Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 2657–2663

# Synthesis of biphenylamines via Suzuki–Miyaura cross-coupling reactions

Anna M. Maj, Lionel Delaude,* Albert Demonceau and Alfred F. Noels

*Center for Education and Research on Macromolecules (CERM), Institut de Chimie (B6a), Université de Liège, Sart-Tilman par B-4000 Liège, Belgium*

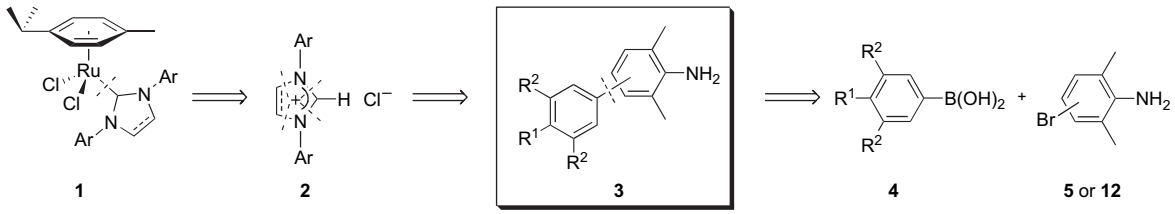
Received 8 December 2006; revised 10 January 2007; accepted 14 January 2007
Available online 17 January 2007

**Abstract**—A small library of *meta*- and *para*-biphenylamines substituted by various alkyl, alkoxy, phenoxy, or halogeno groups on their aromatic rings was synthesized via Suzuki–Miyaura cross-coupling between bromoanilines and arylboronic acids using palladium catalysts. The experimental conditions were carefully adjusted to accommodate a wide range of substituents, in terms of electron-withdrawing or -donating ability and steric bulk. In some cases, protection and deprotection of the amine function via its trifluoroacetamide were added to the reaction sequence in order to facilitate the cross-coupling step.


## 1. Introduction

Structural motives derived from the biphenyl ring system are present in several types of organic compounds, including natural products, polymers, liquid crystals, advanced materials and medicinal drugs.[1] The wide variety of physical and chemical properties available by changing the nature of the substituents on the two aromatic cycles also makes them very attractive ligand components for the fine-tuning of catalysts in organometallic chemistry. In the course of our investigations towards ruthenium–arene complexes bearing *N*-heterocyclic carbene (NHC) ligands (**1**) as catalyst precursors for various organic transformations,[2] we became interested in the synthesis of a small library of imidazolium and imidazolinium salts (**2**) bearing biphenyl units that would differ by the electron-withdrawing or -donating nature and the steric bulk of substituents introduced on different *meta*- and *para*-positions of the remote phenyl rings. To avoid any *ortho*-metallation effect, we also chose to block both *ortho*-positions of the aromatic rings in the vicinity of the metal centre by methyl groups.

Retrosynthetic analysis indicated that the most straightforward access to the target catalyst precursors involved aptly substituted biphenylamines (**3**) as key intermediates (Scheme 1). From a practical point of view, the assembly of these building blocks is often achieved via cross-coupling of two monocyclic units. Among the various methodologies available to accomplish this type of transformation,[3] we elected the Suzuki–Miyaura reaction, one of the most popular and powerful method for the junction of aryl–aryl and aryl–heteroaryl moieties.[4] Thanks to its compatibility with a variety of functional groups, the stability and the commercial availability of a wide range of organoboron starting materials, and the ease of working up the reaction mixtures, this methodology has found many applications both in research laboratories and for large-scale industrial processes.[5,6]




**Scheme 1**. Retrosynthetic pathway showing the formation of biphenylamines **3** via Suzuki–Miyaura cross-coupling.

*Keywords*: Amines; Biaryls; Cross-coupling; Homogeneous catalysis; Palladium.
* Corresponding author. Tel.: +32 4 3663496; fax: +32 4 3663497; e-mail: l.delaude@ulg.ac.be

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.01.023

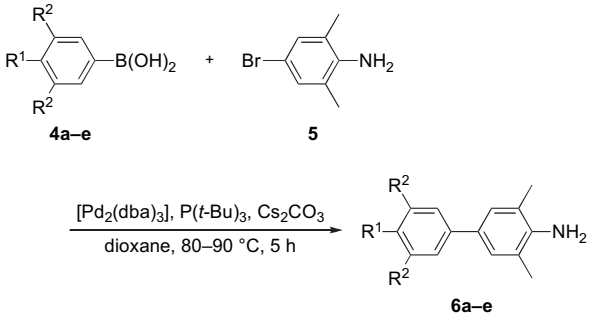
Two commercially available bromoanilines were identified as suitable starting materials for the synthesis of *para*- and *meta*-biphenylamines **3**, namely 4-bromo-2,6-dimethylaniline (**5**) and 3-bromo-2,4,6-trimethylaniline (**12**). In this contribution, we report on their reaction with various arylboronic acids to afford 3,5-dimethyl-4-aminobiphenyl and 2,4,6-trimethyl-3-aminobiphenyl derivatives, respectively, via Suzuki–Miyaura cross-coupling.

