase, $CH_3CN$ (18 mL) was added. Purification by distillation in vacuo gave **25** as a brown solid (342 mg, 1.58 mmol, 80%). $R_f$ = 0.7 (pentane/ethyl acetate = 10:1); $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 2.22 (d, $J$ = 0.7 Hz, 3H), 3.75 (s, 3H), 5.94 (dd, $J$ = 3.3, 0.7 Hz, 1H), 6.52 (d, $J$ = 3.3 Hz. 1H), 7.51 (d, $J$ = 8.7 Hz, 1H), 7.87 ppm (d, $J$ = 8.7 Hz, 1H); $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$ = 13.5 ($CH_3$), 51.7 ($CH_3$), 108.1 (CH), 108.2 (CH), 122.5 (2×CH), 127.6 ($C_q$), 129.8 (2×CH), 134.8 ($C_q$), 151.0 ($C_q$), 153.0 ($C_q$), 166.6 ppm ($C_q$); MS (EI): $m/z$ (%): 216 (100), 185 (88), 157 (13), 128 (23). All analytical data are in agreement with those reported in ref. [50].

***C*-(5-(4-Methoxyphenyl)furan-2-yl)methylamine (27)**: Compound **27** was prepared from *p*-anisidine and **19** according to the modified procedure described for the preparation of **23**. Purification by distillation in vacuo gave **27** as an orange solid (210 mg, 1.03 mmol, 52%). $R_f$ = 0.5 ($CH_2Cl_2$/MeOH/AcOH = 10:1:1); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 3.83 (s, 3H), 3.86 (s, 2H), 6.18 (d, $J$ = 2.9 Hz, 1H), 6.43 (d, $J$ = 3.0 Hz, 1H), 6.91 (d, $J$ = 8.6 Hz, 2H), 7.58 ppm (d, $J$ = 8.6 Hz, 2H); $^{13}$C NMR (150.9 MHz, $CDCl_3$): $\delta$ = 39.5 ($CH_2$), 55.3 ($CH_3$), 104.0 (CH), 107.1 (CH), 114.1 (2×CH), 124.1 ($C_q$), 125.0 (2×CH), 153.1 ($C_q$), 155.7 ($C_q$), 158.9 ppm ($C_q$); MS (EI): $m/z$ (%): 204 (14), 203 (100) [$M^+$], 202 (32), 188 (12), 187 (87), 186 (46), 159 (10), 145 (11), 144 (12), 135 (12), 96 (10), 85 (10), 83 (15), 68 (25); HRMS (EI): $m/z$: calcd for $C_{12}H_{13}NO_2$: 203.0946 [$M^+$]; found: 203.0946.

**Methyl 4-(benzofuran-2-yl)benzoate (29)**[51] was prepared from methyl 4-aminobenzoate and **28** according to the modified procedure described for the preparation of **23**. To increase the solubility of **28** in the aqueous phase $CH_3CN$ (18 mL) was added. Purification by column chromatography (silica gel, pentane/ethyl acetate = 10:1) gave **29** as a white solid (199 mg, 0.79 mmol, 39%). $R_f$ = 0.6 (pentane/ethyl acetate = 10:1); $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 3.80 (s, 3H), 6.99 (s, 1H), 7.38–7.45 (m, 4H), 7.77 (d, $J$ = 8.63, 1H), 7.97 ppm (d, $J$ = 8.63, 1H); $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$ = 52.1 ($CH_3$), 103.4 (CH), 111.3 (CH), 121.2 (CH), 123.2 (CH), 124.5 (2×CH), 125.0 (CH), 128.3 ($C_q$), 129.6 ($C_q$), 130.1 (2×CH), 134.4 ($C_q$), 154.6 ($C_q$), 155.1 ($C_q$), 166.6 ($C_q$); MS (EI): $m/z$ (%): 252 (100), 221 (57), 193 (10), 165 (31), 110 (8), 82 (10). All analytical data are in agreement with those reported in ref. [51].

**Methyl 4-(indol-2-yl)benzoate (31)**:[52] Compound **31** was prepared from methyl 4-aminobenzoate and **30** according to the modified procedure described for the preparation of **23**. White solid; $R_f$ = 0.3 (pentane/ethyl acetate = 6:1); $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 3.96 (s, 3H), 6.97 (s, 1H), 7.14 (t, $J$ = 7.6 Hz, 1H), 7.23 (t, $J$ = 7.5 Hz, 1H), 7.42 (d, $J$ = 8.0 Hz, 1H), 7.67 (d, $J$ = 7.9 Hz, 1H), 7.76 (d, $J$ = 8.3 Hz, 2H), 8.11 (d, $J$ = 8.3 Hz, 2H), 8.67 ppm (brs, 1H); $^{13}$C NMR (91 MHz, $CDCl_3$): $\delta$ = 52.0 ($CH_3$), 101.3 (CH), 111.2 (CH), 120.8 (CH), 122.5 (CH), 123.3 (CH), 124.7 (2×CH), 128.9 ($C_q$), 130.1 (2×CH), 133.0 ($C_q$), 136.7 ($C_q$), 137.5 ($C_q$), 146.1 ($C_q$), 166.7 ppm ($C_q$); MS (EI): $m/z$ (%): 251 (100), 220 (23), 192 (28), 165 (13), 96 (14); All analytical data are in agreement with those reported in ref. [52].

