Selective Sequential Cross-Coupling Reactions on Imidazole towards Neurodazine and Analogues

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Received: 03.12.2012; Accepted after revision: 20.03.2013

Abstract: Polysubstituted imidazoles represent a common structural motif in bioactive molecules. A modular and flexible strategy towards 2,4,5-triarylated imidazoles is reported applying a Suzuki–Miyaura cross-coupling protocol. Employing 1-protected 2,4,5-tribromoimidazole as starting material, both stepwise and one-pot protocols towards the title compounds are disclosed. The utility of the approach was demonstrated by synthesizing neurodazine, a biologically active molecule affecting neuronal cell differentiation.

Key words: heterocycles, cross-coupling, palladium, regioselectivity, homogeneous catalysis

Heterocyclic compounds and especially their arylated analogues are important compounds for a number of applications. Numerous examples of pharmaceuticals,[1] plant protection agents,[2] and organic materials[3] have been reported. Amongst heterocycles, nitrogen-containing systems represent a privileged compound class due to their frequent occurrence in natural products (e.g., alkaloids).[4] Polyfunctionally decorated imidazoles are encountered as common structural core motif in several bioactive molecules.[5] Therefore, the synthesis of such products is an important as well as competitive research area requiring novel versatile synthetic methods for the preparation of these target compounds.

A very interesting example of a bioactive imidazole derivative is neurodazine (Figure 1), a molecule with cell-differentiating properties. Recent reports demonstrated that treatment of C2C12 mouse myoblasts with neurodazine resulted in the development of cells, which display neuron like properties.[6] Neuronal marker proteins were found to be upregulated; however, also skeletal muscle specific markers remained highly expressed. This suggests that an incomplete transformation from a muscle cell to a neuron was observed. Still, this initial finding indicates that transformation of certain cell types into a neuronal phenotype is possible potentially opening up new opportunities for the treatment of neurodegenerative diseases.

Generally, influencing cell differentiation to form certain cell types from easily available tissue received significant attention due to the potential benefits of such therapies. Lately, the transformation of somatic cells to pluripotent stem cells has stirred up much attention.[7] However, the method applied remains problematic since several genes have to be introduced into the cell genome in order to get the desired de-differentiation of a specialized to a pluripotent cell. A retrovirus is required for the insertion of the genes, which reduces the probability for the method of obtaining authority approval to be used in patient treatment. As an alternative, inducing differentiation processes by using synthetic small molecules is highly attractive since protocols for toxicological testing are long established. In several recent studies, a number of small molecules were identified capable to trigger differentiation processes en route to cardiac as well as skeletal muscle, pancreatic, or neuronal tissue, as is the case for neurodazine.[6,8]

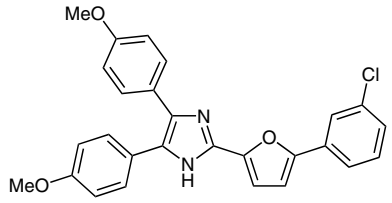


Figure 1 Neurodazine

Due to these reasons, the synthesis of neurodazine analogues for structure activity relationship studies is highly interesting in order to improve this initially found activity. For this purpose an efficient, modular, and rapid synthetic strategy would be required in order to synthesize a compound library of triarylated imidazoles.

A common strategy for the synthesis of substituted imidazoles is the cyclocondensation of 1,2-dicarbonyl compounds with ammonia and an aldehyde.[9] This is definitely an attractive method for the synthesis of single compounds or a small collection of products as well as for production in large scale. Recently, Singh et al.[10] synthesized various 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted compounds using this well established method. In this publication easily available benzil was mainly used as 1,2-diketone. However, employing this strategy towards a library of differently substituted imidazoles quickly becomes quite elaborate: For each substitution pattern the corresponding 1,2-dicarbonyl compounds and aldehydes have to be prepared separately. Alternatively, the preparation of trisubstituted imidazoles from N-protected tribromoimidazole was reported by Lipshutz employing sequential bromine–lithium exchange followed by electrophilic quenching.[11]

SYNTHESIS 2013, 45, 1387–1405
Advanced online publication: 04.04.2013
DOI: 10.1055/s-0032-1316906; Art ID: SS-2012-Z0934-OP

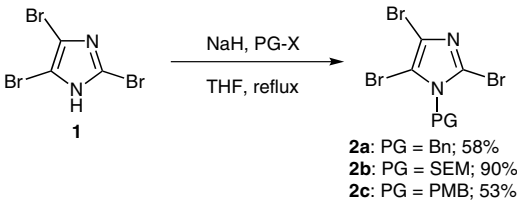
One way to overcome the limitations of cyclization strategies is the use of a common imidazole building block to be functionally decorated with the desired substituents in subsequent steps, for example, via transition metal-catalyzed cross-coupling reactions.[12] Employing suitably functionalized precursors, sequential coupling processes have been demonstrated utilizing the well-established individual coupling protocols.[12b,13] Recently, the synthesis of triarylated imidazoles starting from 5-aryl-*N*-methylimidazole via direct arylation was reported.[13k]

