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Syntheses of extreme sterically hindered 4-methoxyboronic acids

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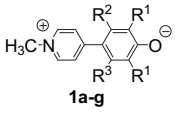
ABSTRACT

4-Iodoanisoles **3a**,**b**, **3d** and 4-bromoanisoles **4a**–**d** were readily obtained. An extreme steric hindrance precluded obtaining **3c**. Catalytic borylation of **3a**,**b**, **3d** followed by hydrolysis of boronic ester **26a**,**b**, **26d** easily provided the boronic acids **5a**,**b**, **5d**. Compounds **5a** and **5d** were also synthesised, starting from **4a** and **4d**, by halogen/metal exchange. Because of a too important steric hindrance, this last reaction failed with **4c** and **4b** led to the unexpected but stable boronic ester **6**. The final obtaining of **5b** required a strongly basic hydrolysis with heating.

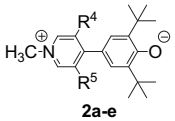
1. Introduction

Our previous work highlighted the efficiency of pyridinium phenolates as model compounds in non-linear optic (NLO) devices (Fig. 1).[1] Our purpose was to confirm experimentally the semiempirical calculations, which indicate an enhancement of the NLO properties of such molecules by increasing the interplanar angle existing between the two aromatic rings.[2] The twist of the pyridinium phenolates was obtained by introduction of alkyl groups of increasing size at α position of the intercyclic bond. Zwitterions **1a**–**g** were unfortunately far too insoluble to allow the determination of NLO properties by conventional EFISHG (Electronic Field-Induced Second Harmonic Generation) measurements or HRS (Hyper Rayleigh Scattering) method. On the other hand, the steric hindrance induced in the neighbouring groups to the phenolate functionality of compounds **2a**–**d** limited the formation of aggregates and enhanced the solubilities of these zwitterions. Experimental measurements performed on compounds **2a**–**d** in agreement with semiempirical calculations indicated an increase of the non-linear response of the chromophore with the raise of dihedral angle existing between the two aromatic rings.[1d] Nevertheless, only moderate twisted conformations have been achieved. Until now, the highest angle reached only a calculated value of 48° with Zwitterion **2d**. The zwitterion **2e** was not yet studied. Our purpose however still remains the synthesis of extremely twisted pyridinium phenolates, that is, tri or tetrasubstituted at α position of the intercyclic bond. The key step of their syntheses may be a Suzuki cross-coupling reaction as Fachetti and co-workers have already used it for the preparation of *ortho-ortho′* tetrasubstituted twisted π-electron system biaryls.[3] We take herein a special interest in the syntheses of precursors of the phenolate moieties. According to their future use in the Suzuki reaction, either as electrophile or nucleophile, these precursors must be either 4-halogeno protected phenols or 4-*O*-protected boronic acids. Two other constraints must



1a-g

	1a	1b	1c	1d	1e	1f	1g
R^1	H	H	H	H	H	Me	Me
R^2	H	Me	Me	Et	*i*Pr	H	Me
R^3	H	H	Me	Et	*i*Pr	H	Me



2a-e

	2a	2b	2c	2d	2e
R^4	H	H	Me	Et	*i*Pr
R^5	H	Me	Me	Et	*i*Pr

Figure 1. Previously synthesised pyridinium phenolates.

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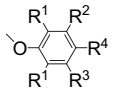
be considered; first, the desired twist of the bicycle implies the introduction of alkyl groups at *meta* positions of the future phenolate functionality, secondly, as for **2a**–**e** (vide supra), in order to avoid a protonation of the phenolate functionality with traces of water and/or a formation of aggregates, the introduction of bulky groups, such as *tert*-butyl, in the neighbouring groups to the phenolate group proved to be a necessity.[1c] We report therefore, herein, the syntheses of both sterically hindered tri- and tetraalkylsubstituted 4-iodoanisoles **3a**–**c** and 4-bromoanisoles **4a**–**c** (Fig. 2). We also disclose their various reactivity during the preparation of the corresponding 4-methoxyboronic acids **5a**–**c**. These acids were synthesised either by catalytic borylation followed by hydrolysis of the intermediate boronic esters or by halogen/metal exchange. The synthesis of 2,3,5,6-tetramethyl-4-methoxyboronic acid **5d** has been undertaken, in order to understand better the influence of the steric hindrance on the formation of the different boronic acids and especially the unexpected obtaining of the boronic ester **6**, by halogen/metal exchange, from **4b**.



3a-d, R^4 = I
4a-d, R^4 = Br
5a-d, R^4 = $B(OH)_2$

	a	b	c	d
R^1	*t*-Bu	*t*-Bu	*t*-Bu	Me
R^2	H	Me	Et	Me
R^3	Me	Me	Et	Me

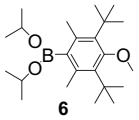


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Figure 2. Derivatives whose syntheses have been attempted and/or performed.

2. Results and discussion

At first, starting from symmetrically dialkylated phenols or from bromophenols, a large variety of direct aromatic electrophile substitutions has been tested in order to prepare 2,3,5,6-tetraalkylphenols or bromophenols (*O*-protected or not). None of these many attempts has been successful.[4] These failures were certainly a consequence of the high desired steric hindrance in the final products and/or electronic facts. To synthesise 4-iodoanisoles **3a**–**c** and 4-bromoanisoles **4a**–**c**, we thus ended up by choosing a much more laborious but successful synthetic pathway consisting in the construction step by step of the *tert*-butyl substituents. Yoshifuji and Coll. have described, in 2003, the synthesis of 1-bromo-2,6-di-*tert*-butyl-4-methoxy-benzene starting from 2-bromo-1,3-bis(bromomethyl)-5-methoxybenzene.[5] In order to apply this method to the syntheses of **3a**–**c** and **4a**–**c**, the starting compounds must obviously be 3,5-dialkyl-2,6-bis(bromomethyl) anisoles **7a**–**c** (Scheme 1).

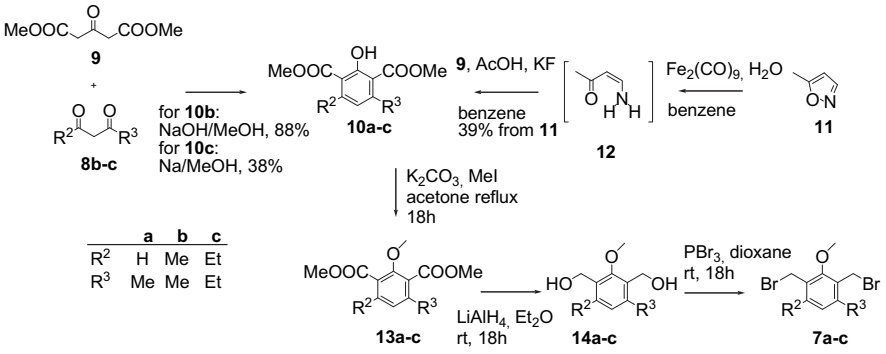
2.1. Synthesis of 3,5-dialkyl-2,6-bis(bromomethyl)anisoles 7a–c

It turned out that anisoles **7a**–**c** were readily synthesised in four steps starting from dimethyl-1,3-acetone dicarboxylate **9** (Scheme 1).

We have previously reported the syntheses of dimethyl phthalates **10b**,**c** (Scheme 1).[1a] It was a condensation of both pentane-2,4-dione **8b** and heptane-3,5-dione **8c** with **9** under strongly basic conditions. The monomethylated isophthalic acid dimethyl ester **10a** was obtained according to lit.[6] After reduction of intracyclic *N*-oxide function of isoxazole **11**, using $Fe_2(CO)_9$, the annelation of the non-isolated β-enaminone **12** with ketone **9** afforded the desired phenol **10a** in a 39% yield. Phenol function of **10a**–**c** was then classically methylated in acetone.[7] The corresponding anisoles **13a**–**c** were recovered in yields higher than 91%. In the next step, the ester functions were reduced into alcohol functions, using $LiAlH_4$ in 56–96% yields. The resulting diols **14a**–**c** were finally brominated by action of PBr_3, in dioxane, at rt, according to Sharghi's procedure.[8] In these conditions, the desired bis(bromomethyl) derivatives **7a**–**c** were quasi-quantatively isolated (Scheme 1). It should be noted that neither starting materials nor by-products were detected at completion of each of these last three steps (protection, reduction or substitution), limiting at each stage the number of purifications. Therefore, compounds **7a**–**c** were easily prepared in four steps starting from dimethyl-1,3-acetone dicarboxylate **9** with global yields ranging from 19% to 60%.

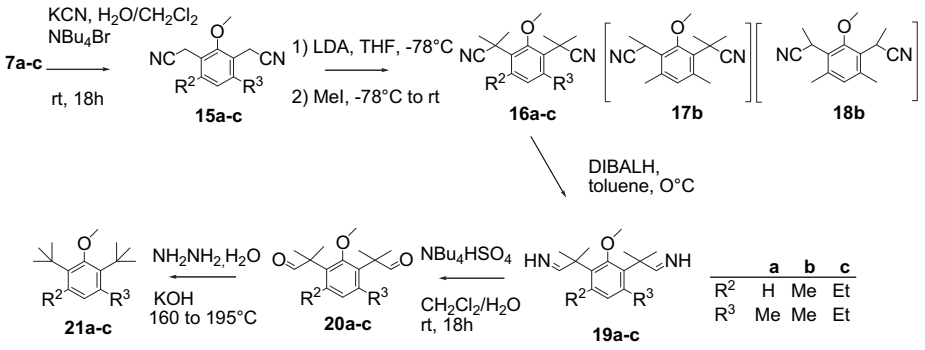
2.2. Synthesis of 2,6-di-*tert*-butylanisoles 21a–c and tetramethylanisole 21d

The bis(bromomethyl) compounds **7a**–**c** in hand, the construction of the *tert*-butyl groups were then considered (Scheme 2) according to Yoshifuji and co-workers procedure.[5] Cyano groups were first introduced in benzylic positions by means of a nucleophilic substitution using KCN in the presence of nBu_4NBr as phase transfer catalyst, in a biphasic solvent (CH_2Cl_2/water). The



Protection of phenol **10a-c**	Yield %	Reduction of esters **13a-c**	Yield %	Substitution of OH in **14a-c**	Yield %
13a	Quant.	**14a**	96	**7a**	Quant.
13b	91	**14b**	80	**7b**	94
13c	92	**14c**	56	**7c**	Quant.

Scheme 1. Preparation of **7a**–**c** from **10a**–**c**.