**6-Amino-3,4-benzocoumarin (33)**:[53] $NaNO_2$ (20 mmol, 1.38 g) in degassed water (10 mL) was added to a solution of methyl anthranilate (**35**) (20 mmol, 3.02 g) in degassed water (20 mL) and hydrochloric acid (3 N, 20 mL) over a period of 10 min at 0 °C. The solution was left to stir for further 10 min at 0 °C. A 50 mL aliquot of the arenediazonium chloride solution (0.4 M) was added to a solution of 4-aminophenol (**36**; 100 mmol, 10.9 g) in degassed water (160 mL) with titanium(III) chloride (40 mmol, 40 mL, of an approximately 1 M solution in 3 N hydrochloric acid) dropwise at room temperature over a period of 15 min. After the addition was complete the solution was left to stir for 10 min. The solution was basified (pH 10) with $Na_2CO_3$ and aqueous $NH_3$ (25%). After extraction with ethyl acetate (2×50 mL), the combined organic phases were washed with brine and dried over sodium sulfate. Concentration in vacuo and purification by column chromatography (EtOAc/pentane = 1:1→ethyl acetate) gave **33** as a light yellow solid (1.50 g, 7.11 mmol, 36%). $R_f$ = 0.3 (pentane/EtOAc = 1:1); $^1$H NMR (360 MHz, $CDCl_3$/$(CD_3)_2SO$): $\delta$ = 6.00 (dd, $J$ = 2.7, 8.7 Hz, 1H), 6.29 (d, $J$ = 8.7 Hz, 1H), 6.49 (d, $J$ = 2.7 Hz, 1H), 6.67–6.72 (m, 1H), 6.93 (ddd, $J$ = 1.4, 7.3, 8.1 Hz, 1H), 7.71 (d, $J$ = 8.1 Hz, 1H), 7.47 ppm (ddd, $J$ = 0.6, 1.4, 8.0 Hz, 1H); $^{13}$C NMR (91 MHz, $CDCl_3$/$(CD_3)_2SO$): $\delta$ = 98.2 (CH), 108.8 (CH), 109.0 ($C_q$), 109.1 (CH), 111.6 ($C_q$), 112.2 (CH), 119.2 (CH), 120.8 (CH), 125.3 (CH), 125.4 ($C_q$), 133.8 ($C_q$), 135.0 ($C_q$), 152.6 ppm ($C_q$). All analytical data are in agreement with those reported in ref. [53].

**(4′-Chloro-6-methoxybiphen-3-ylmethyl)(1-phenylethyl)amine (39)**: Compound **7** was prepared from **2** (8.00 mmol) and **6** (5.49 g, 40.0 mmol) according to the general procedure described above (4-fold quantities). Purification by distillation in vacuo (approximately 0.03 mbar) at 120 °C gave **7** along with minor amounts of remaining benzylamine **6**. A flame-dried round-bottomed flask was charged with molecular sieves (3 Å, 6 g) and dry $CH_2Cl_2$ (10 mL). Acetophenone (**38**; 1.18 g, 9.81 mmol) and biarylamine **7** (1.62 g, 6.54 mmol) were added under argon and the resulting mixture was stirred for 6 d in the presence of *p*-toluenesulfonic acid (92.0 mg, 0.53 mmol). The molecular sieves were separated from the mixture by filtration and the solvent was removed under reduced pressure. Without further purification, the intermediate imine was dissolved in dry diethyl ether (20 mL) and added to a solution of $LiAlH_4$ (1.25 g, 32.7 mmol) in dry diethyl ether (280 mL). After heating at reflux for 19 h under argon the reaction mixture was cooled to 0 °C and was quenched with acetone and water. The solution was extracted with diethyl ether (3×200 mL). The combined organic phases were washed with water (200 mL) and saturated aqueous sodium chloride (200 mL) and were dried over $Na_2SO_4$. After removing the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH = 10:1). Biarylamine **39** (1.13 g, 3.20 mmol, 40%) was obtained as a colorless solid along with minor amounts of (4-methoxybenzyl)(1-phenylethyl)amine. Separation of the byproduct was achieved by preparative HPLC (MeOH/($H_2O$+0.1% $CF_3COOH$) = 60:40). $R_f$ = 0.6 ($CH_2Cl_2$/MeOH = 10:1); $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 1.28 (d, $J$ = 6.8 Hz, 3H), 1.96–2.05 (m, 1H), 3.58–3.67 (m, 2H), 3.65 (s, 3H), 4.10–4.20 (m, 1H), 6.79 (d, $J$ = 9.0 Hz, 1H), 7.17 (d, $J$ = 7.2 Hz, 2H), 7.29 (d, $J$ = 8.6 Hz, 2H), 7.35 (d, $J$ = 8.6 Hz, 2H), 7.36–7.45 ppm (m, 5H); $^{13}$C NMR (91 MHz, $CDCl_3$) $\delta$ = 20.0 ($CH_3$), 49.1 ($CH_2$), 55.7 ($CH_3$), 58.5 (CH), 111.6 (CH), 123.2 ($C_q$), 127.9 (2×CH), 128.4 (2×CH), 129.5 (CH), 129.6 (2×CH), 129.81 ($C_q$), 130.9 (2×CH), 131.1 (CH), 132.80 (CH), 133.4 ($C_q$), 136.0 ($C_q$), 136.4 ($C_q$), 157.2 ppm ($C_q$); MS (ESI): $m/z$: 352 [$^{35}$Cl−$M^+$+H]; HRMS (ESI): $m/z$: calcd for $C_{22}H_{23}{}^{35}ClNO$: 352.1463 [$M^+$+H]; found: 352.1452; HRMS (EI): $m/z$: calcd for $C_{22}H_{22}{}^{35}ClNO$: 351.1390 [$M^+$]; found: 351.1379.

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