## 2. Results and discussion

### 2.1. Cross-coupling of 4-bromo-2,6-dimethylaniline with arylboronic acids

Significant improvements were made over the years to the initial catalytic system reported by Suzuki and Miyaura for the coupling of haloarenes with phenylboronic acid.[7] Yet, to the best of our knowledge, only a few reports describe catalysts that show tolerance to the amino group.[8–13] Applying Fu's conditions ($Pd_2(dba)_3$ (dba=dibenzylideneacetone), tri-*tert*-butylphosphine and cesium carbonate)[8] to the reaction of 4-bromo-2,6-dimethylaniline (**5**) with 3,5-difluorophenylboronic acid (**4a**), 3,5-bis(trifluoromethyl)phenylboronic acid (**4b**), or 4-methoxyphenylboronic acid (**4c**) afforded the corresponding biphenylamines in moderate to good yields (Table 1). However, when 4-phenoxyphenylboronic acid (**4d**) and 4-*tert*-butylphenylboronic acid (**4e**) were reacted with **5** under the same conditions (1.5 mol % $Pd_2(dba)_3$, 3.6 mol % P(*t*-Bu)$_3$, 1.1 equiv $Cs_2CO_3$), only traces of the desired coupling products were obtained. This discrepancy underscores the beneficial influence of electron-withdrawing groups on the reactivity of phenylboronic acid under the experimental conditions adopted. It was an unexpected observation, since the $Pd_2(dba)_3$/P(*t*-Bu)$_3$ catalytic system usually remains largely unaffected by electronic variations within the arylboronic acid component.[8] The difficulties encountered here are probably related to the electron-rich nature of 4-bromo-2,6-dimethylaniline (**5**). Indeed, oxidative addition is known to proceed much slower for aryl halides possessing an electron-donating group in the 2- or 4-position of the arene relative to halide.[14]

**Table 1**. Suzuki–Miyaura cross-coupling of various arylboronic acids (**4a–e**) with 4-bromo-2,6-dimethylaniline (**5**)




| Substrate | $R^1$ | $R^2$ | Product | Isolated yield (%) |
|---|---|---|---|---|
| **4a** | H | F | **6a** | 65 |
| **4b** | H | $CF_3$ | **6b** | 82 |
| **4c** | OMe | H | **6c** | 53 |
| **4d** | OPh | H | **6d** | Traces |
| **4e** | *t*-Bu | H | **6e** | Traces |

**Table 2**. Suzuki–Miyaura cross-coupling of 4-*tert*-butylphenylboronic acid (**4e**) with 4-bromo-2,6-dimethylaniline (**5**)[a]

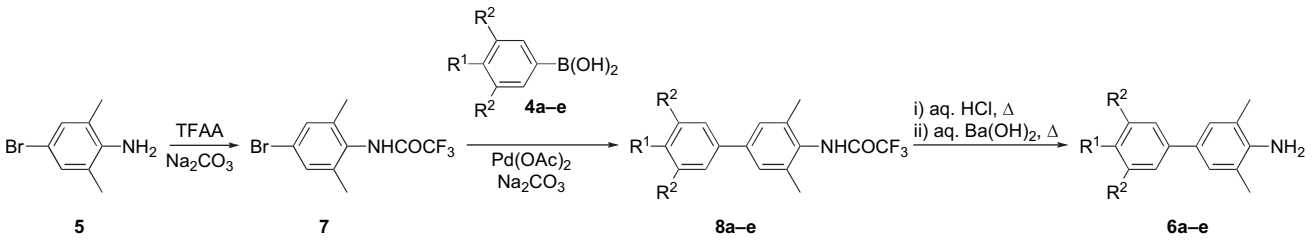
| Entry | Catalyst | Ligand | Base | Solvent | Isolated yield of **6e** (%) |
|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | — | $Na_2CO_3$ | $CH_3OH$ | 0 |
| 2 | $Pd(OAc)_2$ | $PPh_3$ | 2 M aq $Na_2CO_3$ | $PhCH_3$ | 18 |
| 3 | $Pd(PPh_3)_4$ | — | $Et_3N$ | $CH_3CN$ | 0 |
| 4 | $Pd(PPh_3)_4$ | — | 2 M aq $Na_2CO_3$ | $PhCH_3$ | 48 |

[a] Reactions conditions: 4-bromo-2,6-dimethylaniline (**5**) (0.1 g, 0.5 mmol), 4-*tert*-butylphenylboronic acid (**4e**) (0.1 g, 0.56 mmol), 3 mol % of catalyst, 0–12% of ligand, 1.2 equiv of base, solvent (20 mL) and 24 h reflux under an inert atmosphere.

Looking for a more versatile and efficient catalytic system suitable for coupling an electron-rich aniline with phenylboronic acids bearing electron-donating as well as electron-withdrawing substituents, we tried to optimize the coupling of 4-bromo-2,6-dimethylaniline (**5**) with 4-*tert*-butylphenylboronic acid (**4e**) using the classical Suzuki–Miyaura cross-coupling catalysts $Pd(OAc)_2/PPh_3$ and $Pd(PPh_3)_4$. The main results of this study are summarized in Table 2. The combination of $Pd(PPh_3)_4$ and 2 M aqueous $Na_2CO_3$ under biphasic conditions afforded the most efficient catalytic system and the tetrakis(triphenylphosphino)palladium(0) complex always outperformed palladium(II) acetate, whether or not the latter salt was activated with triphenylphosphine (compare entries 2 and 4, for instance). Yet, the yield of the desired coupling product **6e** remained far from quantitative even when the reaction was carried out in refluxing toluene instead of benzene in an attempt to increase the rate of oxidative addition (entry 4). TLC analyses revealed that consumption of the starting materials was not complete even after prolonged reaction times (up to 24 h). We also observed the decomposition of the catalyst into palladium black and the formation of a few by-products. Although these were not characterized, it is known that self-coupling, dehalogenation, or deboronation products are commonly observed in Suzuki reactions. Furthermore, the use of $Pd(PPh_3)_4$ often leads to phosphine-bound aryl derivatives.[6c] Catalyst poisoning by the free aniline function present in compound **5** should also be considered, as it would explain the consistently poor results obtained, despite our numerous attempts to optimize the classical Suzuki–Miyaura cross-coupling catalysts and conditions.

