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Access to the most sterically crowded anilines *via* non-catalysed C–C coupling reactions†

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Variously substituted 2,6-bis(1,1-diarylethyl)anilines and 2,6-bis(trityl)-anilines were prepared by a three-step high-yield process. Dimethyl-2-aminoisophtalate was modified by reaction with arylmagnesium bromides, and the hydroxy-derivatives obtained were etherified. Under the non-catalysed C–C coupling protocol, the formed bis[methyl(methoxy)diaryl]anilines react with various Grignard reagents to give highly substituted products. The buried volumes around the central nitrogen atom of the prepared compounds exceed the parameters for the known most sterically hindered anilines by about 20%.

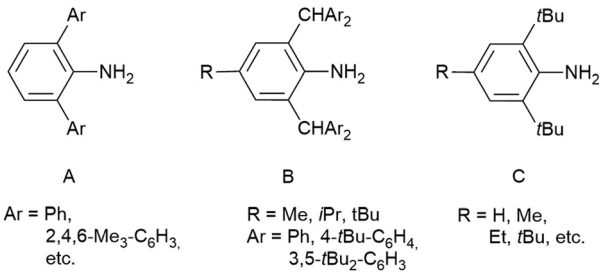

Fig. 1 Examples of known bulky anilines.

The kinetic stabilisation of the reactive metal centres in terms of ligand exchange or oxidation plays an important role in many branches of synthetic chemistry. Sterically demanding ligands, which provide such a kind of stabilisation, have accessed new classes of compounds for example in main-group chemistry by introducing compounds in an unusual oxidation state, which can adopt some properties of transition metals and are therefore active in homogeneous catalysis or small-molecule activation.[1] Next, the so-called double-bond rule, which does not allow the formation of multiple bonds between the elements of the third period or higher, has been broken by the synthesis of various heavier alkene analogues.[2] Moreover, bulky ligands are essential in homogeneous catalysis, *e.g.* the second and third generation of Grubbs catalysts.[3] A considerable part of these modern ligands is based on aniline moieties, which tune their steric properties. Anilines are the core of various sterically demanding ligands, *e.g.* N-heterocyclic carbenes, β-diketiminates, amidinates, guanidinates and others.[4] They have also been used many times as ligands themselves in the form of amides or imides.[3,5]

A large variety of anilines with different backbones have been prepared in the past few decades. The steric properties of anilines, unlike those of aliphatic amines, are very easily tuneable by changing the substituents in the neighbouring positions. Anilines containing a terphenyl backbone (Fig. 1A) are accessible through the reduction of the corresponding azide and have great shielding provided by the *ortho*-aryl substituents, which enables the stabilisation of extremely reactive species such as biradicaloids.[6,7] In the past few decades, 2,6-bis(benzhydryl)-anilines (Fig. 1B) have been the most extensively studied group of sterically demanding anilines. They can be smoothly prepared by melting diphenylmethanol and the appropriate aniline in the presence of concentrated HCl and zinc chloride on a large scale (>60 g). The steric bulk of 2,6-bis(benzhydryl)anilines can be further increased by the use of substituted benzhydrols, *e.g.* $(3,5\text{-}t\text{Bu}_2\text{-C}_6\text{H}_3)_2\text{C(H)OH}$ or $(4\text{-}t\text{Bu-C}_6\text{H}_4)_2\text{C(H)OH}$.[8] The kinetic stabilisation provided by these anilines was demonstrated by Bertrand, who published the first compound containing a terminal phosphorus atom bonded to a main group element centre in the form of a phosphino-phosphinidene.[8] One of the limitations of 2,6-(benzhydryl)anilines is the potential activation of a rather acidic C–H bond in the $\text{C}H\text{Ar}_2$ moiety.[9] Nevertheless, there is no published procedure that would lead to the virtual replacement of this hydrogen atom by any other organic substituent. Simple electrophilic alkylation of anilines by $\text{Ph}_2\text{RC(OH)}$, which was mentioned above, results in *N*-alkylation or exhibits no reaction at all.[10] This fact makes 2,4,6-tri-*tert*-butylaniline (Fig. 1C), one of the oldest examples of a sterically demanding aniline, the only aniline with both *ortho*-positions occupied by a tertiary organic group.