In the present contribution, we investigated site selective cross-coupling reactions of 2,4,5-tribromoimidazole. Since the goal was to develop a method for facile library synthesis of triarylated imidazoles the protocol should meet the following criteria: (1) a cheap and readily available catalyst should be used, ideally $Pd(PPh_3)_4$; (2) reaction conditions for all coupling steps should ideally be identical in order to carry out all steps in one-pot; (3) overall reaction conditions should be environmentally benign; and (4) a readily available substrate should be used.

Our aim was to synthesize 2,4,5-triarylated imidazoles starting from the easily accessible and commercially available substrate tribromoimidazole (**1**) by selective sequential Suzuki–Miyaura cross-coupling reactions. The Suzuki–Miyaura[14] protocol was chosen since a large number of boronic acids are commercially available and toxicity problems often encountered when employing tin organyls in particular in a medicinal chemistry context can be avoided. Additionally, inert conditions are not required further facilitating development of an operationally simple protocol.

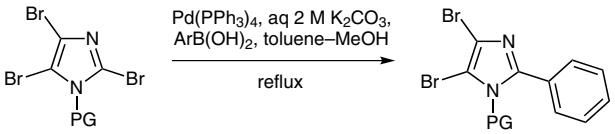
The Suzuki–Miyaura cross-coupling reaction is a common and well-established tool in the arylation of monohalogenated imidazoles.[15] Moreover, selective cross-coupling reactions at positions 2 and 4/5 could be achieved on dihalogenated imidazoles.[16] Additionally, Ohta et al. reported selective coupling at position 2 of MOM-protected tribromoimidazole as well as a subsequent selective cross-coupling reaction at position 5 of 4,5-dibromo-1-MOM-2-phenylimidazole.[16b] The authors do not report a final coupling at position 4. Huang et al. published another protocol for the cross-coupling on SEM-protected tribromoimidazole.[17] To the best of our knowledge, the synthesis of triarylated imidazoles starting from tribromoimidazole has not been reported, so far. Consequently, no one-pot procedure has been reported towards the title compounds, as well. The modular combination of a sequence of iterative and methodologically related steps offers the prospect of reaction automation, ultimately. This is a highly appealing aspect in modern medicinal chemistry and drug discovery, as access to large compound libraries is enabled.[13]

Our initial experiments confirmed that the free NH group of imidazole was not well tolerated under general Suzuki coupling conditions. Hence, 1-protected tribromoimidazoles were prepared using different protecting groups with orthogonal properties. Introduction of benzyl (Bn), [2-(trimethylsilyl)ethoxy]methyl (SEM), and *p*-methoxybenzyl (PMB) proceeded well using a common protocol (Scheme 1). Attempts to install the common N-protecting group BOC, however, failed most probably due to steric hindrance of the bromine substituents.



Scheme 1 Introducing protecting groups on 2,4,5-tribromoimidazole (**1**)

Next, selective cross-coupling at position 2 was investigated using substrates **2a**–**c** and (het)arylboronic acids as coupling partners (Scheme 2). The group of Ohta reported selective cross-coupling at position 2 of MOM-protected tribromoimidazole using 5 mol% $Pd(PPh_3)_4$ as catalyst, 1 equivalent of 2 M aqueous Na_2CO_3, 1.1 equivalents of phenylboronic acid, and a mixture of benzene–methanol (5:1) as solvent.[16b] In our hands it was found that benzene can very well be replaced by more benign toluene and additionally, higher yields were obtained by using 2 M aqueous K_2CO_3 instead of Na_2CO_3 as the base.



Scheme 2 Cross-coupling at 2 position

All protecting groups were suitable for the coupling reaction and a variety of protected 2-aryl-4,5-dibromo-1*H*-imidazoles were synthesized with high regioselectivity (Table 1).

All reactions using arylboronic acids were over within a few hours (reaction monitoring by TLC). In some cases (compounds **3**, **7**, **11**), a slightly larger excess of boronic acid had to be added to complete consumption of imidazole starting material. Yields are usually good for coupling with arylboronic acids (55–82%). The protecting group had no major influence on the yields of the cross-coupling process; for example, cross-coupling using phenylboronic acid yielded 81% using benzyl (Table 1, entry 1, compound **3**), 82% using SEM (entry 7, compound **9**), and 74% using PMB (entry 13, compound **15**) as protecting groups, respectively. Both electron-donating (OMe, entries 2, 8, 14) and electron-withdrawing substituents (NO_2, entries 3, 4, 9, 10, 15) on the phenyl ring were well accepted in the cross-coupling reaction. Sterically challenging *o*-tolylboronic acid gave a good yield of **7** using benzyl (entry 5, 79%) or SEM (entry 11, 74%) as protecting group, whereas with PMB a somewhat lower yield was obtained (entry 16, 59%).