### 2.2. Cross-coupling of *N*-(4-bromo-2,6-dimethylphenyl)-2,2,2-trifluoroacetamide with arylboronic acids

The possible deleterious interaction between the amino group of 4-bromo-2,6-dimethylaniline and palladium(0) during the catalytic cycle was circumvented by protecting compound **5** via its trifluoroacetamide.[15] Thus, treatment of a diethyl ether solution of **5** with an excess of trifluoroacetic anhydride (TFAA) in the presence of sodium carbonate afforded a quantitative conversion to *N*-(4-bromo-2,6-dimethylphenyl)-2,2,2-trifluoroacetamide (**7**) within 40 min at 0 °C (Scheme 2).[16,17] This intermediate was isolated in pure form and subsequently coupled with 1.1 equiv of an arylboronic acid in methanol as solvent using palladium(II) acetate as catalyst (5 mol %) and sodium carbonate as a base. The Suzuki reactions were carried out under sonochemical irradiation in an ultrasonic cleaning bath operating at




**Scheme 2**. Multi-step synthesis of 3,5-dimethyl-4-biphenylamines (**6a–e**) via Suzuki–Miyaura cross-coupling.

50 kHz.[18] This phosphineless procedure required only a very simple catalytic system made of commercially available components and led to the protected biaryl coupling products **8a–e** under rather mild conditions within 4 h. A final deprotection step of the aniline function with concentrated aqueous hydrochloric acid, followed by neutralization with barium hydroxide led to a range of *meta*- or *para*-substituted 3,5-dimethyl-4-biphenylamines (**6a–e**) (Scheme 2).

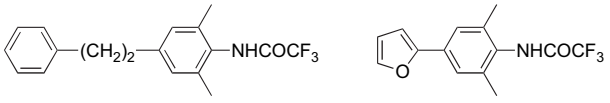
The experimental results summarized in Table 3 underscore once again the strong influence of substituents on the reactivity of arylboronic acids in our Suzuki–Miyaura cross-coupling experiments. In the ligandless procedure, the *para*-methoxy electron-donating group present in substrate **4c** led to a high yield of coupling product with **7**, while the two electron-withdrawing substituents in **4a** and **4b** (*meta*-fluoro and *meta*-trifluoromethyl, respectively) reduced the reaction rate and led to lower yields of biaryl products. There was also a significant difference of reactivity between 4-methoxyphenylboronic acid (**4c**) and 4-phenoxyphenylboronic acid (**4d**). The latter substrate afforded a much lower yield of coupling product than the former, a trend already observed in Table 1.

A survey of the literature confirmed that although fluorinated biaryls are highly demanded for medical applications, their synthesis via Suzuki–Miyaura cross-coupling of fluorinated precursors remains notoriously difficult and usually requires specific non-commercial ligands. Electron-poor arylboronic acids are less nucleophilic and undergo the transmetallation step at a slower rate than their electron-neutral or electron-rich counterparts.[14] Additionally, they are prone to homocoupling[19,20] and to metal-catalyzed protodeboronation.[21] Thus, the poor results obtained in the cross-coupling of fluorinated phenylboronic acids with **7** may be ascribed to a more easy decomposition of boronic acids **4a** and **4b** compared to **4c–e**. The low reaction rates observed in some cases with arylboronic acids bearing electron-withdrawing groups could also arise from catalyst poisoning by the impurities or the functional groups present in the starting materials.[22]

**Table 3**. $Pd(OAc)_2/Na_2CO_3$-catalyzed Suzuki–Miyaura cross-coupling of various arylboronic acids (**4a–e**) with *N*-(4-bromo-2,6-dimethylphenyl)-2,2,2-trifluoroacetamide (**7**)

| Substrate | $R^1$ | $R^2$ | Suzuki–Miyaura cross-coupling | | Deprotection step | |
|---|---|---|---|---|---|---|
| | | | Product | Isolated yield (%) | Product | Isolated yield (%) |
| **4a** | H | F | **8a** | 34 | **6a** | 64 |
| **4b** | H | $CF_3$ | **8b** | 38 | **6b** | 60 |
| **4c** | OMe | H | **8c** | 90 | **6c** | 81 |
| **4d** | OPh | H | **8d** | 31 | **6d** | 54 |
| **4e** | *t*-Bu | H | **8e** | 74 | **6e** | 67 |

To widen our set of NHC ligand precursors, we have attempted to further synthesize two *para*-substituted 2,6-dimethylanilines that could be used to generate new imidazolium and imidazolinium salts. First, we reasoned that inserting an ethylene bridge between two phenyl rings, as depicted in structure **9**, should result in a higher flexibility of the aryl substituents and could favour additional coordination to a metal centre. Also, adding a furan group onto the *para*-position of a phenyl ring (see structure **10**) could have a significant influence on the electronic properties and solubility of the carbene ligand derived thereof. Therefore, we investigated various catalytic systems susceptible of promoting the Suzuki–Miyaura cross-coupling of *N*-(4-bromo-2,6-dimethylphenyl)-2,2,2-trifluoroacetamide (**7**) with phenethylboronic acid and 2-furanboronic acid. Since recourse to $Pd(OAc)_2$ and $Na_2CO_3$ in MeOH under ultrasound irradiation as described above did not give any satisfactory results, additional experiments were carried out under conventional heating conditions with $Pd(OAc)_2$/IMes·HCl/$Cs_2CO_3$ (IMes·HCl is 1,3-dimesitylimidazolium chloride),[23] $Pd_2(dba)_3$/IMes·HCl/$Cs_2CO_3$[23] and $[Pd(allyl)Cl]_2$/IMes·HCl/KO-*t*-Bu in dioxane,[24] with $PdCl_2$(dppf)/aqueous $Na_2CO_3$ in DMF[25] (dppf is 1,1′-bis(diphenylphosphino)-ferrocene) or with Pd/C/$Et_3N$ in EtOH.[26] Unfortunately and rather surprisingly, none of these reactions afforded the desired coupling product **9** or **10**.