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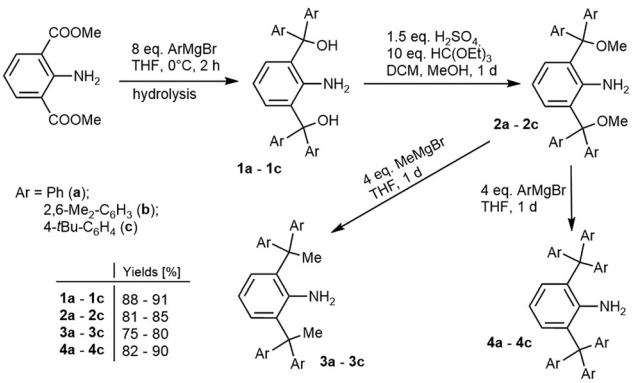
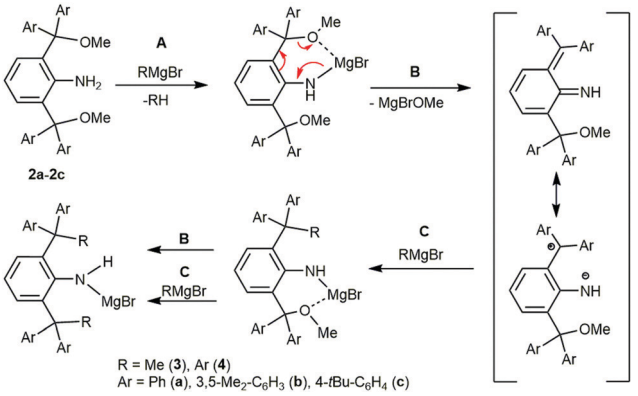
Interestingly, it is the only amine that can stabilize iminochlorophosphane Ar–N=P–Cl in its monomeric form even in the solid state, while slightly smaller substituents such as 2,6-bis-(2,4,6-trimethylphenyl)phenyl or 2,6-diisopropylphenyl allow dimerisation to 1,3-dichloro-cyclo-diphosphadiazanes, $[ClP(\mu\text{-}NAr)]_2$.[11,12] No aniline bearing a different tertiary organic group other than *t*Bu has been published even though there has been a high demand for bulky ligands in the last decade. Therefore, we present a simple, high-yielding synthesis of a series of sterically demanding anilines bearing CAr_3 and CAr_2Me substituents in the *ortho*- positions.

The synthesis of anilines derived from 2,6-benzhydrylanilines (Fig. 1B) by the virtual replacement of the hydrogen atoms by different functional groups could not be achieved by direct alkylation of anilines. Therefore, we have modified the synthetic procedure for the preparation of anilines 1-NH_2-2,6-$(CH(CH_2R)_2)_2$-C_6H_3, where R = Me, Et, *n*Pr, which were used as building blocks for sterically hindered N-heterocyclic carbenes.[13] Dimethyl-2-aminoisophtalate reacts with an overstoichiometric amount of the appropriate aryl-Grignard reagent (Scheme 1), giving anilines 1-NH_2-2,6-$[C(OH)Ar_2]_2$-C_6H_3 (**1a–c**) after hydrolysis. When compared to the direct alkylation mentioned above, this method leads directly to anilines bearing functionalised benzhydryl groups.