Introduction of nitriles in **7a-c**	Yield %	Tetramethylation of **15a-c**	Yield %	Reduction of nitriles of **16a-c**	Yield %	Reduction of aldehydes of **20a-c**	Yield %
15a	97	**16a**	52	**20a**	99	**21a**	58
15b	96	**16b**	95	**20b**	81	**21b**	64
15c	89	**16c**	82	**20c**	83	**21c**	61

Scheme 2. Preparation of **21a–c**.

cyanomethyl derivatives **15a–c** were isolated in excellent yields (from 89% to 97%). The next stage of the synthesis of anisoles **21a–c** involved the introduction of two methyl groups at each benzylic position. The proximity of both aromatic ring and cyano functions enhanced the acidity of the benzylic protons. Yoshifuji and Coll. removed them using NaH[5a] or KOH.[5b,5c] In the case of the dimethylated compound **15b**, attempts using KOH,[5b,5c] NaOH,[9] NaH,[10] $NaNH_2$[11] or *t*-BuOK[12] mainly gave a monomethylation at each benzylic position, leading to **18b**. Better results were obtained using lithium di*iso*propyl amide (LDA), in-situ synthesised by deprotonation of di*iso*propylamine with butyllithium.[13] Using, for example, five equivalents of LDA and methyliodide, an NMR analysis indicated that 55% of tetramethylated anisole **16b** was recovered mixed with 32% of trimethylated derivative **17b** and 13% of the symmetrically dimethylated anisole **18b**. The use of eight equivalents of LDA and five equivalents of methyliodide induced an increase in yield to 71%. The optimisation of the reaction conditions indicated that an excess of 8 equiv of LDA and 12 equiv of methyliodide afforded the completion of the tetramethylation of anisoles in a 95% yield. Using these optimised conditions, the tetramethylation of anisoles **15a** and **15c** was achieved in, respectively, 52% and 82% yields (Scheme 2).

In order to reduce α,α,α′,α′-tetramethylated anisole **16b**, di*iso*-butylaluminium hydride (DIBALH) was tested according to the lit.[5] Surprisingly, as well an acidic as a basic hydrolysis of the reaction mixture mainly led to diimine **19b**. Only traces of the expected dialdehyde **20b** were detected by NMR analysis. The diimine **19b** was stable enough to be isolated. Its hydrolysis into dialdehyde **20** was achieved by treatment with tetrabutylammonium hydrogenosulphate in a biphasic solvent (water/CH_2Cl_2). Dialdehyde **20b** was finally recovered in a 81% yield. This last synthetic sequence (reduction with DIBALH following by treatment with tetrabutylammonium hydrogenosulphate) was efficiently applied to the conversion of **16a** and **16c** into the dialdehydes **20a** and **20c** in, respectively, 99% and 83% isolated yields.

Aldehyde functions of **20a–c** were then reduced in methyl groups by the Huang–Minlon modification of the Wolff–Kishner reaction.[14] Heating at 160–195 °C, in the presence of hydrazine hydrate and powdered KOH in diethylene glycol, involved the achievement of the *tert*-butyl substituents. In these conditions, the three expected anisoles **21a–c** were isolated in moderate yields (58–64%).

At the same time, 2,3,5,6-tetramethylanisole **21d** had been synthesised (Fig. 3). Two different pathways were tested. The first one ended with the hydrogenolysis of diol **14b**, on Pd/C. Unfortunately, the expected compound **21d** was obtained in a disappointing 55% yield. As a consequence, starting from isophthalate **10b**, the total synthesis of **21d**, in three steps (protection, reduction of ester and hydrolysis), only reached a 40% yield. Subsequently, still starting from **10b**, another alternative was considered. As we have it previously published,[1a] esters functions of **10b** were first reduced in a 96% yield. The two hydroxymethyl groups were then hydrogenolysed in a 92% yield. The obtained tetramethylphenol was finally *O*-methylated in a 90% yield. This time, starting from **10b**, a global yield of 79% was achieved.

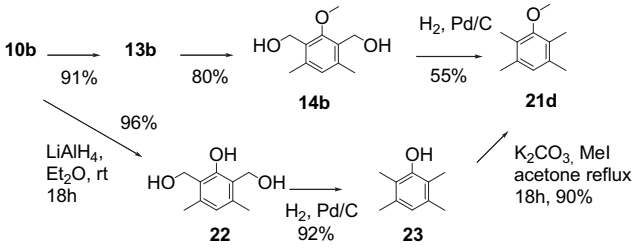
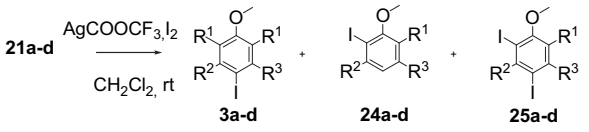


Figure 3. Preparation of **21d**.

2.3. Halogenation of anisoles 21a–d

para-Iodination of anisoles **21a–d** was performed by treatment with iodine in dichloromethane in presence of silver trifluoroacetate (Scheme 3). In the presence of *tert*-butyl substituents, the experimental results underscored decreasing yields with the steric hindrance of the alkyl groups (R^2 and R^3) anchored at *meta* position of the methoxy function. Attempts of iodination of the diethylanisole **21c** only led to *ipso*-substitution of one of the *tert*-butyl groups with iodine. The structure of the obtained compound **24c** was unambiguously determined by ^{1}H NMR Nuclear-Overhauser-effect (NOE) experiments. Irradiation of protons at α position of the ethyl substituent at 2.85 ppm enhanced H-C(4) and protons of a *tert*-butyl group, whereas, irradiation of protons at



	a	b	c	d
R^1	*t*-Bu	*t*-Bu	*t*-Bu	Me
R^2	H	Me	Et	Me
R^3	Me	Me	Et	Me

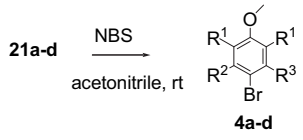
Substrates	Product obtained (%)[a]		
	3a-d	**24a-d**	**25a-d**
21a	(100)[b]	-	-
21b	83 (71)[b]	13.5	3.5
21c	-	100 (78)[b]	-
21d	100 (61)[b]	-	-

[a]yields determined by NMR.
[b]isolated yields.

Scheme 3. Iodination of anisoles **21a–d**.

α position of the ethyl substituent at 2.71 ppm only enhanced H-C(4). In the case of **21b** the reaction was not complete any longer. The desired *para*-iodinated product (83%) was recovered mixed with by-products resulting once more from the substitution of a *tert*-butyl group (13.5%) followed by iodination of the free position (3.5%). These results suggested that the substitution of a *tert*-butyl group is dramatically furthered by the increase of the steric hindrance induced in the neighbouring groups to the free *para* position. On the other hand, iodinations of **21a** and tetramethylanisole **21d** gave the only expected iodoanisoles **3a** and **3d** in, respectively quantitative and 61% yields.

Bromination of anisoles **21a–d** at *para* position was performed by using *N*-bromosuccinimide in acetonitrile at rt (Scheme 4).[15] The desired bromoanisoles **4a–d** were recovered in good to excellent yields. Contrary to iodination, no abstraction of *tert*-butyl groups was observed during bromination of anisoles **21a–d**.



	a	b	c	d
R^1	*t*-Bu	*t*-Bu	*t*-Bu	Me
R^2	H	Me	Et	Me
R^3	Me	Me	Et	Me

Substrates	Bromo anisoles	Yields %
21a	**4a**	98
21b	**4b**	83
21c	**4c**	67
21d	**4d**	98

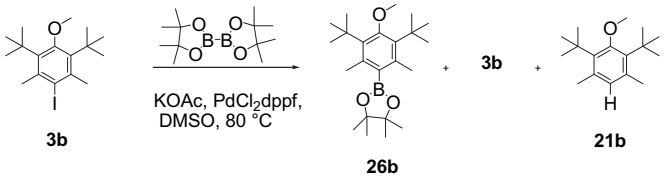
Scheme 4. Bromination of anisoles **21a–d**.

2.4. Synthesis of boronic esters 26 and acids 5

The next stage involved in the preparation of the boronic acids starting from either *para*-iodoanisoles **3a–b**, **3d** or *para*-bromoanisoles **4a–d**. Two synthetic pathways were consequently considered.

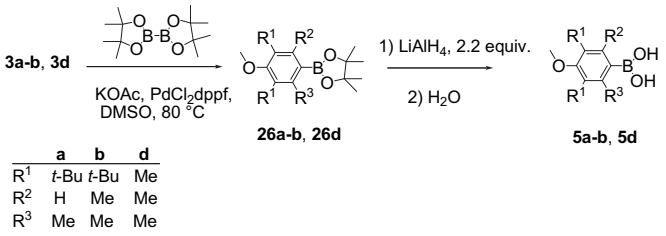
The first alternative consisted in the hydrolysis of the boronic ester obtained through the Miyaura's procedure from the foregoing iodoanisole **3a–b**, **3d**.[16] The borylation of iodoanisole **3b** was first run by using the accurate Miyaura's experimental conditions. A NMR analysis of the reaction mixture indicated the presence of three compounds in almost equal proportions: the desired boronic ester **26b**, the starting iodoanisole **3b** and the reduced anisole **21b** (Scheme 5, entry 1). The enhancement of the concentration of bis(pinacolato)diboron limited dehalogenation. Unfortunately, the amount of starting material still remained high (entry 2). On the contrary, the enhancement of concentration of catalyst bettered the borylation yield but still furthered the reduction of iodoanisole **3b** (entry 3). Finally, the best result was achieved with 2.2 equiv of bis(pinacolato)diboron in the presence of 10 mol% of catalyst (entry 4). These optimised conditions were extended to the preparation of the other boronic esters **26a** and **26d** (Scheme 6).

Many alternatives involving the hydrolysis of pinacol boronic esters into boronic acids are reported in lit.[17–20] To prepare boronic acid **5b**, we have tested three of them (Table 1).[17c,19,20c] No hydrolysis was detected using sodium periodate or diethanolamine (entry 5 and 6). In the presence of 1.1 equiv of $LiAlH_4$, an important amount of unconsumed **27b** was still recovered (entry 3). The best



Entry	Relative quantity of reagents			Products detected in the reaction mixture by NMR (%)		
	Iodoanisole **3b** (equiv.)	Bis(pinacolato)diboron (equiv.)	$PdCl_2dppf$ mol%	**26b**	**3b**	**21b**
1	1	1.2	3	35	34	31
2	1	2.2	3	51	30	19
3	1	1.2	10	53	15	32
4	1	2.2	10	89	-	11

Scheme 5. Optimisation of the syntheses of **26b**.