Table 1 Substrate Scope of Suzuki–Miyaura Cross-Coupling at Position 2 of 2,4,5-Tribromoimidazole[a]

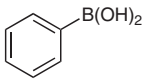
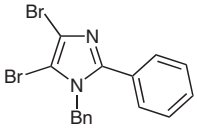
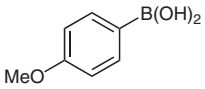
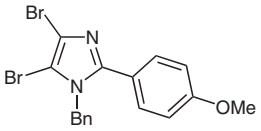
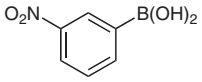
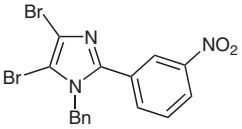
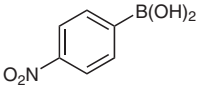
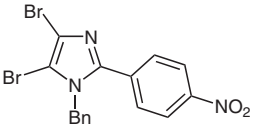
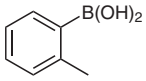
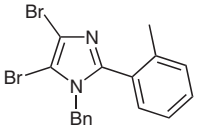
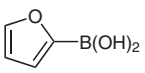
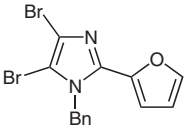
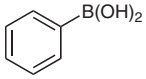
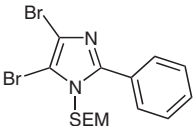
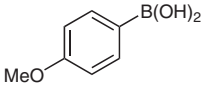
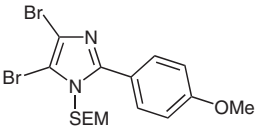
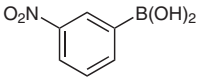
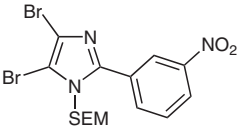
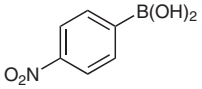
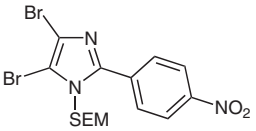
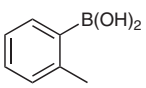
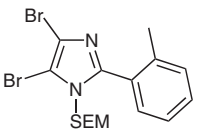
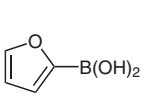
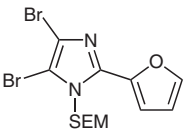
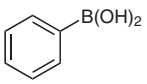
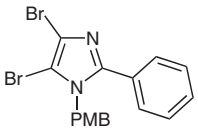
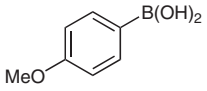
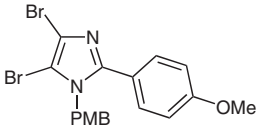
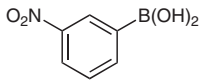
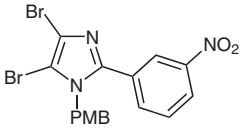
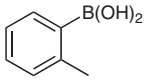
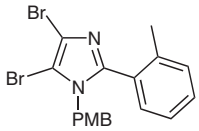
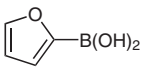
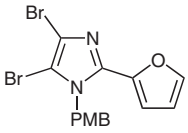
Entry	Substrate	Boronic acid	Product	Yield (%)
1	**2a**		**3**		81[b]
2	**2a**		**4**		78
3	**2a**		**5**		55
4	**2a**		**6**		64
5	**2a**		**7**		79[c]
6	**2a**		**8**		43[d]
7	**2b**		**9**		82
8	**2b**		**10**		74
9	**2b**		**11**		65[b]
10	**2b**		**12**		68
11	**2b**		**13**		74
12	**2b**		**14**		31[e]

Table 1 Substrate Scope of Suzuki–Miyaura Cross-Coupling at Position 2 of 2,4,5-Tribromoimidazole[a] (continued)

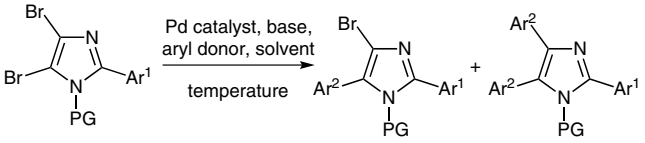
Entry	Substrate	Boronic acid	Product	Yield (%)
13	**2c**		**15**		74
14	**2c**		**16**		77
15	**2c**		**17**		63
16	**2c**		**18**		59
17	**2c**		**19**		35[e]

[a] Reaction conditions: $Pd(PPh_3)_4$ (5 mol%), 2 M aq K_2CO_3 (1 equiv), boronic acid (1.1 equiv), toluene–MeOH (5:1) as solvent.
[b] Boronic acid used: 1.2 equiv.
[c] Boronic acid used: 1.3 equiv.
[d] Boronic acid used: 4.1 equiv in total.
[e] Boronic acid used: 3.6 equiv in total.