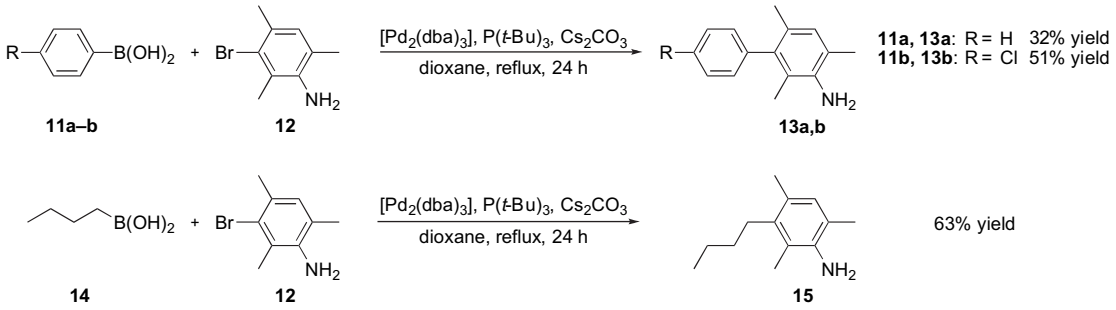



**9** **10**

## 2.3. Cross-coupling of 3-bromo-2,4,6-trimethylaniline with alkyl- or arylboronic acids

In order to extend our library of 4-aminobiphenyl derivatives with some 3-biphenylamine isomers, we have substituted 3-bromo-2,4,6-trimethylaniline (**12**) for 4-bromo-2,6-dimethylaniline (**5**) as the coupling partner with various alkyl- or arylboronic acids in Suzuki reactions. The choice of this particular *meta*-bromoaniline was dictated by its commercial availability and by the presence of protecting methyl groups on both positions *ortho* to the amino function, a feature required to prevent later *ortho*-metallation of the catalyst.

The cross-coupling reactions were performed on the non-protected aniline in the presence of 5 mol % $Pd_2(dba)_3$,




**Scheme 3**. Suzuki–Miyaura cross-coupling of various alkyl- or arylboronic acids with 3-bromo-2,4,6-trimethylaniline (**12**).

12 mol % P(*t*-Bu)$_3$ and 1.2 equiv $Cs_2CO_3$ using slightly modified Fu's conditions (24 h reaction in refluxing dioxane).[8] Two arylboronic acids were investigated in this series of experiments, namely phenylboronic acid (**11a**) and 4-chloro-phenylboronic acid (**11b**). They led to the desired biaryl products 2,4,6-trimethyl-3-biphenylamine (**13a**) and 4′-chloro-2,4,6-trimethyl-3-biphenylamine (**13b**) in modest yields (Scheme 3). Additionally, a simple alkylboronic acid, namely *n*-butylboronic acid (**14**) was successfully coupled with 3-bromo-2,4,6-trimethylaniline (**12**) to afford 3-butyl-2,4,6-trimethylaniline (**15**) in 63% isolated yield (Scheme 3). Although far from quantitative, these results were deemed satisfactory considering the steric hindrance imposed by the two methyl groups flanking the bromine atom in **12**.[27]

The introduction of a *para*-chloro substituent on phenylboronic acid had a favourable impact on the Suzuki reaction, since the yield increased from 32% for **13a** to 51% for **13b**. These results confirm that in our hands, electron-withdrawing substituents activated the arylboronic acid towards the coupling with electron-rich bromoanilines catalyzed by $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ (cf. Table 1). A reverse tendency was observed when the amino group was protected via its trifluoroacetamide and a phosphineless catalytic system was employed (cf. Table 3).

## 3. Conclusion

In this study, we have devised a synthetic pathway based on a Suzuki–Miyaura cross-coupling reaction to prepare a small library of biphenylamine derivatives bearing various substituents on their aromatic rings. The experimental conditions were carefully adjusted to accommodate a range of substituents, in terms of electron-withdrawing or -donating ability and steric bulk. It should be pointed out that in all cases, under thermal or sonochemical conditions and with or without protection of the amine function, we always observed decomposition of the catalysts and formation of palladium black that was eventually responsible for the relatively low yields obtained. Our goal was nevertheless achieved, since we now have in our hands a representative set of di-*ortho*-substituted biarylamines to transform into imidazolium and imidazolinium NHC precursors. Our investigations on the Suzuki–Miyaura cross-coupling reaction highlighted the crucial (and yet unexplained) role of some *para*-substituents on the phenyl groups. They also confirmed that no universal experimental procedure is available for this transformation, and that a unique combination of catalyst, ligand, solvent and base must be found for each pair of substrates in order to get high yields of biaryl products.

## 4. Experimental section

### 4.1. General information

Solvents were freshly distilled from standard drying agents and kept under argon. $^1$H and $^{13}$C NMR spectra (400 and 100 MHz, respectively) were recorded at 298 K on a Bruker DRX 400 spectrometer in $CDCl_3$ with TMS as an internal standard. All assignments are tentative, based on additivity rules[28] and comparison between related structures. Melting points were recorded on an Electrothermal OSI 9100 apparatus and are not corrected. 4-Bromo-2,6-dimethylaniline (**5**) and tri-*tert*-butylphosphine were purchased from Fluka. All the other starting materials and catalysts were obtained from Aldrich.