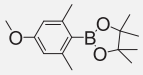
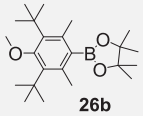


	a	b	d
R^1	*t*-Bu	*t*-Bu	Me
R^2	H	Me	Me
R^3	Me	Me	Me

Boronic esters	Yield %	Boronic acids	Yield %
26a	72	**5a**	67
26b	89	**5b**	63
26d	72	**5d**	68

Scheme 6. Syntheses of boronic esters **26a**,**b** and **26d**, boronic esters **5a**,**b** and **5d**, starting from bromoanisoles **3a**,**b** and **3d**.

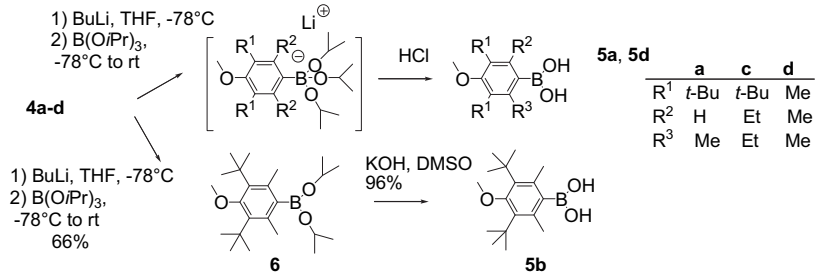
Table 1
Hydrolysis of boronic esters **26b** and **26e**

Ar–B(O)(O)	Entry	Conditions of the reaction	ArH[a]	Ar–B(OH)(OH) [a]	Ar–B(O)(O) [a]
 **26e**	1	(1) $LiAlH_4$ (2.2 equiv)[20] (2) H_2O	0% **21e**	100% **5e**	0% **26e**
	2	(1) $LiAlH_4$ (2.2 equiv) (2) H_2O	15% **21b**	65% (63%)[b] **5b**	20% **27b**
 **26b**	3	(1) $LiAlH_4$ (1.1 equiv) (2) H_2O	14% **21b**	52% **5b**	34% **27b**
	4	(1) $LiAlH_4$ (0.55 equiv) (2) H_2O	9% **21b**	0% **5b**	91% **27b**
	5	$NaIO_4$, NH_4OAc in acetone/H_2O[18c]	0% **21b**	0% **5b**	100% **27b**
	6	(1) Diethanolamine in *i*-PrOH/Et_2O [21c] (2) HCl	0% **21b**	0% **5b**	100% **27b**

[a] Yields determined by NMR.
[b] Isolated yield.

results were obtained using 2.2 equiv of $LiAlH_4$ as reducing agent.[19] Only 63% of boronic ester **26b** were converted into **5b** (entry 2). Besides, 15% of anisole **21b**, resulting from protodeboronation, and 20% of starting material **26b** were detected by NMR in the reaction mixture. And yet, starting from boronic ester **26e**, we had prepared as a model, the expected boronic acid **5e** was recovered quantitatively (entry 1). Nevertheless, this method was applied to the preparation of the other boronic acids **5a** and **5d** (Scheme 6).

Bromoanisoles **4a**–**d** were the starting point of a second alternative for the syntheses of boronic acids **5a**–**d**. Bromoanisoles were first treated with butyllithium in THF to lead to aryllithium compounds via a metal/halogen exchange. Addition of tri*iso*propyl borate to the reaction mixture was supposed to give lithium aryltri*iso*propyl borates.[21] An immediate hydrolysis afforded the expected boronic acids.[22] As for the reported borylations of 4-bromo-3,5-dimethylanisole[23] and 4-bromo-2,6-di*tert*butylanisole,[24] such reactional sequences were observed during the preparation of boronic acids **5a** and **5d** (Scheme 7).Unexpectedly, the reaction involving **5b**, gave the only aryldi*iso*propyl borate **6** in a 66% yield. To the best of our knowledge, during a bromide/lithium exchange, such a derivative is only obtained by acidification of lithium aryltri*iso*propyl borate intermediates with anhydrous



	a	c	d
R^1	*t*-Bu	*t*-Bu	Me
R^2	H	Et	Me
R^3	Me	Et	Me

Boronic acids	Yield %
5a	58
5c	0
5d	55

Scheme 7. Syntheses of boronic acids **5a**,**b**, **5d**, starting from **4a**,**b**, **4d**.

Table 2
Global yields from **10a–c**

Substrates	Iodoanisoles	Number of steps from **10a–c**	Yields %	Boronic acids	Number of steps from **10a–c**	Yields %
10a	**3a**	8	28	**5a**	10	13
10b	**3b**	8	23	**5b**	10	13
10c	**3c**	8	—	**5c**		—
10b	**3d**	4	48	**5d**	6	27
Substrates	Bromoanisoles	Number of steps from **10a–c**	Yields %	Boronic acids	Number of steps from **10a–c**	Yields %
10a	**4a**	8	27	**5a**	9	16
10b	**4b**	8	27	**5b**	10	17
10c	**4c**	8	13	**5c**		—
10b	**4d**	4	78	**5d**	5	43

hydrogen chloride.[21] This unexpected acyclic boronic ester was stable enough to be chromatographed and can be handled in air without special precautions. Its easy obtaining was probably a consequence of its stability attributable to the presence at the same time, on the aromatic ring, of *tert*-butyl and methyl groups. The leaving space between the two methyl groups was actually too narrow for a bulky tri*iso*propyl ester functionality. Moreover, ester **6** was stable as well in an acidic or a basic medium at rt. The extreme steric hindrance considerably slowed hydrolysis of boronic ester function. This hydrolysis was however performed by heating at 60 °C for two hours, using sodium hydroxide in a mixture of DMSO/water, even though the hydrolysis of all acyclic boronic esters is known to be very rapid.[25] The expected boronic acid **5b** was thus recovered in a 96% yield. It must be pointed out that the hydrolysis of the pinacol ester **26b**, in the above conditions of reaction, did not succeed.

Attempts to convert bomoanisole **4c** into boronic acid **5c** gave a complete protodeboronation of the substrate leading to the only recovery of **21c**. The gap existing between the two ethyl groups was certainly too narrow to allow a reaction with borate. This result was however in accordance with the unsuccessful synthesis of iodoanisole **3c**.

3. Conclusion

In conclusion, sterically hindered iodoanisoles **3a–b** and **3d** were readily synthesised, as their corresponding boronic esters **26a–b**, **26d** and acids **5a–b**, **5d**. Global yields are tabulated in Table 2. A too large steric hindrance precluded the recovering of iodoanisole **3c**.

Sterically hindered bromoanisoles **4a–d** and boronic acids **5a** and **5d** were readily synthesised too (Table 2). However, after a metal-lithium exchange, as the steric hindrance increased, the reaction with tri*iso*propyl borate became more and more difficult. The bulky *tert*-butyl groups must lead to a bending of the molecule. The two substituents at *meta* of the anisole function moving away from *tert*-butyl groups, narrowed *para* position. The steric hindrance in the vicinity of boron atom was extreme. As a consequence, the reaction of dimethylbromoanisoles **4b** afforded the unexpected and stable aryldi*iso*propyl borate **6**, and the reaction of diethylbromoanisole **4c** was totally unsuccessful, only protodeboronation occurred, leading to the only recovery of dehalogenated anisole **21c**. The final obtaining of **5b** from ester **6** required a strong basic hydrolysis (DMSO/water) with heating.

4. Experimental

4.1. General points

Reagents were purchased from commercial suppliers and used without further purification. THF and toluene were freshly distilled from sodium/benzophenone, DMSO and dioxane was dried over 3 Å molecular sieves. All melting points were taken on a Kofler bench. IR spectra (cm^{-1}) were recorded on a Nicolet 205 FTIR spectrometer. ^1H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were measured on a Brucker Avance serie 400 at 295 K. Chemical shifts are reported in ppm relative to $SiMe_4$. HPLC analyses were performed on an Agilent Technologies 1100 series system using a Kromasil column (C18 4.6×250 mm, 100 Å, 5 μm) at an outflow of 1 mL/min, and a UV detection at 230 nm. Microanalyses were performed by the analytical service of the *Service de Microanalyse du CNRS* in Vernaison and high resolution MS was measured either on a Waters Micromass Q-TOF Ultima API spectrometer in the firm *Basilea Pharmaceuticals* in Basel (Switzerland) or by the analytical service of the *Service de Microanalyse du CNRS* in Vernaison.

Previously reported procedures were used to prepare dimethyl 2-hydroxy-4-methylisophtalate **10a**,[6a] dimethyl 2-hydroxy-4,6-dimethylisophtalate **10b**,[1a] dimethyl 4,6-diethyl-2-hydroxyisophthalate **10c**,[1a] 2,3,5,6-tetramethyphenol **23**[1a] and 4-bromo-3,5-dimethyl anisole **4e**.[3a]

4.2. General procedures

4.2.1. Procedure A, protection of phenol. To a solution of phenol **10a–c** (1 equiv) in acetone (3 mL per mmol of **10a–c**) were successively added, under Ar, K_2CO_3 (1.2 equiv) and MeI (2 equiv). The reaction mixture was heated at reflux overnight and was then allowed to reach rt. Solids were filtered off and washed with acetone. The filtrate was then evaporated under reduced pressure and the crude dissolved in Et_2O. This organic layer was successively washed with aqueous 1 M Na_2CO_3 and water, dried over $MgSO_4$ and evaporated under reduced pressure to afford **13a–c**. These crude materials were used in the next step without further purification.

4.2.2. Procedure B, reduction of the dimethyl ester. To a suspension of $LiAlH_4$ (2.5 equiv) in anhydrous THF (2.5 mL per mmol of **13a–c**) was added dropwise, under Ar, at 0 °C, a solution of protected dimethyl esters **13a–c** (1 equiv) in anhydrous THF (2.5 mL per mmol of **13a–c**). The reaction mixture was stirred overnight at rt. AcOEt was then carefully added at 0 °C in order to neutralise $LiAlH_4$ in excess. The reaction mixture was acidified with aqueous 1 M HCl until total dissolution of the aluminium salts. The resulting aqueous solution was extracted three times with AcOEt. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to afford **14a–c**, which were used in the next step without further purification.

4.2.3. Procedure C, substitution with Br. To a suspension of **14a–c** in dioxane (5 mL per mmol of **14a–c**) was added dropwise, under Ar, a solution of PBr_3 in dioxane (1 mL per mmol of **14a–c**). The reaction mixture was stirred overnight at rt. The reaction mixture was then poured over crushed ice and neutralised by addition of

solid K_2CO_3. The aqueous solution was extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to afford **7a–c**, which were used in the next step without further purification.