The cross-coupling of 2-furylboronic acid with N-protected 2,4,5-tribromoimidazole – the first step in the synthesis of neurodazine – was more complicated. It is known that, generally, heterocyclic boronic acids are less stable than their carbocyclic counterparts and 2-furylboronic acid represents a particularly troublesome case.[18] As the reaction had to be performed at 120 °C, 2-furylboronic acid decomposed very quickly. Hence, more equivalents of boronic acid had to be added in portions to drive the reaction to completion. However, even after adding up to 4.1 equivalents of 2-furylboronic acid conversion was not complete and a larger excess was not considered based on economics. Still, coupling products were obtained in only 43% using Bn (entry 6), 31% with SEM (entry 12), and 35% in case of PMB (entry 17).

As the next logical extension, cross-coupling at 5-position was attempted, eventually elaborating selectivity relative to position 4. In the literature only the report by Ohta et al.[16b] can be found where a selective coupling at position 5 was obtained without compromising position 4: When coupling phenylboronic acid with 1-methoxymethyl-2-phenyl-4,5-dibromo-1*H*-imidazole they obtained 1-methoxymethyl-2,5-diphenyl-4-bromo-1*H*-imidazole in 70% yield after 10 hours.

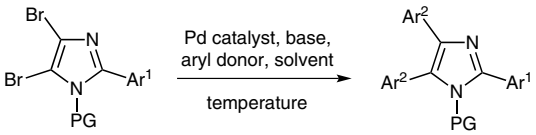
In our case, the protecting groups (PGs) have a negligible electronic influence and hence positions 5 and 4 were expected to have quite similar reactivity. Additionally, the steric effect of nitrogen PGs disfavors position 5 and, hence, only limited selectivity was expected. Indeed, when using the benzyl protected analogue, we could not obtain comparable selectivity as Ohta et al.[16b] did and only 30% of impure 5-coupled product could be obtained. Even after extensively screening of reaction parameters such as temperature, base, solvent, catalyst, and aryl donor (boronic acid, boronic acid ester, and $PhSnBu_3$) only low selectivity could be achieved with 2,5-diarylated imidazole as major product and overarylation as competitive process (Scheme 3, maximum selectivity 2:1 in favor of the 2,5-diaryl over the 2,4,5-triaryl product).



Scheme 3 Cross-coupling at positions 4 and 5

Since selective cross-coupling could not be achieved in 5-position and, hence, formation of 2,4,5-triarylated imidazoles with three different substituents was not possible in good yields, conversion of N-protected 2-aryl-4,5-dibromoimidazoles to triarylated compounds was studied in a one-step protocol with identical aryl substituents in posi-

tions 4 and 5. Thus, N-protected 2-aryl-4,5-dibromoimidazoles were reacted with 3 equivalents of boronic acid. The same conditions [2 M aq K_2CO_3, $Pd(PPh_3)_4$, toluene–MeOH, 5:1] as for the first coupling step were employed (Scheme 4). The results of this coupling step are summarized in Table 2; in case arylation was not complete after a few hours, more equivalents of boronic acid were added.



Scheme 4 Cross-coupling at positions 4 and 5

Table 2 Substrate Scope of Suzuki–Miyaura Cross-Coupling at Positions 4 and 5 of 2-Aryl-4,5-dibromoimidazole[a]

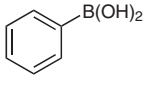
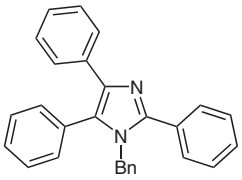
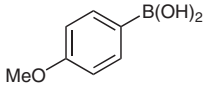
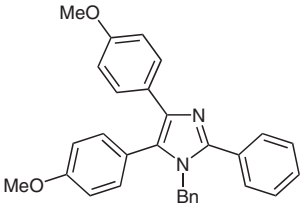
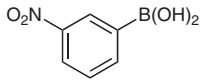
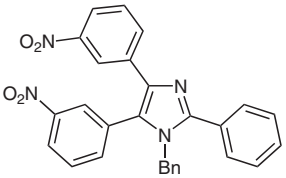
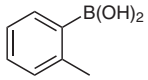
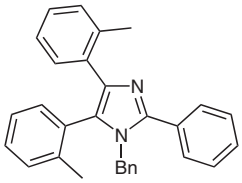
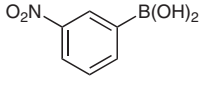
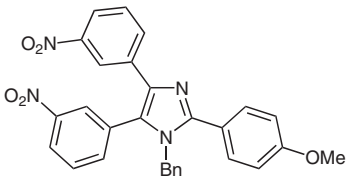
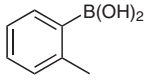
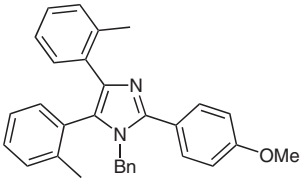
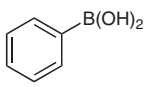
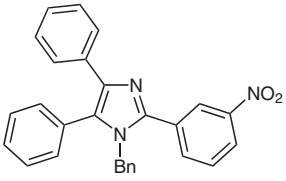
Entry	Substrate	Boronic acid	Product	Yield (%)
1	**3**		**20**		79
2	**3**		**21**		85
3	**3**		**22**		55
4	**3**		**23**		37
5	**4**		**24**		60
6	**4**		**25**		32
7	**5**		**26**		85