### 4.2. Preparation of *para*-substituted biphenylamines via Suzuki cross-coupling

A two-necked 50-mL round-bottom flask equipped with a magnetic stirring bar and a three-way stopcock was charged with 4-bromo-2,6-dimethylaniline (**5**) (0.5 g, 2.5 mmol), a substituted phenylboronic acid (2.75 mmol), $Pd_2(dba)_3$ (0.0343 g, 0.0375 mmol) and $Cs_2CO_3$ (0.9775 g, 3 mmol). The reactor was purged of air by applying three vacuum/argon cycles before tri-*tert*-butylphosphine (0.0182 g, 0.09 mmol) was added in a glove-box. The flask was taken out of the glove-box, equipped with a reflux condenser under a slow stream of argon, and degassed dioxane (10 mL) was added with a syringe under an inert atmosphere. The reaction mixture was stirred at in an oil bath at 80–90 °C for 5 h. It was then cooled to room temperature, diluted with $Et_2O$ (25 mL), filtered through a Celite pad, concentrated on a rotary evaporator and purified by column chromatography on silica gel with $CHCl_3$ as an eluent.

**4.2.1. 3′,5′-Difluoro-3,5-dimethylbiphenyl-4-amine (6a).** Brown oil, yield: 65%. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=2.23 (s, 6H, *ortho*-$CH_3$), 3.47 (s, 2H, $NH_2$), 6.64–6.69 (m, 1H, $CH_{ar}$), 7.03 (d, $J$=20 Hz, 2H, $CH_{ar}$), 7.15 (s, 2H, $CH_{ar}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=17.9 (*ortho*-$CH_3$), 100.9 (*para*-$CH_{ar}$), 108.9 ($CH_{ar}$), 122.1 ($C_{ar}$), 127.0 ($CH_{ar}$), 128.5 ($C_{ar}$), 143.5 ($C_{ar}$), 145.0 ($C_{ar}$N), 164.6 ($C_{ar}$F) ppm.

**4.2.2. 3,5-Dimethyl-3′,5′-bis(trifluoromethyl)biphenyl-4-amine (6b).** Brown oil, yield: 82%. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=2.26 (s, 6H, *ortho*-$CH_3$), 3.78 (s, 2H, $NH_2$), 7.21 (s, 2H, $CH_{ar}$), 7.72 (s, 1H, $CH_{ar}$), 7.94 (s, 2H, $CH_{ar}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=18.7 (*ortho*-$CH_3$), 120.3 (*para*-$CH_{ar}$), 123.2 ($CF_3$), 125.9 ($C_{ar}$), 127.1 ($CH_{ar}$), 127.9 ($C_{ar}$), 128.5 ($CH_{ar}$), 132.6 ($C_{ar}CF_3$), 132.9 ($C_{ar}$), 144.7 ($C_{ar}N$) ppm.

**4.2.3. 4′-Methoxy-3,5-dimethylbiphenyl-4-amine (6c).** Brown oil, yield: 53%. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=2.23 (s, 6H, *ortho*-$CH_3$), 3.60 (s, 2H, $NH_2$), 3.82 (s, 3H, $OCH_3$), 6.92 (d, $J$=8.6 Hz, 2H, $CH_{ar}$), 7.15 (s, 2H, $CH_{ar}$), 7.47 (d, $J$=8.6 Hz, 2H, $CH_{ar}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=18.0 (*ortho*-$CH_3$), 55.3 ($OCH_3$), 114.0 ($CH_{ar}$), 122.0 ($C_{ar}$), 124.7 ($C_{ar}$), 126.8 ($CH_{ar}$), 127.3 ($CH_{ar}$), 130.7 ($C_{ar}$), 141.8 ($C_{ar}N$), 150.7 ($C_{ar}O$) ppm.

### 4.3. Synthesis of *N*-(4-bromo-2,6-dimethylphenyl)-2,2,2-trifluoroacetamide (7)

A two-necked 100-mL round-bottom flask equipped with a magnetic stirring bar and capped with a three-way stopcock was charged with 4-bromo-2,6-dimethylaniline (**5**) (1 g, 5 mmol) and $Na_2CO_3$ (5.83 g, 55 mmol). The reactor was purged of air by applying three vacuum/argon cycles. Dry $Et_2O$ (50 mL) was added and the resulting suspension was cooled in an ice–water bath before trifluoroacetic anhydride (7.5 mL, 55 mmol) was carefully added. The mixture was first stirred for 5 min at 0 °C then for 40 min at room temperature. Next, 40 mL of $CHCl_3$ was added and the excess of trifluoroacetic anhydride was destroyed by slow addition of ice (50 mL). The resulting biphasic mixture was transferred into a separation funnel. The organic phase was collected and the aqueous phase was extracted with $CHCl_3$ (3×50 mL). All the organic phases were gathered, dried over $MgSO_4$ and evaporated. Crude *N*-(4-bromo-2,6-dimethylphenyl)-2,2,2-trifluoroacetamide (**7**) was obtained as a white-grey solid in 95% yield and used without any further purification, mp 140–141 °C. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=2.10 (s, 6H, *ortho*-$CH_3$), 7.19 (s, 2H, $CH_{ar}$), 7.48 (s, 1H, NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=18.0 ($CH_3$), 114.7 ($CF_3$), 122.4 ($C_{ar}$), 129.9 ($CH_{ar}$), 131.6 ($C_{ar}$), 137.5 ($C_{ar}$), 155.6 (CO) ppm.