4.2.4. Procedure D, substitution with CN. To an aqueous 0.25 M NBu_4Br solution (2 mL per mmol of **7a–c**) were successively added KCN (4 equiv) and a solution of **7a–c** (1 equiv) in CH_2Cl_2 (2 mL per mmol of **7a–c**). The reaction mixture was vigorously stirred overnight and then diluted with CH_2Cl_2. The organic layer was separated and washed twice with water. CH_2Cl_2 was removed under reduced pressure and the crude product dissolved in Et_2O. This organic layer was washed three times with water, dried over $MgSO_4$, and evaporated under reduced pressure to afford **15a–c**. The isolated products were used in the next step without further purification.

4.2.5. Procedure E, tetramethylation. To a solution of $NHiPr_2$ (8.2 equiv) in anhydrous THF (3.6 mL per mmol of **15a–c**), at −78 °C, were successively added dropwise, under Ar, BuLi (1.6 M in hexanes, 8.1 equiv) and **15a–c** dissolved in anhydrous THF (5.6 mL per mmol of **15a–c**). The reaction mixture was stirred for 20 min at −78 °C. Methyliodide (12 equiv) was then added dropwise. After two more hours, at −78 °C, the reaction mixture was allowed to reach rt. After a careful hydrolysis with water, this aqueous layer was extracted with CH_2Cl_2. The organic layer was thoroughly washed twice with aqueous 1 M HCl and once with water. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to afford **16a–c**, which were used in the next step without further purification.

4.2.6. Procedure F, reduction. To a solution of **16a–c** (1 equiv) in anhydrous toluene (2.5 mL per mmol of **16a–c**) was added dropwise, under Ar, at 0 °C, a solution of DIBALH (2.3 equiv) in anhydrous toluene. The reaction mixture was stirred at 0 °C for 2 h and then hydrolysed under stirring with water and made basic with aqueous 1 M NaOH. 30 min later, the obtained solution was diluted with aqueous 1 M NaOH and was extracted three times with Et_2O. The combined organic layers were then dried over $MgSO_4$, and evaporated under reduced pressure. The obtained residue was dissolved in CH_2Cl_2 (5 mL per mmol of **16a–c**). Water (5 mL per mmol of **16a–c**) and NBu_4HSO_4 (2.2 equiv) were successively added and the reaction mixture was vigorously stirred at rt overnight. The aqueous layer was separated and thoroughly extracted with CH_2Cl_2. The organic layers were combined and evaporated under reduced pressure. The crude product dissolved in Et_2O was washed three times with water. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to afford **20a–c**, which were used in the next step without further purification.

4.2.7. Procedure G, Wolff–Kishner reaction. A Dean-Stark apparatus was fitted on a flask under Ar, containing **20a–c** (1 equiv), $NH_2NH_2{\cdot}H_2O$ (7 equiv) and powdered KOH (6.5 equiv) in diethylene glycol (4 mL per mmol of **20a–c**). The reaction mixture was heated by means of an oil bath at 160 °C during 1.5 h and then at 200 °C. The internal temperature of the reaction mixture raised 195 °C and allowed the elimination of the excess of water and hydrazine by an azeotropic distillation. The reaction mixture was then allowed to reach rt. Water was then added. This aqueous solution was extracted three times with cyclohexane. The combined organic layers were washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (cyclohexane) afforded the pure anisoles **21a–c**.

4.2.8. Procedure H, iodination. To a solution of anisoles **21a–d** (1 equiv) in chloroform (12 mL per mmol of **21a–d**) were added, under Ar, first $AgCO_2CF_3$ (1.2 equiv) then a solution of I_2 (1.2 equiv) in chloroform (12 mL per mmol of **21a–d**). On completion of the reaction (about 15 min), the suspended silver salts were filtered off. The filtrate was successively washed with aqueous saturated solution of $Na_2S_2O_3$ and water. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (cyclohexane) afforded the different iodoanisoles.

4.2.9. Procedure I, bromination. To a solution of **21a–d** (1 equiv) in MeCN (8 mL per mmol of **21a–d**) was added, under Ar, NBS (1.4 equiv). The reaction mixture was stirred at rt overnight. The solvent was evaporated under reduced pressure. Cyclohexane was then added to the crude residue. Insoluble solids were filtered off and rinsed with another portion of cyclohexane. The filtrate was evaporated under reduced pressure. Purification by column chromatography (cyclohexane) afforded the pure bromoanisoles **4a–d**.

4.2.10. Procedure J, preparation of the boronic esters. 4-Iodoanisoles **3a–b**, **3d** (1 equiv), $PdCl_2dppf$, CH_2Cl_2 (0.1 equiv), K_2CO_3 (3 equiv), bis(pinacolato)diboron (2.2 equiv) and DMSO (6 mL per mmol of iodoanisole) were successively added in a flask under Ar. After heating at 80 °C overnight, the reaction mixture was allowed to reach rt. Et_2O was added and the organic layer was extracted three times with water. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography afforded desired boronic esters **26a–b**, **26d**.

4.2.11. Procedure K, hydrolysis of boronic esters. To a suspension of $LiAlH_4$ (2.2 equiv) in anhydrous THF (2.5 mL per mmol of **26a–b**, **26d**) was added dropwise, under Ar, at 0 °C, a solution of boronic ester **26a–b**, **26d** (1 equiv) in anhydrous THF (2.5 mL per mmol of **26a–b**, **26d**). The reaction mixture was stirred for 2 h at 0 °C and 1 h more, at rt. $Na_2SO_4{\cdot}10H_2O$ (4 equiv) was then added, to the reaction mixture. The aluminium salts were dissolved by addition of aqueous 1 M H_2SO_4. The obtained aqueous solution was extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (cyclohexane/ethyl acetate) afforded pure **5a–b**, **5d**.

4.2.12. Procedure L. To a solution of **4a–d** (1 equiv) in anhydrous THF (7 mL per mmol of **4a–d**) under Ar, at −78 °C, was added dropwise BuLi (2.5 M in cyclohexane, 2.2 equiv). The reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was then transferred via cannula into a solution at −78 °C of tri*iso*propyl borate (5 equiv) in anhydrous THF (2.5 mL per mmol of **4a–d**). The mixture was further stirred 1 h at −78 °C and then allowed to reach rt. Aqueous 1 M HCl (21.5 mL per mmol of **4a–d**) was added. The obtained aqueous phase was extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (cyclohexane/ethyl acetate) afforded **5**, **6**, **5d**, **21c**.

4.3. Synthesis of derivatives

*4.3.1. Dimethyl-2-methoxy-4-methylisophthalate (**13a**).* Starting from **10a** (2.39 g, 10.7 mmol), following procedure A, was obtained **13a** (2.54 g, quant.) as a colourless solid. Mp<40 °C. ^{1}H NMR ($CDCl_3$) δ=2.33 (3H, s), 3.87 (3H, s), 3.91 (3H, s), 3.93 (3H, s), 7.01 (1H, d, J=8.1 Hz), 7.80 (1H, d, J=8.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ=19.6, 52.3, 52.5, 63.8, 121.9, 125.6, 130.7, 132.8, 141.7, 157.7, 165.8, 168.1 ppm. IR (KBr) ν_{max}: 799, 811, 1002, 1069, 1115, 1145, 1153, 1216, 1246, 1266, 1312, 1401, 1435, 1450, 1459, 1482, 1604, 1733,

2952 cm^{-1}. HRMS (ESI-Q-Tof) *m/z* calcd for $C_{12}H_{14}O_5$ $[M+Li]^{\bullet+}$ 245.1001, found 245.0990.

*4.3.2. Dimethyl-2-methoxy-4,6-dimethylisophthalate (**13b**).* Starting from **10b** (10 g, 42 mmol), following procedure A, was obtained **13b** (9.66 g, 91%) as a colourless solid. Mp 64 °C. ^1H NMR ($CDCl_3$) δ=2.27 (6H, s), 3.80 (3H, s), 3.90 (6H, s), 6.82 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=19.6, 52.4, 63.6, 126.0, 127.6, 138.5, 155.1, 168.1 ppm. IR (KBr) ν_{max}: 864, 890, 933, 954, 1004, 1026, 1043, 1084, 1120, 1194, 1207, 1264, 1284, 1308, 1386, 1399, 1443, 1481, 1610, 1687, 1720, 1728, 2950, 2994 cm^{-1}. HRMS (ESI-Q-Tof) *m/z* calcd for $C_{13}H_{16}O_5$ $[M+Li]^{\bullet+}$ 259.1158, found 259.1130.

*4.3.3. Dimethyl-4,6-diethyl-2-methoxyisophthalate (**13c**).* Starting from **10c** (6.4 g, 24.1 mmol), following procedure A, was obtained **13c** (6.20 g, 92%) as a colourless oil. ^1H NMR ($CDCl_3$) δ=1.20 (6H, t, *J*=7.6 Hz), 2.59 (4H, q, *J*=7.6 Hz), 3.81 (3H, s), 3.90 (6H, s), 6.88 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=15.5, 26.8, 52.4, 63.6, 124.6, 125.8, 144.7, 154.7, 168.3 ppm. IR (film) ν_{max}: 913, 975, 987, 1038, 1072, 1095, 1113, 1180, 1202, 1233, 1263, 1303, 1330, 1403, 1434, 1455, 1463, 1469, 1559, 1564, 1605, 1732, 1737, 2877, 2904, 2950, 2971 cm^{-1}. HRMS (ESI-Q-Tof) *m/z* calcd for $C_{15}H_{20}O_5$ $[M+H]^{\bullet+}$ 281.1389, found 281.1367.

*4.3.4. 2,6-Bis(hydroxymethyl)-3-methylanisole(**14a**).* Starting from **13a** (2.88 g, 12.1 mmol), following procedure B, was obtained, after purification by column chromatography (AcOEt/cyclohexane 3:7), **14a** (2.11 g, 96%) as a colourless solid. Mp was in agreement with the lit.[26] ^1H NMR ($CDCl_3$) δ=2.00 (2H, br s), 2.41 (3H, s), 3.87 (3H, s), 4.70 (2H, s), 4.76 (2H, s), 6.98 (1H, d, *J*=7.8 Hz), 7.22 (1H, d, *J*=7.8 Hz) ppm.

*4.3.5. 2,6-Bis(hydroxymethyl)-3,5-dimethylanisole (**14b**).* Starting from **13b** (5 g, 19.8 mmol), following procedure B was obtained **14b** (3.09 g, 80%) as a colourless solid. Mp was in agreement with the lit.[27] ^1H NMR ($CDCl_3$) δ=1.84 (2H, t, *J*=5.3 Hz), 2.37 (6H, s), 3.88 (3H, s), 4.73 (4H, d, *J*=5.3 Hz), 6.86 (1H, s) ppm.