Table 2 Substrate Scope of Suzuki–Miyaura Cross-Coupling at Positions 4 and 5 of 2-Aryl-4,5-dibromoimidazole[a] (continued)

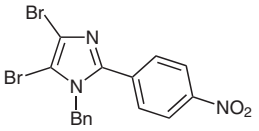
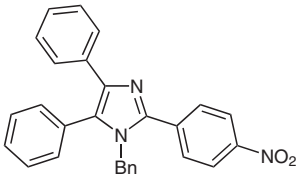
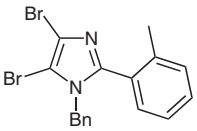
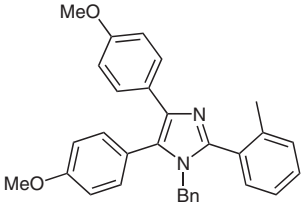
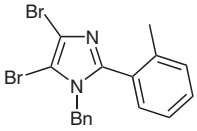
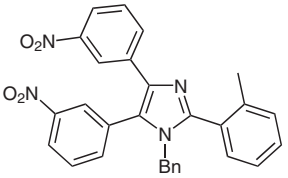
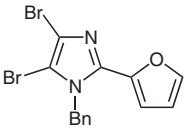
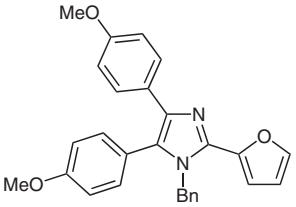
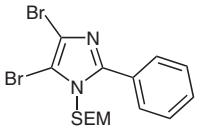
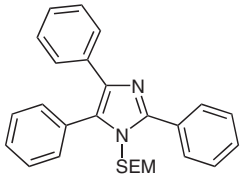
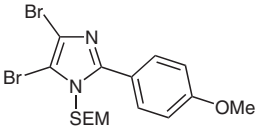
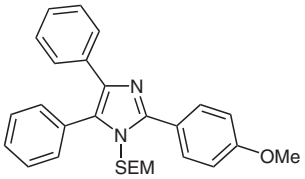
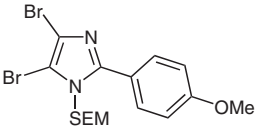
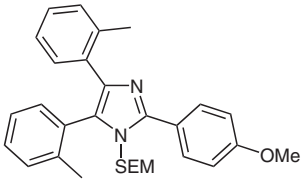
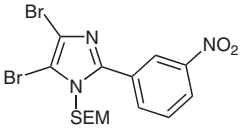
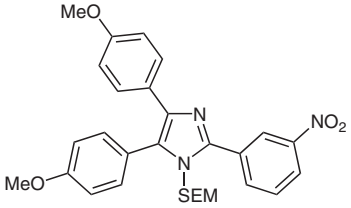
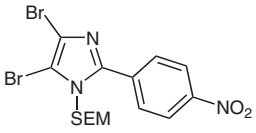
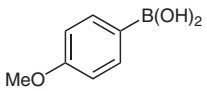
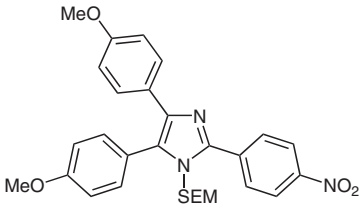
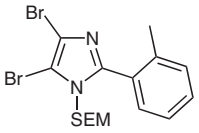
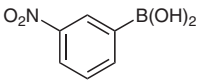
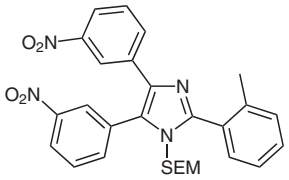
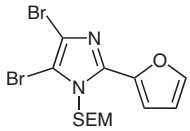
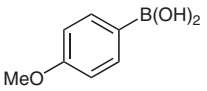
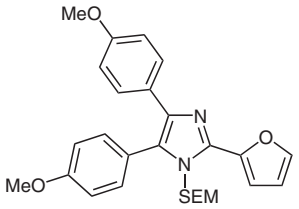
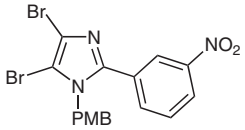
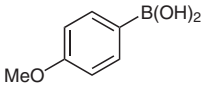
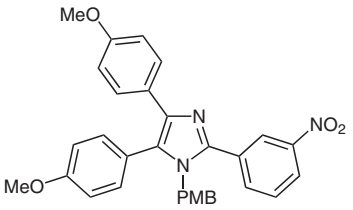
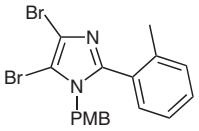
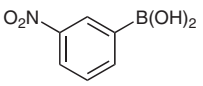
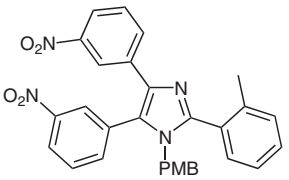
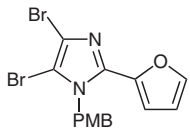
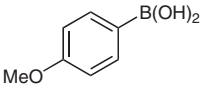
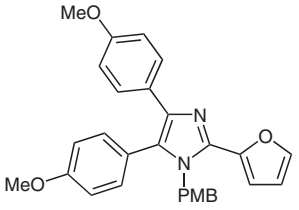
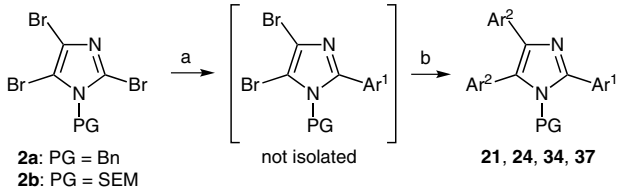
Entry	Substrate	Boronic acid	Product	Yield (%)
8	**6**		**27**		79
9	**7**		**28**		68
10	**7**		**29**		39[b]
11	**8**		**30**		81
12	**9**		**31**		91
13	**10**		**32**		80
14	**10**		**33**		11[c]
15	**11**		**34**		53