Moreover, these reactions can be performed on a large scale with high yields (~90%). However, the hydroxy-groups are not suitable for subsequent C–C coupling. Therefore, they have been converted to a methoxy group by etherification with methanol in the presence of sulphuric acid and triethyl orthoformate. Triethyl orthoformate is not essential for the reaction, but it shortens the reaction time from two weeks to one day. The treatment of **2a–c** with methyl/arylmagnesium bromide (Scheme 1) led to the replacement of the methoxy groups with a methyl/aryl group, giving anilines **3a–c**/**4a–c**. Analogical Kumada–Corriu-type coupling requires catalysis by various Ni-or Pd-catalysts.[14] Our coupling reactions proceed rapidly (full conversion after one day) giving high yields (75–90% of isolated yield) under mild conditions without a catalyst. Moreover, this is the first coupling reaction of the bulky triaryl-moiety substituted with a rather unreactive methoxy-group. A similar alkylation procedure was performed only in the cases of 2-methoxymethyl-6-methylaniline and 2-methoxymethylaniline, which were alkylated by vinyl- and allylmagnesium bromides.[15]



Scheme 1 Synthesis of bulky anilines.



Scheme 2 Synthesis of bulky anilines, C–C coupling.

The reaction mechanism of these reactions was investigated by Mann and Stewart in 1954 and later confirmed by Görl and Alt in 2007.[16,17]

In our system, the mechanism is suggested to be analogical, despite the system being more complex. In the first step (Scheme 2, step A), the amine group is deprotonated by the first equivalent of the Grignard reagent. The coordination of the magnesium atom with the methoxy group weakens the C–O bond (Scheme 2, step B), which is cleaved and the methoxy-magnesium bromide is eliminated. The resulting dearomatized imine is less stable when compared to the 1,4-dipolar tautomeric form, which reacts with the second equivalent of the Grignard reagent (Scheme 2, step C). The steps B and C repeat again replacing the second methoxy-group with a methyl or aryl group. The hydrolysis of the final product leads to the desired anilines **3a–c** and **4a–c**. All prepared compounds were isolated as colourless solids soluble in THF, aromatic and chlorinated solvents with the exception of **4a**, which is only sparingly soluble in chlorinated solvents. The ^1H and ^{13}C NMR spectra of the prepared anilines exhibited one set of expected signals. The signals of amine groups in the ^1H spectra of **1a–c** (~4.0 ppm) and **2a–c** (~4.9 ppm) were shifted downfield in comparison with **3a–c** and **4a–c** (~3.5 ppm), which indicates the presence of the hydrogen bond NH···O. Similarly, the signals of the hydroxy groups in **1a–c** were also shifted downfield with respect to analogous Ph_3COH (2.78 ppm), indicating the presence of OH···N hydrogen bonding.[18]

Despite the diversity of the substituents on the benzhydryl moieties, the molecular structures of **1a–4a**, **1b–4b** and **4c** are analogous (see Fig. 2 and 3 for examples; for further information, see the ESI†). Expectedly, the intramolecular H-bonding is promoted within the series of **1** and **2** (see the ESI†). In the series of **3** and **4**, significant steric shielding by hydrocarbon moieties did not allow stronger intermolecular contacts within the crystal lattice. In structures of the methoxy or trityl-substituted compounds of series **2** and **4**, the C–N bond is much shorter (1.370(3)–1.373(4) and 1.377(5)–1.392(3) Å) than that in the structures with hydroxyl groups (series **1** (1.407(4)–1.422(2) Å)) or diarylethyl-substituted compounds of series **3** (1.405(1)–1.412(5) Å). Surprisingly enough, the only compound with the *anti*-orientation of the oxygen atoms is **1a** (Fig. 2).