*4.3.6. 3,5-Diethyl-2,6-bis(hydroxymethyl)anisole (**14c**).* Starting from **13c** (6.3 g, 22.5 mmol), following procedure B, was obtained, after purification by column chromatography (AcOEt/cyclohexane 5:5), **14c** (2.84 g, 56%) as a colourless solid. An analytically pure sample was obtained by sublimation (120 °C, 1 Torr). Mp 112 °C. ^1H NMR ($CDCl_3$) δ=1.23 (6H, t, *J*=7.6 Hz), 1.98 (2H, t, *J*=5.6 Hz), 2.73 (4H, q, *J*=7.6 Hz), 3.90 (3H, s), 4.74 (4H, d, *J*=5.6 Hz), 6.90 (1H, br s) ppm. ^{13}C NMR ($CDCl_3$) δ=16.1, 26.0, 57.1, 63.4, 125.7, 129.2, 144.9, 158.3 ppm. IR (KBr) ν_{max}: 876, 979, 998, 1018, 1026, 1044, 1077, 1092, 1336, 1408, 1425, 1453, 1459, 1481, 1605, 2905, 2965, 3310 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_3$ (224.30): C, 69.61; H, 8.99, found: C, 69.35; H, 8.97. HRMS (ESI-Q-Tof) *m/z* calcd for $C_{13}H_{20}O_3$ $[M+Na]^{\bullet+}$ 247.1310, found 247.1315.

*4.3.7. 2,6-Bis(bromomethyl)-3-methylanisole (**7a**).* Starting from **14a** (1.82 g, 10 mmol), following procedure C, was obtained compound **7a** (3.08 g, quant.) as a colourless solid. An analytically pure sample was obtained by sublimation (100 °C, 1 Torr). Mp 95 °C. ^1H NMR ($CDCl_3$) δ=2.41 (3H, s), 4.03 (3H, s), 4.55 (2H, s), 4.62 (2H, s), 6.97 (1H, d, *J*=7.8 Hz), 7.28 (1H, d, *J*=7.8 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ=19.0, 25.7, 28.1, 62.4, 127.1, 129.3, 130.3, 131.9, 140.7, 157.1 ppm. IR (KBr) ν_{max}: 584, 743, 788, 826, 925, 971, 997, 1051, 1123, 1132, 1198, 1208, 1239, 1260, 1406, 1427, 1443, 1459, 1487, 1576, 1602, 2941 cm^{-1}. Anal. Calcd for $C_{10}H_{12}Br_2O$ (308.01): C, 38.99; H, 3.93. Found: C, 39.28; H, 4.01. HRMS (ESI-Q-Tof) *m/z* calcd for $C_{10}H_{12}Br_2O$ $[M+Na]^{\bullet+}$ 328.9153, found 328.9164.

*4.3.8. 2,6-Bis(bromomethyl)-3,5-dimethylanisole (**7b**).* Starting from **14b** (392 mg, 2 mmol), following procedure C, was obtained compound **7b** (608 mg, 94%) as a colourless solid. An analytically pure sample was obtained by sublimation (100 °C, 1 Torr). Mp 124 °C. ^1H NMR ($CDCl_3$) δ=2.38 (6H, s), 4.04 (3H, s), 4.61 (4H, s), 6.85 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=18.9, 26.3, 62.3, 127.6, 129.1, 140.2, 157.5 ppm. IR (KBr) ν_{max}: 459, 539, 556, 566, 582, 816, 871, 933, 996, 1028, 1057, 1142, 1187, 1198, 1208, 1243, 1299, 1401, 1426, 1439, 1458, 1561, 1564, 1608, 2956 cm^{-1}. Anal. Calcd for $C_{11}H_{14}Br_2O$ (322.04): C, 41.03; H, 4.38. Found: C, 40.86; H, 4.25. HRMS (ESI-Q-Tof) *m/z* calcd for $C_{11}H_{14}Br_2O$ $[M+Na]^{\bullet+}$ 342.9309, found 342.9319.

*4.3.9. 2,6-Bis(bromomethyl)-3,5-diethylanisole (**7c**).* Starting from **14c** (2.76 g, 12.3 mmol), following procedure C, was obtained compound **7c** (4.41 g, quant.) as a colourless solid. An analytically pure sample was obtained by sublimation (90 °C, 0.1 mmHg). Mp 90 °C. ^1H NMR ($CDCl_3$) δ=1.29 (6H, t, *J*=7.6 Hz), 2.76 (4H, q, *J*=7.6 Hz), 4.06 (3H, s), 4.64 (4H, s), 6.91 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=14.9, 25.2, 25.7, 62.3, 125.2, 127.0, 146.1, 157.7 ppm. IR (KBr) ν_{max}: 469, 501, 577, 665, 884, 920, 967, 983, 1028, 1052, 1068, 1143, 1209, 1228, 1236, 1259, 1280, 1405, 1426, 1446, 1450, 1561, 1597, 2834, 2873, 2965, 2994 cm^{-1}. Anal. Calcd for $C_{13}H_{18}Br_2O$ (350.09): C, 44.60; H, 5.18. Found: C, 44.53; H, 5.18. HRMS (ESI-Q-Tof) *m/z* calcd for $C_{13}H_{18}Br_2O$ $[M+Na]^{\bullet+}$ 370.9622, found 370.9631.

*4.3.10. 2,6-Bis-(cyanomethyl)-3-methylanisole (**15a**).* Starting from **7a** (2.55 g, 8.3 mmol), following procedure D, was obtained compound **15a** (1.61 g, 97%) as a colourless solid. An analytically pure sample was obtained by sublimation (120 °C, 1 Torr). Mp 75–80 °C. ^1H NMR ($CDCl_3$) δ=2.42 (3H, s), 3.72 (2H, s), 3.73 (2H, s), 3.86 (3H, s), 7.06 (1H, d, *J*=7.8 Hz), 7.32 (1H, d, *J*=7.8 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ=15.1, 18.5, 19.6, 62.1, 117.4, 117.8, 121.9, 123.5, 127.2, 129.7, 139.4, 156.1 ppm. IR (KBr) ν_{max}: 817, 950, 1004, 1065, 1197, 1220, 1260, 1276, 1300, 1417, 1451, 1459, 1488, 1579, 2251, 2931, 2944, 2968 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O$ (200.24): C, 71.98; H, 6.04; N, 13.9. Found: C, 72.06; H, 6.20; N, 13.61.

*4.3.11. 2,6-Bis-(cyanomethyl)-3,5-dimethylanisole (**15b**).* Starting from **7b** (3.8 g, 11.8 mmol), following procedure D, was obtained compound **15b** (2.42 g, 96%) as a colourless solid. An analytically pure sample was obtained by sublimation (110 °C, 1 Torr). Mp 138 °C. ^1H NMR ($CDCl_3$) δ=2.38 (6H, s), 3.69 (4H, s), 3.87 (3H, s), 6.92 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=15.1, 19.5, 62.6, 117.6, 120.8, 129.0, 138.7, 156.5 ppm. IR (KBr) ν_{max}: 628, 880, 954, 998, 1036, 1078, 1216, 1305, 1384, 1407, 1424, 1449, 1463, 1482, 1567, 1615, 2248, 2935, 2969, 2978, 3010 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O$ (214.26): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.88; H, 6.59; N, 13.00.

*4.3.12. 2,6-Bis-(cyanomethyl)-3,5-diethylanisole (**15c**).* Starting from **7c** (3.95 g, 11.3 mmol), following procedure D, was obtained compound **15c** (2.43 g, 89%) as a colourless solid. An analytically pure sample was obtained by sublimation (110 °C, 1 Torr). Mp 93 °C. ^1H NMR ($CDCl_3$) δ=1.29 (6H, t, *J*=7.6 Hz), 2.72 (4H, q, *J*=7.6 Hz), 3.71 (4H, s), 3.90 (3H, s), 6.96 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=14.6, 14.7, 26.1, 62.5, 118.1, 120.3, 125.3, 144.6, 156.7 ppm. IR (KBr) ν_{max}: 881, 936, 972, 986, 1034, 1077, 1086, 1207, 1284, 1328, 1414, 1451, 1459, 1469, 1569, 1608, 2249, 2873, 2936, 2969 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O$ (242.32): C, 74.35; H, 7.49; N, 11.56. Found: C, 74.52; H, 7.39; N, 11.23.

*4.3.13. 2,6-Bis[2-(2-cyanopropyl)]-3-methylanisole (**16a**).* Starting from **15a** (1.51 g, 7.55 mmol), following procedure E, was obtained compound **16a** (1.0 g, 52%) as a colourless solid. An analytically pure sample was obtained by sublimation (120 °C, 1 Torr). Mp 145 °C. ^1H NMR ($CDCl_3$) δ=1.76 (6H, s), 2.01 (6H, s), 2.61 (3H, s), 3.87 (3H, s), 6.96 (1H, d, *J*=8.1 Hz), 7.14 (1H, d, *J*=8.1 Hz) ppm. ^{13}C NMR ($CDCl_3$)

δ=22.5, 28.9 (2C), 28.9 (2C), 33.5, 36.1, 65.2, 125.5, 125.6, 125.8, 128.5, 133.0, 133.6, 139.0, 158.0 ppm. IR (KBr) ν_{max}: 815, 997, 1018, 1039, 1167, 1206, 1227, 1251, 1376, 1388, 1446, 1459, 1467, 2231, 2948, 2989 cm^{-1}. HRMS (ESI-Q-Tof) *m/z* calcd for $C_{16}H_{20}N_2O$ $[M+H]^{\bullet+}$ 257.1654, found 257.1664.

*4.3.14. 2,6-Bis[2-(2-cyanopropyl)]-3,5-dimethylanisole (**16b**).* Starting from **15b** (1.07 g, 5 mmol), following procedure E, was obtained compound **16b** (1.28 g, 95%) as a colourless solid. An analytically pure sample was obtained by sublimation (120 °C, 1 Torr). Mp 120 °C. ^1H NMR ($CDCl_3$) δ=1.91 and 1.98 (12H, br s, 2 rotamers), 2.53 (6H, s), 3.67 (3H, s), 6.80 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=22.3 ($2CH_{3aryl}$), 29.0 and 29.7 (br s, $4CH_{3propyl}$, 2 rotamers), 35.6 ($2C_{propyl}$, 2 rotamers), 65.1 (OCH_3), 125.9 (2CN), 130.8 ($C_{(2)}$, $C_{(6)}$), 133.1 ($C_{(4)}$), 136.9 ($C_{(3)}$, $C_{(5)}$), 158.0 ($C_{(1)}$) ppm. IR (KBr) ν_{max}: 847, 996, 1023, 1034, 1065, 1106, 1124, 1177, 1188, 1232, 1286, 1376, 1388, 1438, 1485, 1471, 2229, 2943, 2985 cm^{-1}. HRMS (ESI-Q-Tof) *m/z* calcd for $C_{17}H_{22}N_2O$ $[M+NH_4]^{\bullet+}$ 288.2076, found 288.2072.