### 4.4. Preparation of *N*-protected biphenylamines via Suzuki cross-coupling

A two-necked 100-mL round-bottom flask equipped with a reflux condenser capped with a three-way stopcock was charged with a phenylboronic acid (4.4 mmol), *N*-(4-bromo-2,6-dimethylphenyl)-2,2,2-trifluoroacetamide (**7**) (1.1843 g, 4 mmol), $Pd(OAc)_2$ (45 mg, 0.2 mmol) and $Na_2CO_3$ (0.9 g, 8.5 mmol). The reactor was purged of air by applying three vacuum/argon cycles before degassed methanol (50 mL) was added. The reaction mixture was sonicated for 4 h in an ultrasound cleaning bath initially at room temperature. The temperature slightly increased during the run due to the sonication process. The resulting suspension was filtered through a Celite pad and the filtrate was evaporated. The residue was dissolved in $CHCl_3$ (20 mL) and washed with water (2×30 mL). The organic layer was dried over $MgSO_4$ and evaporated. The crude product was recrystallized from $CHCl_3$/*n*-hexane.

**4.4.1. *N*-(3′,5′-Difluoro-3,5-dimethylbiphenyl-4-yl)-2,2,2-trifluoroacetamide (8a).** White-grey solid, yield: 34%. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=2.26 (s, 6H, *ortho*-$CH_3$), 6.77–6.81 (m, 1H, $CH_{ar}$), 7.04 (d, $J$=16 Hz, 2H, $CH_{ar}$), 7.25 (s, 2H, $CH_{ar}$), 7.72 (s, 1H, NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=18.3 (*ortho*-$CH_3$), 103.0 (*para*-$CH_{ar}$), 109.9 ($CH_{ar}$), 110.1 ($C_{ar}$), 122.4 ($CF_3$), 127.3 ($C_{ar}$), 131.1 ($CH_{ar}$), 136.1 ($C_{ar}$), 139.2 ($C_{ar}$), 162.2 (CO), 164.7 ($C_{ar}F$) ppm.

**4.4.2. *N*-(3,5-Dimethyl-3′,5′-bis(trifluoromethyl)biphenyl-4-yl)-2,2,2-trifluoroacetamide (8b).** White-grey solid, yield: 38%. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=2.19 (s, 6H, *ortho*-$CH_3$), 7.26 (s, 2H, $CH_{ar}$), 7.35 (s, 2H, $CH_{ar}$), 7.50 (m, 1H, $CH_{ar}$), 7.87 (s, 1H, NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=18.6 (*ortho*-$CH_3$), 114.3 ($CF_3$), 126.6 ($CH_{ar}$), 126.8 ($CF_3$), 127.3 ($C_{ar}$), 127.6 ($CH_{ar}$), 128.1 ($CH_{ar}$), 133.3 ($C_{ar}$), 137.6 ($C_{ar}$), 148.8 ($C_{ar}$), 159.2 ($C_{ar}$), 163.6 (CO) ppm.

**4.4.3. *N*-(4′-Methoxy-3,5-dimethylbiphenyl-4-yl)-2,2,2-trifluoroacetamide (8c).** White-grey solid, yield: 90%. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=2.26 (s, 6H, *ortho*-$CH_3$), 3.84 (s, 3H, $OCH_3$), 6.95 (d, $J$=8.0 Hz, 2H, $CH_{ar}$), 7.27 (s, 2H, $CH_{ar}$), 7.47 (d, $J$=8.4 Hz, 2H, $CH_{ar}$), 7.57 (s, 1H, NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=17.9 (*ortho*-$CH_3$), 55.5 ($OCH_3$), 114.4 ($CH_{ar}$), 117.4 ($CF_3$), 127.0 ($CH_{ar}$), 128.3 ($CH_{ar}$), 129.5 ($C_{ar}$), 132.9 ($C_{ar}$), 135.6 ($C_{ar}$), 141.2 ($C_{ar}$), 155.7 (CO), 159.5 ($C_{ar}O$) ppm.

**4.4.4. *N*-(3,5-Dimethyl-4′-phenoxybiphenyl-4-yl)-2,2,2-trifluoroacetamide (8d).** White-grey solid, yield: 31%, mp 134 °C. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=2.27 (s, 6H, *ortho*-$CH_3$), 6.97–7.11 (m, 4H, $CH_{ar}$), 7.13–7.24 (m, 2H, $CH_{ar}$), 7.34–7.48 (m, 2H, $CH_{ar}$), 7.51–7.72 (m, 3H, $CH_{ar}$), 8.16 (s, 1H, NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=19.2 ($CH_3$), 115.6 ($CF_3$), 119.9 ($CH_{ar}$), 120.0 ($CH_{ar}$), 124.4 ($CH_{ar}$), 128.1 ($CH_{ar}$), 129.4 ($CH_{ar}$), 131.1 ($CH_{ar}$), 136.2 ($C_{ar}$), 136.5 ($C_{ar}$), 141.9 ($C_{ar}$), 141.2 ($C_{ar}$), 157.9 (CO), 158.1 ($C_{ar}O$), 159.0 ($C_{ar}O$) ppm.

**4.4.5. *N*-(4′-*tert*-Butyl-3,5-dimethylbiphenyl-4-yl)-2,2,2-trifluoroacetamide (8e).** White-grey solid, yield: 74%, mp 113–114 °C. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=1.36 (s, 9H, $C(CH_3)_3$), 2.28 (s, 6H, *ortho*-$CH_3$), 7.31 (d, 2H, $CH_{ar}$), 7.44–7.50 (m, 4H, $CH_{ar}$), 7.55 (s, 1H, NH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=18.4 (*ortho*-$CH_3$), 31.5 ($C(CH_3)_3$), 34.7 ($C(CH_3)_3$), 125.9 ($CH_{ar}$), 126.9 ($CH_{ar}$), 127.4 ($CH_{ar}$), 129.7 ($C_{ar}$), 131.6 ($CF_3$), 135.6 ($C_{ar}$), 137.5 ($C_{ar}$), 141.6 ($C_{ar}$), 150.8 ($C_{ar}$), 155.6 (CO) ppm.