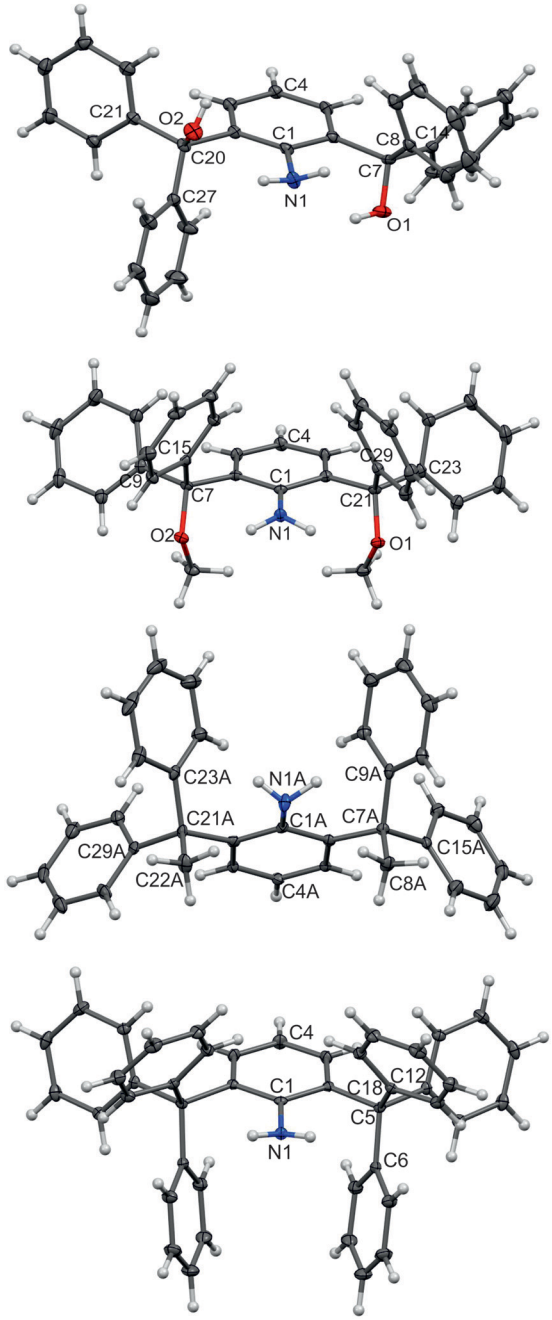


Fig. 2 The molecular structures of **1a**, **2a**, **3a** and **4a**. ORTEP diagrams, 35–50% probability level; solvent molecules have been omitted for clarity. Selected interatomic distances [Å]: **1a**: O1 N1 2.830(5), O2 N1 2.891(5), C7 C20 5.106(5), C1 N1 1.407(4); **2a**: O1 N1 2.907(4), O2 N1 2.866(4), C7 C21 5.097(4), C1 N1 1.373(4); **3a**: (the second independent molecule is omitted for clarity, its parameters are given in parentheses): C8A N1A 3.082(6) (3.087(6)), C22A N1A 3.018(6) (2.995(6)), C7A C21A 5.159(5) (5.176(5)), C1A N1A 1.412(5) (1.411(5)); **4a**: C1 N1 1.392(3), C5 C5i 5.148(4).

Within series **4**, the sterical hindrance changes resonate with the differences in the interplanar angles between the plane of the middle (aniline) ring and the planes defined by three pivotal carbon atoms (for example C6 C12 and C18 for **4a**) of the phenyl rings. These values range from the ideal perpendicular value found for **4a**, to 84.44° and 88.41° in the case of **4b**,