*4.3.15. 2-(1-Cyanoethyl)-6-[2-(2-cyanopropyl)]-3,5-dimethylanisole (**17**) and 2,6-bis-(1-cyanoethyl)-3,5-dimethylanisole (**18**).* Compounds **17** and **18** were separated from **16b** by HPLC (Acetonitrile/Water 60:40) and were only characterised by NMR.

Compound **17**: ^1H NMR ($CDCl_3$) δ=1.62 (3H, d, *J*=8 Hz), 1.91 (3H, s), 1.94 (3H, s), 2.49 (3H, s), 2.54 (3H, s), 3.75 (3H, s), 4.51 (1H, q, *J*=8 Hz), 6.84 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=18.4 (CH_{3ethyl}), 19.3 ($C_{(3)}$-CH_{3aryl}), 22.4 (C_{ethyl}), 22.7 ($C_{(5)}$-CH_{3aryl}), 29.6 ($CH_{3propyl}$), 29.7 ($CH_{3propyl}$), 35.6 (C_{propyl}), 63.9 (OCH_3), 121.5 (CN_{ethyl}), 126.0 (CN_{propyl}), 129.6 ($C_{(6)}$), 132.5 ($C_{(4)}$), 137.3 ($C_{(3)}$), 137.5 ($C_{(5)}$), 156.1 ($C_{(1)}$) ppm.

Compound **18**: ^1H NMR ($CDCl_3$) δ=1.615 (6H, d, *J*=8 Hz, 2 diastereomers), 1.625 (6H, d, *J*=8 Hz, 1 diastereomer), 2.47 (6H, s, 2 diastereomers), 2.48 (6H, s, 2 diastereomers), 3.82 (3H, s), 4.41 (2H, q, *J*=8 Hz, 2 diastereomers), 4.42 (2H, q, *J*=8 Hz, 2 diastereomers), 6.86 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=18.4 ($2CH_{3ethyl}$, 1 diastereomer), 18.5 ($2CH_{3ethy}$, 1 diastereomer), 19.5 ($2CH_{3aryl}$, 2 diastereomers), 22.7 ($2C_{ethyl}$, 2 diastereomers), 63.3 (OCH_3, 2 diastereomers), 121.4 (2CN, br, 2 diastereomers), 126.7 ($C_{(2)}$, $C_{(6)}$, br, 2 diastereomers), 130.9 ($C_{(4)}$, 1 diastereomer), 131.0 ($C_{(4)}$, 1 diastereomer), 137.6 ($C_{(3)}$, $C_{(5)}$, br, 2 diastereomers), 155.3 ($C_{(1)}$, 1 diastereomer), 155.4 ($C_{(1)}$, 1 diastereomer) ppm.

*4.3.16. 2,6-Bis[2-(2-cyanopropyl)]-3,5-diethylanisole (**16c**).* Starting from **15c** (250 mg, 1.03 mmol), following procedure E, was obtained compound **16c** (252 mg, 82%) as a colourless oil. ^1H NMR ($CDCl_3$) δ=1.31 (6H, t, *J*=7.3 Hz), 1.89 (6H, br s), 2.00 (6H, br s), 2.85 (2H, m), 2.92 (2H, m), 3.63 (3H, s), 6.94 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=16.4, 26.7, 30.0 (br), 30.6 (br), 35.7, 65.3, 126.6, 129.7, 130.1, 143.8, 157.5 ppm. IR (film) ν_{max}: 978, 1033, 1059, 1079, 1104, 1124, 1188, 1231, 1276, 1372, 1387, 1463, 1534, 1598, 2229, 2877, 2940, 2979 cm^{-1}. HRMS (ESI-Q-Tof) *m/z* calcd for $C_{19}H_{26}N_2O$ $[M+Na]^{\bullet+}$ 321.1943, found 321.1907.

*4.3.17. 2,6-Bis[2-(2-iminomethylpropyl)]-3,5-dimethylanisole (**19b**).* ^1H NMR ($CDCl_3$) δ=1.49–1.54 (12H, m), 2.44 (6H, s), 3.19 (3H, s), 6.77 (1H, s), circa 8 (2H, br s), 8.22 (2H, s) ppm.

The other unstable diimines **19a** and **19c** were not isolated.

*4.3.18. 3-Methyl-2,6-bis[2-(2-formylpropyl)]anisole (**20a**).* Starting from **16a** (1.81 g, 7.07 mmol), following procedure F, was obtained compound **20a** (1.83 mg, 99%) as a colourless solid. Mp 108 °C. ^1H NMR ($CDCl_3$) δ=1.36 (6H, s), 1.48 (6H, s), 2.50 (3H, s), 3.22 (3H, s), 7.04 (1H, d, *J*=8.1 Hz), 7.17 (1H, d, *J*=8.1 Hz), 9.36 (1H, s), 9.51 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=22.6, 24.5 (4C), 48.8, 49.1, 61.8, 126.7, 130.5, 136.5, 137.3, 138.2, 154.4, 195.8, 199.6 ppm. IR (KBr) ν_{max}: 728, 833, 901, 994, 1002, 1042, 1235, 1362, 1384, 1391, 1447, 1459, 1465, 1710, 1724, 2718, 2816, 2940, 2979 cm^{-1}. HRMS (ESI-Q-Tof): *m/z* calcd for $C_{16}H_{22}O_3$ $[M+H]^{\bullet+}$ 263.1647, found 263.1633.

*4.3.19. 3,5-Dimethyl-2,6-bis[2-(2-formylpropyl)]anisole (**20b**).* Starting from **16b** (9.5 g, 35.2 mmol), following procedure F, was obtained compound **20b** (7.9 g, 81%) as a colourless solid. An analytically pure sample was obtained by recrystallisation from *i*-PrOH. Mp 173–174 °C. ^1H NMR ($CDCl_3$) δ=1.44 (12H, s), 2.44 (6H, s), 3.14 (3H, s), 6.83 (1H, s), 9.35 (2H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=20.4, 22.1, 24.1, 48.8, 60.9, 134.6, 134.7, 137.0, 154.3, 195.5 ppm. IR (KBr) ν_{max}: 712, 832, 892, 913, 989, 1004, 1039, 1061, 1100, 1184, 1209, 1246, 1279, 1363, 1389, 1444, 1465, 1596, 1719, 2708, 2806, 2940, 2984, 3418 cm^{-1}. HRMS (ESI-Q-Tof): *m/z* calcd for $C_{17}H_{24}O_3$ $[M+H]^{\cdot+}$ 277.1804, found 277.1805.

*4.3.20. 3,5-Diethyl-2,6-bis[2-(2-formylpropyl)]anisole (**20c**).* Starting from **16c** (2.12 g, 7.11 mmol), following procedure F, was obtained compound **20c** (1.79 g, 83%) as a colourless solid. Mp 153 °C. ^1H NMR ($CDCl_3$) δ=1.30 (6H, t, *J*=7.1 Hz), 1.46 (6H, s), 1.48 (6H, s), 2.71 (2H, dq, *J*=14.5, *J*=7.1 Hz), 2.86 (2H, dq, *J*=14.5, *J*=7.1 Hz), 3.12 (3H, s), 6.97 (1H, s), 9.36 (2H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=16.4, 21.5, 24.8, 26.5, 48.6, 60.9, 131.1, 133.9, 143.5, 153.6, 195.2 ppm. IR (KBr) ν_{max}: 710, 834, 885, 902, 968, 1005, 1021, 1056, 1077, 1100, 1268, 1335, 1366, 1391, 1438, 1444, 1453, 1457, 1467, 1474, 1476, 1542, 1594, 1648, 2813, 2817, 2885, 2940, 2965, 2980, 2993 cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_3$ (304.42): C, 74.96; H, 9.27. Found: C, 74.62; H, 9.29.

*4.3.21. 2,6-Di-tert-butyl-3-methylanisole (**21a**).* Starting from **20a** (627 mg, 2.39 mmol), following procedure G, was obtained compound **21a** (324 mg, 58%) as a colourless solid. An analytically pure sample was obtained by sublimation (70 °C, 1 Torr). Mp 32 °C. ^1H NMR ($CDCl_3$) δ=1.38 (9H, s), 1.53 (9H, s), 2.51 (3H, s), 3.57 (3H, s), 6.79 (1H, d, *J*=8.1 Hz), 7.04 (1H, d, *J*=8.1 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ=24.0, 31.7 (3C), 32.6 (3C), 35.4, 37.1, 64.5, 124.5, 127.5, 137.0, 141.4, 141.8, 160.7 ppm. IR (KBr) ν_{max}: 650, 794, 815, 873, 930, 996, 1018, 1046, 1109, 1166, 1190, 1210, 1233, 1363, 1369, 1380, 1440, 1455, 1465, 1478, 1616, 2872, 2914, 2931, 2964, 2987, 3027, 3440 cm^{-1}. HRMS (ESI-Q-Tof): *m/z* calcd for $C_{16}H_{26}O$ $[M+H]^{\bullet+}$ 235.3850, found 235.2065.

*4.3.22. 2,6-Di-tert-butyl-3,5-dimethylanisole (**21b**).* Starting from **20b** (7.05 g, 25.5 mmol), general procedure G, afforded compound **21b** (4.06 g, 64%) as a colourless solid. An analytically pure sample was obtained by sublimation (70 °C, 1 Torr). Mp 93 °C. ^1H NMR ($CDCl_3$) δ=1.49 (18H, s), 2.45 (6H, s), 3.46 (3H, s), 6.61 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=24.2, 32.9 (6C), 37.3, 64.4, 132.8, 134.9, 139.7, 161.7 ppm. IR (KBr) ν_{max}: 861, 931, 996, 1024, 1065, 1106, 1203, 1245, 1267, 1357, 1361, 1379, 1442, 1458, 1471, 1589, 2833, 2874, 2927, 2956, 3012 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O$ (248.40): C, 82.20; H, 11.36. Found: C, 82.15; H, 11.54.