Table 2 Substrate Scope of Suzuki–Miyaura Cross-Coupling at Positions 4 and 5 of 2-Aryl-4,5-dibromoimidazole[a] (continued)

Entry	Substrate	Boronic acid	Product	Yield (%)
16	**12** 		**35** 	21
17	**13** 		**36** 	74[d]
18	**14** 		**37** 	96
19	**17** 		**38** 	92
20	**18** 		**39** 	42
21	**19** 		**40** 	53

[a] Reaction conditions: $Pd(PPh_3)_4$ (5 mol%), 2 M aq K_2CO_3 (3 equiv), boronic acid (3.0 equiv), toluene–MeOH (5:1) as solvent.
[b] Boronic acid used: 3.5 equiv.
[c] Boronic acid used: 5 equiv.
[d] Boronic acid used: 6 equiv.

The yields of this two-fold coupling step were generally good. The nature of the N-protecting group did not impose a major influence. The highest yields were obtained when using phenylboronic acid (Table 2, entries 1, 7, 8, 12, 13) or 4-methoxyphenylboronic acid as coupling partner (Table 2, entries 2, 9, 11, 18, 19). The neurodazine precursors **30**, **37**, and **40** were synthesized in 81% (**30**, entry 11), 96% (**37**, entry 18), and 53% (**40**, entry 21), respectively. Hence, the SEM group gave the best result in the coupling step. 3-Nitrophenylboronic acid usually gave somewhat lower yields (39–60%) in the coupling step (entries 3, 5, 10, 20). Only within the synthesis of compound **36**, starting from the substrate **13** having the sterically demanding *o*-tolyl group as the substituent, a more pronounced PG effect was observed with SEM (74%, entry 17) giving superior results compared to Bn and PMB (entries 9, 10, 20). Use of *o*-tolylboronic acid in the second coupling step resulted in the lowest yields for the two-fold coupling reaction (entries 4, 6, 14). This is not surprising and can be explained by steric hindrance.