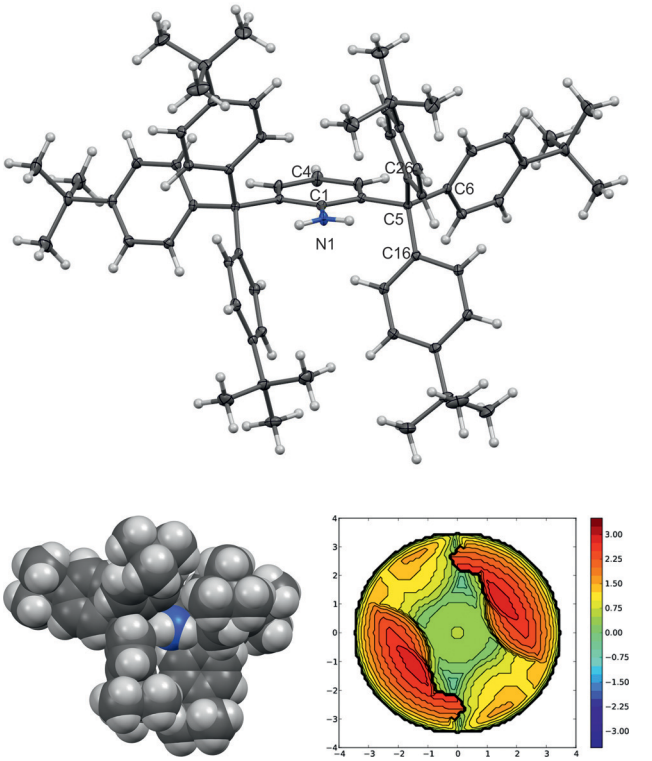
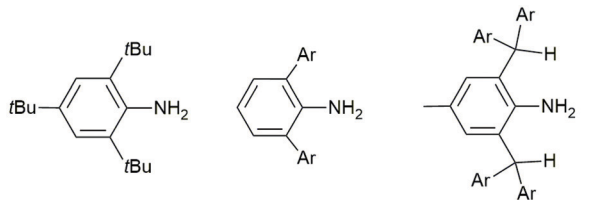


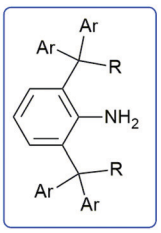
Fig. 3 The molecular structure of **4c**, ORTEP diagram (left), 40% probability level, space-filling model (middle), the dichloromethane solvate molecule has been omitted for clarity. Selected interatomic distances [Å]: C5 N1 2.929(3), C5 C5i 5.193(5), C1 N1 1.377(5). A steric map of **4c** (right).

to a rather unsymmetrical situation in the case of **4c** (80.66° and 89.67°).

In order to quantify the steric shielding of the *ortho*-substituents, we calculated buried volumes, *i.e.* the percentage of the volume of a sphere centred around the nitrogen atom with a radius of 3.5 Å, which is occupied by the bulky aryl backbone (Scheme 3).[19] For comparison, we also calculated the buried volumes of the other published sterically demanding



Ar; V_{bur} [%] -; 54.9 2,4,6-Me_3-C_6H_4; 52.8 Ph; 51.7 4-*t*Bu-C_6H_4; 50.1



Ar/R	OMe	Me	Ar
C_6H_5	67.2	64.4	73.6
3,5-Me_2-C_6H_3	66.1	62.6	73.0
4-*t*Bu-C_6H_4	---	---	76.9

Scheme 3 Buried volumes of published (upper part) and prepared anilines.

anilines (Scheme 3) mentioned above (Fig. 1). The anilines **4a–c** exhibit the highest percentage of the buried volume, which is provided by the bulky trityl moieties. This percentage decreases in the order **4a–c** > **2a**/**2b** > **3a**/**3b** > **1a**/**1b**, but all prepared anilines exhibit similar or higher values than the bulkiest crystallographically characterised anilines published to date.[20] This fact has also been visualised by steric maps (Fig. 3; for more information, see ESI†), which document the effectivity of the steric shielding around the central nitrogen atom. Interestingly, the anilines **1a–4a** exhibit a slightly higher percentage of buried volume than the series **1b–4b**, which indicates the less influence of the derivatisation of the phenyl substituents of the benzhydryl groups on the steric hindrance around the nitrogen atom. A similar trend could also be observed in the case of published 2,6-benzhydryl-anilines (Scheme 3).

In summary, the most sterically demanding 2,6-benzhydryl-anilines were not accessible by conventional methods before. Our synthetic approach enables a high yield and a large-scale synthesis of this type of compound by a straightforward three-step alkylation/arylation procedure involving a non-catalysed substitution of the methoxy group using Grignard reagents. All anilines exhibit higher steric hindrance around the central nitrogen atom when compared to the published analogues as judged from the buried volumes. With this feature, they could be applied in many branches of synthetic chemistry.

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Conflicts of interest

There are no conflicts to declare.

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