*4.3.23. 2,6-Di-tert-butyl-3,5-diethylanisole (**21c**).* Starting from **20c** (1.61 g, 5.3 mmol), following procedure G, was obtained compound **21c** (896 mg, 61%) as a colourless solid. An analytically pure sample was obtained by sublimation (70 °C, 1 Torr). Mp 63 °C. ^1H NMR ($CDCl_3$) δ=1.25 (6H, t, *J*=7.6 Hz), 1.48 (18H, s), 2.79 (4H, q, *J*=7.6 Hz), 3.41 (3H, s), 6.73 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=17.6, 28.2, 33.9 (6C), 37.4, 64.7, 129.8, 138.6, 142.1, 160.8 ppm. IR (KBr) ν_{max}: 720, 847, 881, 907, 1024, 1035, 1058, 1079, 1108, 1191, 1202, 1242, 1264, 1319, 1364, 1378, 1396, 1455, 1478, 1523, 1591, 2878, 2968, 3010 cm^{-1}. Anal. Calcd for $C_{19}H_{32}O$ (276.47): C, 82.55; H, 11.67. Found: C, 82.55; H, 11.87.

*4.3.24. 2,4,5,6-Tetramethylanisole (**21d**).* (a) Compound **14b** (389 mg, 1.98 mmol), was hydrogenolysed over 5% Pd/C (90 mg) in MeOH

(7 mL) at rt for 8 h. The catalyst was removed by filtration through Celite using CH_2Cl_2 as eluent. After evaporation under reduced pressure, the crude product was purified by column chromatography (cyclohexane/CH_2Cl_2, 3:1). Anisole **21d** was obtained as a colourless solid (180 mg, 55%)

(b) Starting from 2,3,5,6-tetramethylphenol **23** (2.77 g, 18.47 mmol), following procedure A, was obtained compound **21d** (2.72 g, 90%) as a colourless solid after purification by column chromatography.

Spectroscopic data were in agreement with lit.[28]

*4.3.25. 2,6-Di-tert-butyl-4-iodo-3-methylanisole (**3a**).* Starting from **21a** (90 mg, 0.38 mmol), following procedure H, was obtained compound **3a** (138 mg, quant.) as a colourless oil after purification by column chromatography (cyclohexane). ^{1}H NMR ($CDCl_3$) δ=1.35 (9H, s), 1.51 (9H, s), 2.57 (3H, s), 3.58 (3H, s), 7.64 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=30.9, 31.3 (3C), 32.7 (3C), 35.3, 37.9, 64.6, 100.1, 135.7, 139.3, 143.3, 143.9, 161.2 ppm. IR (film) ν_{max}: 873, 1021, 1049, 1107, 1207, 1228, 1234, 1243, 1348, 1364, 1401, 1409, 1446, 1471, 1479, 2873, 2960, 3015 cm^{-1}. HRMS (ESI-Q-Tof): *m*/*z* calcd for $C_{16}H_{25}IO$ [M]$^{\bullet+}$ 360.2736, found 360.0965.

*4.3.26. 2,6-Di-tert-butyl-4-iodo-3,5-dimethylanisole (**3b**), 2-tert-butyl-6-iodo-3,5-dimethyl anisole (**24b**) and 2-tert-butyl-4,6-diiodo-3,5-dimethylanisole (**25b**).* Starting from **21b** (30 mg, 0.12 mmol), following procedure H, was obtained compound **3b** (32 mg, 71%) as a colourless solid after purification and separation from **24b** and **25b** by column chromatography (cyclohexane). Compound **24b** and **25b** were only characterised by ^{1}H NMR, and **24b** from the crude mixture.

Compound **3a**: mp 132 °C. ^{1}H NMR ($CDCl_3$) δ=1.50 (18H, s), 2.66 (6H, s), 3.43 (3H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=33.0, 33.3 (6C), 38.1, 64.6, 113.7, 138.6, 140.8, 161.6 ppm. IR (KBr) ν_{max}: 661, 882, 917, 936, 988, 1025, 1065, 1099, 1191, 1211, 1232, 1270, 1348, 1361, 1378, 1398, 1425, 1446, 2834, 2925, 2955, 3018 cm^{-1}. Anal. Calcd for $C_{17}H_{27}IO$ (374.30): C, 54.55; H, 7.27; I, 33.90, found: C, 54.53; H, 7.31; I, 33.77.

Compound **24b**: ^{1}H NMR ($CDCl_3$) δ=1.51 (9H, s), 2.37 (3H, s), 2.48 (3H, s), 3.66 (3H, s), 6.82 (1H, s) ppm.

Compound **25b**: mp 78 °C. ^{1}H NMR ($CDCl_3$) δ=1.52 (9H, s), 2.68 (3H, s), 2.92 (3H, s), 3.62 (3H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=29.8, 33.0 (3C), 33.3, 38.2, 62.4, 98.6, 107.2, 140.3, 142.3, 143.3, 158.8 ppm. IR (KBr) ν_{max}: 633, 919, 933, 969, 989, 1070, 1218, 1283, 1336, 1375, 1448, 2927, 2955 cm^{-1}.

*4.3.27. 2-tert-Butyl-3,5-diethyl-6-iodoanisole (**24c**).* Starting from **21c** (296 mg, 1.07 mmol), following procedure H, was obtained compound **24a** (289 mg, 78%) as a colourless solid after purification by column chromatography (cyclohexane). Mp 45 °C. ^{1}H NMR ($CDCl_3$) δ=1.20 (3H, t, *J*=7.6 Hz), 1.25 (3H, t, *J*=7.6 Hz), 1.51 (9H, s), 2.71 (2H, q, *J*=7.6 Hz), 2.85 (2H, q, *J*=7.6 Hz), 3.64 (3H, s), 6.87 (1H, s) ppm. ^{13}C NMR (100 MHz) δ=14.6, 17.4, 28.2, 33.4 (3C), 34.4, 37.2, 62.5, 98.7, 127.7, 138.6, 145.9, 146.1, 158.2 ppm. IR (KBr) ν_{max}: 690, 875, 914, 976, 1010, 1024, 1036, 1062, 1076, 1085, 1204, 1226, 1274, 1365, 1380, 1450, 1455, 1459, 1480, 2873, 2894, 2932, 2948, 2968 cm^{-1}. HRMS (ESI-Q-Tof): *m*/*z* calcd for $C_{15}H_{23}IO$ [M+H]$^{\cdot+}$ 347.0872, found 347.0861.

*4.3.28. 4-Iodo-2,3,5,6-tetramethylanisole (**3d**).* Starting from **21d** (180 mg, 1.10 mmol), following procedure H, was obtained compound **3d** (195 mg, 61%) as a colourless solid, after purification by column chromatography (cyclohexane/AcOEt 95:5). ^{1}H NMR spectroscopic data were in agreement with lit.[29] ^{1}H NMR ($CDCl_3$) δ=2.29 (6H, s), 2.48 (6H, s), 3.64 (3H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=14.4, 27.1, 60.1, 105.5, 127.5, 135.5, 156.7 ppm. IR (KBr) ν_{max}: 903, 1002, 1093, 1172, 1212, 1295, 1374, 1387, 1420, 1433, 1438, 2923, 2934, 2950, 2997 cm^{-1}.

*4.3.29. 4-Bromo-2,6-di-tert-butyl-3-methylanisole (**4a**).* Starting from **21a** (236 mg, 1.01 mmol), following procedure I, was obtained compound **4a** (309 mg, 98%) as a colourless solid after purification by column chromatography (cyclohexane). Mp 30.5 °C. ^{1}H NMR ($CDCl_3$) δ=1.35 (9H, s), 1.52 (9H, s), 2.51 (3H, s), 3.57 (3H, s), 7.35 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=24.7, 31.3 (3C), 32.7 (3C), 35.5, 37.8, 64.6, 122.6, 128.9, 136.2, 142.9, 144.1, 160.1 ppm. IR (film) ν_{max}: 871, 996, 1022, 1050, 1112, 1208, 1228, 1237, 1353, 1380, 1392, 1401, 1411, 1446, 1471, 2873, 2929, 2961, 3015 cm^{-1}. Anal. Calcd for $C_{16}H_{25}BrO$ (313.27): C, 61.34; H, 8.04; Br, 25.51. Found: C, 61.19; H, 8.15; Br, 25.67.

*4.3.30. 4-Bromo-2,6-di-tert-butyl-3,5-dimethylanisole (**4b**).* Starting from **21b** (222 mg, 0.89 mmol), general procedure I afforded compound **4b** (242 mg, 83%) as a colourless solid. An analytically pure sample was obtained by recrystallisation from CH_3CN. Mp 97 °C. ^{1}H NMR ($CDCl_3$) δ=1.50 (18H, s), 2.57 (6H, s), 3.43 (3H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=25.9, 33.3 (6C), 37.9, 64.6, 129.4, 135.6, 141.2, 160.3 ppm. IR (KBr) ν_{max}: 680, 991, 1064, 1210, 1236, 1272, 1353, 1362, 1380, 1444, 1448, 1459, 2927, 2944, 2959 cm^{-1}. Anal. Calcd for $C_{17}H_{27}BrO$ (327.30): C, 62.38; H, 8.31; Br, 24.41, found: C, 62.60; H, 8.36; Br, 24.28.

*4.3.31. 4-Bromo-2,6-di-tert-butyl-3,5-diethylanisole (**4c**).* Starting from **21c** (500 mg, 1.81 mmol), following procedure I, was obtained compound **4c** (431 mg, 67%) as a colourless oil after purification by column chromatography (cyclohexane). ^{1}H NMR ($CDCl_3$, *T*=338 K) δ=1.26 (6H, t, *J*=7.3 Hz), 1.52 (18H, s), 3.14 (4H, q, *J*=7.3 Hz), 3.40 (3H, s) ppm. ^{13}C NMR ($CDCl_3$, *T*=338 K) δ=15.6, 29.0, 34.0 (6C), 38.3, 64.4, 127.9, 140.7, 142.3, 161.3 ppm. IR (film) ν_{max}: 668, 780, 827, 1025, 1035, 1053, 1080, 1192, 1211, 1229, 1262, 1357, 1367, 1399, 1451, 1482, 2833, 2936, 2968 cm^{-1}. HRMS (ESI-Q-Tof): *m*/*z* calcd for $C_{19}H_{31}BrO$ [M]$^{\bullet+}$ 354.1558, found 354.1553.