### 4.5. Cleavage of the trifluoroacetamide group

A 250-mL round-bottom flask was charged with a substituted *N*-(3,5-dimethylbiphenyl-4-yl)-2,2,2-trifluoroacetamide (5 mmol), water (10 mL) and concentrated hydrochloric acid (10 mL). The reaction mixture was heated to reflux for 17 h. The resulting solution was brought back to room temperature and evaporated to dryness. The residue was taken up with water (100 mL) and refluxed with $Ba(OH)_2 \cdot 8H_2O$

(9 g) for 1.5 h. After cooling to room temperature, the basic aqueous solution was extracted with $CHCl_3$ (3×20 mL). The organic phases were dried over $MgSO_4$ and evaporated. The remaining oily product was dried under high vacuum.

**4.5.1. 3′,5′-Difluoro-3,5-dimethylbiphenyl-4-amine (6a).** Brown oil, yield: 64%. See Section 4.2.1 for NMR data.

**4.5.2. 3,5-Dimethyl-3′,5′-bis(trifluoromethyl)biphenyl-4-amine (6b).** Brown oil, yield: 60%. See Section 4.2.2 for NMR data.

**4.5.3. 4′-Methoxy-3,5-dimethylbiphenyl-4-amine (6c).** Brown oil, yield: 81%. See Section 4.2.3 for NMR data.

**4.5.4. 3,5-Dimethyl-4′-phenoxybiphenyl-4-amine (6d).** Brown oil, yield: 54%. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=2.27 (s, 6H, *ortho*-$CH_3$), 3.68 (s, 2H, $NH_2$), 7.04 (m, 2H, $CH_{ar}$), 7.11 (m, 2H, $CH_{ar}$), 7.28 (m, 3H, $CH_{ar}$), 7.36 (m, 2H, $CH_{ar}$), 7.48 (m, 2H, $CH_{ar}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=19.2 (*ortho*-$CH_3$), 115.6 ($CH_{ar}$), 118.5 ($CH_{ar}$), 120.0 ($C_{ar}$), 124.4 ($CH_{ar}$), 128.1 ($CH_{ar}$), 129.4 ($C_{ar}$), 130.6 ($CH_{ar}$), 132.4 ($CH_{ar}$), 136.5 ($C_{ar}$), 141.9 ($C_{ar}$), 141.2 ($C_{ar}$N), 157.9 ($C_{ar}$O), 158.1 ($C_{ar}$O) ppm.

**4.5.5. 4′-*tert*-Butyl-3,5-dimethylbiphenyl-4-amine (6e).** Brown oil, yield: 67%. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=1.37 (s, 9H, $C(CH_3)_3$), 2.27 (s, 6H, *ortho*-$CH_3$), 3.26 (s, 2H, $NH_2$), 7.31 (d, $J$=4 Hz, 2H, $CH_{ar}$), 7.44–7.50 (m, 4H, $CH_{ar}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=18.3 (*ortho*-$CH_3$), 31.4 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$), 125.8 ($CH_{ar}$), 126.8 ($CH_{ar}$), 127.2 ($CH_{ar}$), 129.6 ($C_{ar}$), 135.5 ($C_{ar}$), 137.3 ($C_{ar}$), 141.4 ($C_{ar}$N), 150.7 ($C_{ar}$) ppm.

### 4.6. Preparation of *meta*-substituted arylamines via Suzuki cross-coupling

A two-necked 100-mL round-bottom flask equipped with a magnetic stirring bar and a reflux condenser capped with a three-way stopcock was charged with 3-bromo-2,4,6-trimethylaniline (**12**) (1 g, 4.67 mmol), a substituted boronic acid (5.14 mmol), $Pd_2(dba)_3$ (0.213 g, 0.23 mmol) and $Cs_2CO_3$ (1.826 g, 5.60 mmol). The reactor was purged of air by applying three vacuum/argon cycles before degassed dioxane (10 mL) was added. Tri-*tert*-butylphosphine (0.113 g, 0.56 mmol) was weighted separately in a glove-box and dissolved in degassed dioxane (3 mL) in a 25-mL round-bottom flask capped with a three-way stopcock. This solution was transferred into the main reactor under an argon atmosphere and the reaction mixture was stirred at 115 °C for 24 h. It was then cooled to room temperature, diluted with $Et_2O$ (50 mL), filtered through a Celite pad, concentrated on a rotary evaporator and purified by column chromatography on silica gel with $CHCl_3$.

**4.6.1. 2,4,6-Trimethylbiphenyl-3-amine (13a).** Brown oil, yield: 32%. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=1.85 (s, 3H, $CH_3$), 1.92 (s, 3H, $CH_3$), 2.19 (s, 3H, $CH_3$), 3.47 (s, 2H, $NH_2$), 6.86 (s, 1H, 5-$CH_{ar}$), 7.11 (d, $J$=8 Hz, 2H, $CH_{ar}$), 7.27–7.31 (m, 1H, *para*-$CH_{ar}$), 7.36–7.39 (m, 2H, $CH_{ar}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=14.9 ($CH_3$), 17.6 ($CH_3$), 20.2 ($CH_3$), 120.2 ($C_{ar}$), 120.8 ($C_{ar}$), 125.5 ($C_{ar}$), 128.3 ($CH_{ar}$), 129.1 ($CH_{ar}$), 129.5 ($CH_{ar}$), 140.3 ($C_{ar}$), 140.6 ($C_{ar}$), 141.4 ($CH_{ar}$), 141.9 ($C_{ar}$N) ppm.