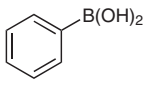
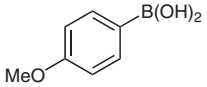
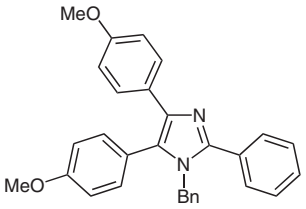
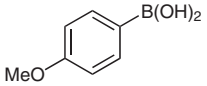
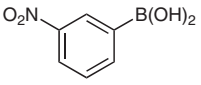
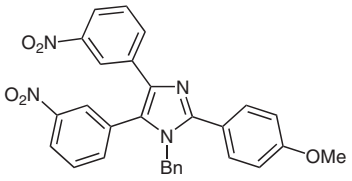
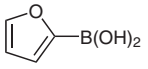
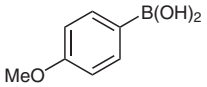
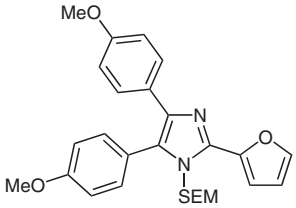
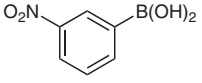
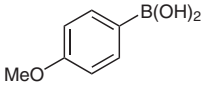
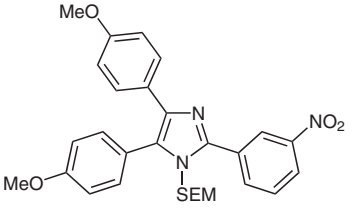
Scheme 5 One-pot synthesis of triarylated imidazoles. *Reagents and conditions*: a) $Pd(PPh_3)_4$ (5 mol%), 2 M aq K_2CO_3 (4 equiv), toluene–MeOH (5:1); b) 3 equiv of second boronic acid added.

Based on identical reaction conditions for all coupling steps, synthesis of triarylated imidazoles in a single one-pot process was attempted. Reactions were conducted using 5 mol% of $Pd(PPh_3)_4$ and 4 equivalents of 2 M aqueous potassium carbonate solution in toluene–methanol (5:1) as solvent. In the first step, 1.1 equivalents of boronic acid reacted with the protected tribromoimidazole **2a** or **2b**. When consumption of the substrate was complete according to TLC, 3 equivalents of another boronic acid were added to the reaction solution (Scheme 5). On selected examples, this one-pot process was compared to sequential-step preparation (Table 3). In general, yields were higher in the one-pot procedure (3 out of 4 cases). Compound **21** was synthesized in 89% yield starting from **2a** in the one-pot process as compared to 68% over the two-step protocol (Table 3, entry 1). Also **24** (entry 2, 73% one pot vs. 46% stepwise), and **34** (entry 4, 58% one pot vs. 34% stepwise) gave significantly higher yield demonstrating the great utility of this approach. The only exception was the synthesis of the neurodazine precursor **37** where a similar yield was obtained for both processes (entry 3, 25% one pot vs. 29% stepwise). The overall low yield is again caused by the instability of the heterocyclic boronic acid and, hence, the overall challenge of handling this specific transformation. Still, the one-pot process is superior to the stepwise protocol in cases where such stability problems are not an issue.

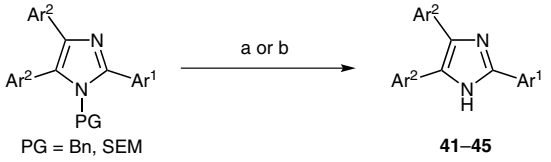
If neurodazine (**50**) should be synthesized via this coupling sequence, deprotection of the protecting group is mandatory (Scheme 6). Hence, possibilities to cleave the different protecting groups were investigated. Standard reductive cleavage of the benzyl group did not give a positive result under several reaction conditions frequently applied (e.g., MeOH–formic acid, 10% Pd/C, 5 bar H_2;[19] transfer hydrogenation using anhydrous EtOH, 10% of Pd/C, cyclohexa-1,4-diene[20]).

Gratifyingly, the benzyl group was cleaved by the oxidative deprotection protocol of Deaton-Rewoliski et al.[21] This protocol uses DMSO and potassium *tert*-butoxide in combination with oxygen to obtain the unprotected prod-

Table 3 One-Pot Synthesis of 2,4,5-Triarylated Imidazoles

Entry	Substrate	Boronic acid 1	Boronic acid 2	Product	Yield (%)
1	**2a**			**21**	 89 (68)[a]
2	**2a**			**24**	 73 (46)[a]
3	**2b**			**37**	 25 (29)[a]
4	**2b**			**34**	 58 (34)[a]

[a] The overall yields for the two-step process are given in parentheses.



Scheme 6 Deprotection protocols. *Reagents and conditions*: a) benzyl deprotection: DMSO, oxygen, *t*-BuOK; b) SEM deprotection: 1 M Bu_4NF (5 equiv) in THF, reflux.