*4.3.32. 4-Bromo-2,3,5,6-tetramethylanisole (**4d**).* Starting from **21d** (2.103 mg, 12.81 mmol), following procedure I, was obtained compound **4d** (3.04 g, 98%) as a colourless oil after purification by column chromatography (cyclohexane/AcOEt 7:3). Spectroscopic data were in conformity with the lit.[26]

*4.3.33. 2-(3,5-Di-tert-butyl-4-methoxy-2-methylphenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**26a**).* Starting from **3a** (215 mg, 0.59 mmol), following procedure J, was obtained compound **26a** (155 mg, 72%), after column chromatography (cyclohexane/AcOEt 98:2) as a colourless solid. Mp 130 °C. ^{1}H NMR ($CDCl_3$) δ=1.33 (12H, s), 1.37 (9H, s), 1.52 (9H, s), 2.65 (3H, s), 3.56 (3H, s), 7.49 (1H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=23.1, 24.8 (4C), 31.4 (3C), 32.7 (3C), 35.10, 36.9, 64.1, 83.1 (2C), 125.5, 131.7, 139.7, 141.4, 143.9, 163.0 ppm. IR (KBr) ν_{max}: 883, 970, 1047, 1119, 1145, 1229, 1294, 1326, 1344, 1362, 1380, 1390, 1400, 1450, 1468, 2934, 2961 cm^{-1}. HRMS (ESI-Q-Tof): *m*/*z* calcd for $C_{22}H_{37}BO_3$ [M+Na]$^{\bullet+}$ 383.2733, found 283.2725.

*4.3.34. 2-(3,5-Di-tert-butyl-4-methoxy-2,6-dimethylphenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**26b**).* Starting from **3b** (598 mg, 1.6 mmol), following procedure J, was obtained compound **26b** (536 mg, 89%), after column chromatography (cyclohexane/AcOEt 95:5) as a colourless solid. Mp 188 °C. ^{1}H NMR ($CDCl_3$) δ=1.40 (12H, s), 1.46 (18H, s), 2.48 (6H, s), 3.36 (3H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=23.5, 25.3 (4C), 33.1 (6C), 37.1, 64.2, 83.8, *C*-B was invisible, 137.7, 138.9, 162.4 ppm. IR (KBr) ν_{max}: 860, 1058, 1120, 1142, 1212, 1237, 1262, 1302, 1320, 1363, 1372, 1380, 1381, 1399, 1447, 1537, 2872, 2881, 2932, 2961, 2979, 3009 cm^{-1}. Anal. Calcd for

$C_{23}H_{39}BO_3$ (374.36): C, 73.79; H, 10.50; B, 2.89. Found: C, 73.67; H, 10.44; B, 2.84.

*4.3.35. 2-(4-Methoxy-2,3,5,6-tetramethylphenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**26d**).* Starting from **3d** (100 mg, 0.34 mmol), following procedure J, was obtained compound **26d** (72 mg, 72%), after column chromatography (cyclohexane/AcOEt 98:2) as a colourless solid. Mp 117 °C. ^{1}H NMR ($CDCl_3$) δ=1.40 (12H, s), 2.16 (6H, s), 2.28 (6H, s), 3.62 (3H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=12.3, 19.6, 35.17 (4C), 60.0, 83.8, circa 120 (*C*-B), 126.3, 138.3, 157.6 ppm. IR (KBr) ν_{max}: 707, 698, 857, 957, 1006, 1020, 1098, 1144, 1166, 1209, 1295, 1348, 1352, 1363, 1371, 1379, 1420, 1448, 1572, 2935, 2978 cm^{-1}. Anal. Calcd for $C_{17}H_{27}BO_3$ (290.21): C, 70.36; H, 9.38; B, 3.73. Found: C, 70.66; H, 9.09; B, 3.47.

*4.3.36. 2-(4-Methoxy-2,6-dimethylphenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**26e**).* NEt_3 (557 μL, 4 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol) and pinacolborane (435 μL, 3 mmol.) were successively added, under Ar, to a solution of 4-bromo-3,5-dimethyl anisole **4e** (215 mg, 1 mmol) in anhydrous dioxane (2.4 mL per mmol of **4e**). The reaction mixture was heated, overnight, at 80 °C and then allowed to reach rt. Aqueous saturated solution of NH_4Cl was added. The obtained aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$, filtrated and evaporated under reduced pressure. Purification by column chromatography (cyclohexane/CH_2Cl_2 5:5) afforded pure **26e** (199 mg, 76%) as a colourless solid. An analytically pure sample was obtained by sublimation (120 °C, 1 mmHg). Mp 62 °C. ^{1}H NMR ($CDCl_3$) δ=1.37 (12H, s), 2.40 (6H, s), 3.76 (3H, s), 6.51 (2H, s) ppm. ^{13}C NMR ($CDCl_3$) δ=22.7, 25.1 (4C), 55.0, 83.5, 112.5, 144.6, 160.5, *C*-B was invisible ppm. IR (KBr) ν_{max}: 832, 857, 1049, 1141, 1160, 1191, 1274, 1297, 1311, 1337, 1363, 1370, 1378, 1603, 2839, 2921, 2939, 2978, 2987, 2991 cm^{-1}. Anal. Calcd for $C_{15}H_{23}BO_3$: C, 68.72; H, 8.84; B, 4.12. Found: C, 68.62; H, 9.02; B, 4.05. HRMS (ESI-Q-Tof): *m*/*z* calcd for $C_{15}H_{23}BO_3$ $[M+H]^{\bullet+}$ 263.1819, found 263.1815.

*4.3.37. (3,5-di-tert-Butyl-4-methoxy-2-methyl)-phenyl-1-boronic acid (**5a**).* Starting from **26a** (102 mg, 0.28 mmol), following procedure K, was obtained compound **5a** (53 mg, 67%), after column chromatography (cyclohexane/AcOEt 7:3) as a colourless solid.

Starting from **4a** (243 mg, 0.78 mmol), following procedure L was obtained compound **5a** (125 mg, 58%), after column chromatography.

Mp 239 °C. ^{1}H NMR (CD_3OD) δ=1.36 (9H, s), 1.53 (9H, s), 2.45 (3H, s), 3.55 (3H, s), 6.97 (1H, s) ppm. ^{13}C NMR (CD_3OD) δ=23.8, 32.0 (3C), 33.2 (3C), 35.8, 37.8, 64.9, *C*-B was invisible, 127.9, 139.8, 142.5, 162.3 ppm. IR (KBr) ν_{max}: 1050, 1209, 1227, 1250, 1318, 1376, 1392, 1413, 2937, 2962, 3399 cm^{-1}. HRMS (ESI-Q-Tof): *m*/*z* calcd for $C_{16}H_{27}BO_3$ $[M+Na]^{\bullet+}$ 301.1951, found 301.1940.

*4.3.38. (3,5-di-tert-Butyl-4-methoxy-2,6-dimethyl)-phenyl boronic acid (**5b**).* Starting from **26b** (45 mg, 0.12 mmol), following procedure K, was obtained compound **5b** (23 mg, 63%), after column chromatography (cyclohexane/AcOEt 7:3) as a colourless solid.

Under Ar, 10 M aqueous KOH (0.73 mL, 10 equiv) was added to a suspension of boronic ester **6** (273 mg, 0.73 mmol) in DMSO (3.6 mL). The reaction mixture was heated at 60 °C for 2 h, and then allowed to reach rt. Aqueous 1 M HCl (40 mL) was added. The obtained aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$, filtrated and evaporated under reduced pressure. Purification by column chromatography (cyclohexane/AcOEt 7:3) afforded pure **5b** (203 mg, 96%) as a colourless solid.

Mp 200 °C. ^{1}H NMR (DMSO-d_6) δ=1.44 (18H, s), 2.29 (6H, s), 3.36 (3H, s), 8.03 (2H, s) ppm. ^{13}C NMR (DMSO-d_6) δ=23.4, 33.0 (6C), 36.6, 64.2, circa 120 (C-B), 135.4, 137.7, 160.3 ppm. IR (KBr) ν_{max}: 991, 1071, 1184, 1239, 1267, 1301, 1357, 1401, 1438, 1449, 1457, 2956, 3247, 3254, 3261 cm^{-1}. HRMS (ESI-Q-Tof): *m*/*z* calcd for $C_{17}H_{29}BO_3$ $[MH]^{\bullet+}$ 293.2288, found 293.2275.

*4.3.39. (4-Methoxy-2,3,5,6-tetramethyl)-phenyl boronic acid (**5d**).* Starting from **26d** (35 mg, 0.12 mmol), following procedure K, was obtained compound **5d** (17 mg, 68%), after column chromatography (cyclohexane/AcOEt 7:3) as a colourless solid.

Starting from **4d** (400 mg, 1.6 mmol), following procedure L was obtained compound **5d** (188 mg, 55%), after column chromatography.

Mp 160 °C. ^{1}H NMR (CD_3OD) δ=2.14 (6H, s), 2.23 (6H, s), 3.60 (3H, s) ppm. ^{13}C NMR (CD_3OD) δ=12.4, 20.3, 60.4, *C*-B was invisible, 126.5, 137.0, 157.7 ppm. IR (KBr) ν_{max}: 998, 1087, 1215, 1232, 1385, 1354, 1383, 1408, 1422, 1448, 1571, 1575, 2490, 2940, 2952, 3363, 3665 cm^{-1}. HRMS (ESI-Q-Tof): *m*/*z* calcd for $C_{11}H_{17}BO_3$ $[M+Na]^{\bullet+}$ 231.1168, found 231.1167.

*4.3.40. Diisopropyl (3,5-di-tert-butyl-4-methoxy-2,6-dimethyl)-phenyl boronate (**6**).* Starting from **4b** (607 mg, 1.86 mmol), following procedure L was obtained compound **6** (464 mg, 66%) after column chromatography (cyclohexane/CH_2Cl_2 85:15) as a colourless solid. Mp 79 °C. ^{1}H NMR (CD_3OD) δ=1.18 (12H, d, *J*=6.3 Hz), 1.47 (18H, s), 2.40 (6H, s), 3.39 (3H, s), 4.23–4.31 (2H, m) ppm. ^{13}C NMR ($CDCl_3$) δ=23.8, 24.5, 24.7, 33.1, 37.1, 64.2, 65.9, 66.6, *C*-B was invisible, 136.1, 138.9, 161.7 ppm. IR (KBr) ν_{max}: 1065, 1113, 1122, 1235, 1262, 1304, 1370, 1380, 1397, 1445, 1457, 1465, 2930, 2973, 3012 cm^{-1}. HRMS (ESI-Q-Tof): *m*/*z* calcd for $C_{23}H_{41}BO_3$ $[M]^{\bullet+}$ 376.3149, found 376.3115.

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