**4.6.2. 4′-Chloro-2,4,6-trimethylbiphenyl-3-amine (13b).** Brown oil, yield: 51%. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=1.92 (s, 3H, $CH_3$), 1.98 (s, 3H, $CH_3$), 2.37 (s, 3H, $CH_3$), 3.60 (s, 2H, $NH_2$), 6.94 (s, 1H, 5-$CH_{ar}$), 7.12 (d, $J$=8 Hz, 2H, $CH_{ar}$), 7.44 (d, $J$=8 Hz, 2H, $CH_{ar}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=15.9 ($CH_3$), 18.7 ($CH_3$), 21.2 ($CH_3$), 121.1 ($C_{ar}$), 122.1 ($C_{ar}$), 126.3 ($C_{ar}$), 129.5 ($CH_{ar}$), 130.2 ($CH_{ar}$), 130.7 ($CH_{ar}$), 131.9 ($C_{ar}$), 133.4 ($C_{ar}$), 140.0 ($C_{ar}$), 142.5 ($C_{ar}$N) ppm.

**4.6.3. 3-Butyl-2,4,6-trimethylaniline (15).** Brown oil, yield: 63%. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$=1.13 (t, 3H, $CH_3$), 1.59 (m, 4H, $CH_2$), 2.28 (m, 6H, $CH_3$), 2.37–2.40 (m, 3H, $CH_3$), 2.76 (m, 2H, $CH_2$), 3.58 (m, 2H, $NH_2$), 6.92 (s, 1H, $CH_{ar}$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$=13.1 ($CH_3$), 14.0 ($CH_3$), 17.5 ($CH_3$), 19.5 ($CH_2$), 23.3 ($CH_2$), 29.8 ($CH_3$), 32.1 ($CH_2$), 119.2 ($C_{ar}$), 120.1 ($C_{ar}$), 125.4 ($C_{ar}$), 129.6 ($CH_{ar}$), 137.6 ($C_{ar}$), 140.9 ($C_{ar}$N) ppm.

## Acknowledgements

Financial support of the EU through contracts HPRN-CT-2000-00010 ‘Polycat’ and G5RD-CT-2001-00554 ‘Dentalopt’ is gratefully acknowledged.

## References and notes

1. (a) Stanforth, S. *Tetrahedron* **1998**, *54*, 263–303; (b) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145–157.
2. (a) Delaude, L.; Demonceau, A.; Noels, A. F. *Chem. Commun.* **2001**, 986–987; (b) Simal, F.; Jan, D.; Delaude, L.; Demonceau, A.; Spirlet, M.-R.; Noels, A. F. *Can. J. Chem.* **2001**, *79*, 529–535; (c) Delaude, L.; Szypa, M.; Demonceau, A.; Noels, A. F. *Adv. Synth. Catal.* **2002**, *344*, 749–756; (d) Delaude, L.; Delfosse, S.; Richel, A.; Demonceau, A.; Noels, A. F. *Chem. Commun.* **2003**, 1526–1527; (e) Richel, A.; Delfosse, S.; Cremasco, C.; Delaude, L.; Demonceau, A.; Noels, A. F. *Tetrahedron Lett.* **2003**, *44*, 6011–6015; (f) Delaude, L.; Demonceau, A.; Noels, A. F. *Curr. Org. Chem.* **2006**, *10*, 203–215.
3. (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; (b) *Cross-Coupling Reactions. A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry; Springer: Berlin, 2002; Vol. 219.
4. Hassan, J.; Sévignon, C.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470.
5. For monographs, see: (a) Suzuki, A. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 49–97; (b) Miyaura, N. *Cross-Coupling Reactions. A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry; Springer: Berlin, 2002; Vol. 219, pp 11–59.
6. For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168; (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695; (d) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440.
7. Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519.

8. (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388; (b) Littke, A. F.; Chaoyang, D.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
9. (a) Leadbeater, N. E.; Marco, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1407–1409; (b) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161–168.
10. Arcadi, A.; Cerichelli, G.; Chiarini, M.; Correa, M.; Zorzan, D. *Eur. J. Org. Chem.* **2003**, 4080–4086.
11. Wu, Y.; Li, J.; Fu, Y.; Bo, Z. *Org. Lett.* **2004**, *6*, 3485–3487.
12. Tao, B.; Boykin, D. W. *J. Org. Chem.* **2004**, *69*, 4330–4335.
13. Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. *J. Org. Chem.* **2005**, *70*, 388–390.
14. Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
15. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, NY, 1999.
16. Newman, H. *J. Org. Chem.* **1965**, *30*, 1287–1288.
17. Wolfrom, M. L.; Bhat, H. B. *J. Org. Chem.* **1967**, *32*, 1821–1823.
18. Rajagopal, R.; Jarikote, D. V.; Srinivasan, K. V. *Chem. Commun.* **2002**, 616–617.
19. Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087–4089.
20. Koza, D. J.; Carita, E. *Synthesis* **2002**, 2183–2186.
21. Kuivila, H. G.; Reuwer, J. F., Jr.; Mangravite, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2666–2670.
22. Feuerstein, M.; Berthiol, F.; Doucet, H.; Santelli, M. *Synlett* **2002**, 1807–1810.
23. Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866–2873.
24. Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173–3180.
25. Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.
26. McClure, M. S.; Roschangar, F.; Hodson, S. J.; Millar, A.; Osterhout, M. H. *Synthesis* **2001**, 1681–1685.
27. Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207–210.
28. Pretsch, E.; Bühlmann, P.; Affolter, C. *Structure Determination of Organic Compounds*, 3rd ed.; Springer: Berlin, 2003.