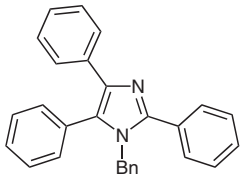
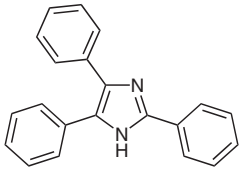
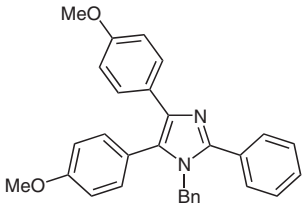
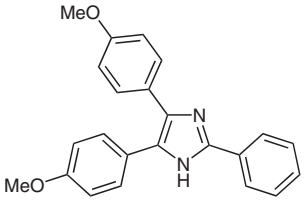
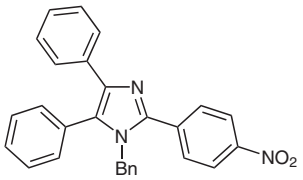
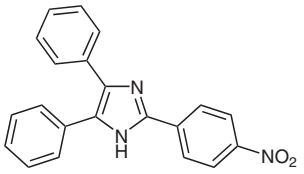
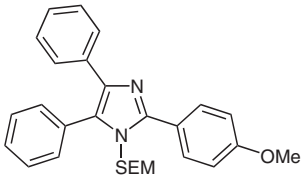
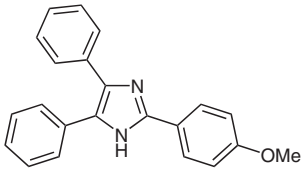
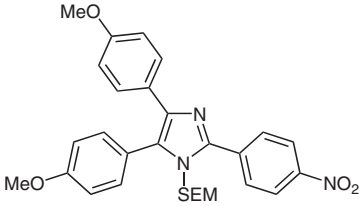
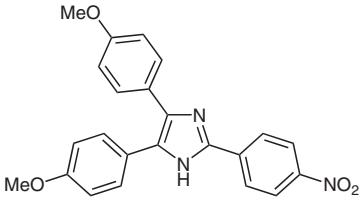
uct. Although all tested substrates could be deprotected, only in the case of compound **21** an excellent yield of 92% could be obtained (Table 4, entry 2). In the other two cases the yields were significantly lower (Table 4, entries 1, 3); the reason for this is not quite clear.

The cleavage of SEM protected 2,4,5-triarylated imidazoles was performed according to a procedure by Whitten et al.[22] employing Bu_4NF (TBAF). This protocol enabled access to unprotected 2,4,5-triaryl-1*H*-imidazoles (1 equiv) in excellent yields in all cases investigated (Table 4, entries 4, 5).

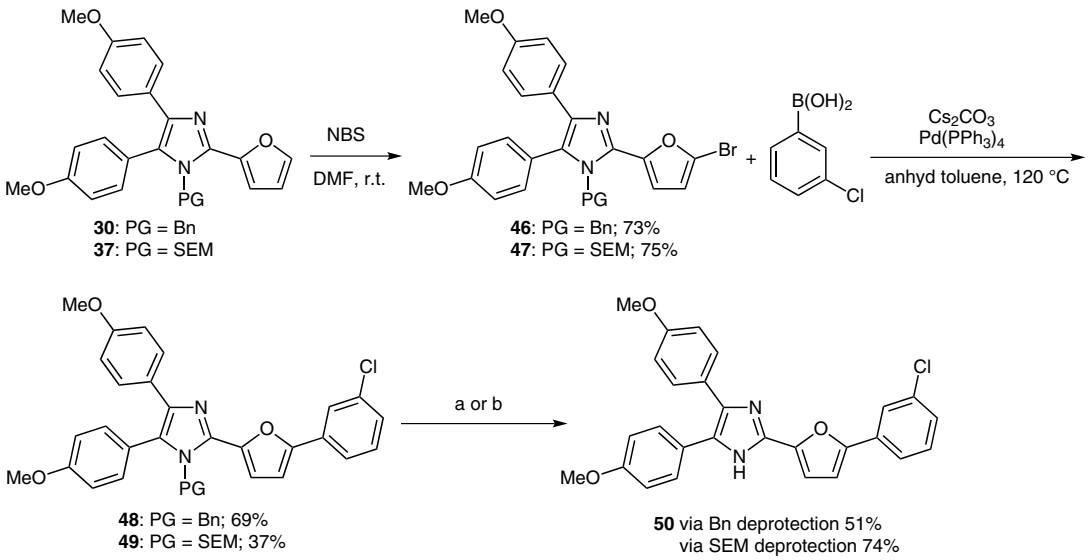
Several conditions were investigated for cleavage of the PMB group (trifluoroacetic acid at 65–80 °C; 2.2 equiv of DDQ toluene/H_2O, 80 °C); however, none of them led to the formation of the required product. Since the other two protecting groups could be removed efficiently and the PMB group does not provide an advantage in the previous coupling steps, this is only a minor drawback.

To demonstrate the utility of the developed cross-coupling chemistry in the synthesis of an interesting target molecule, the synthesis of neurodazine (**50**) (Scheme 7) was completed starting from benzyl and SEM protected precursors **30** and **37** based on the above developed successful deprotection conditions. The furan ring was brominated by NBS in position 5 in 73% (**46**, PG = Bn) and 75% yield (**47**, PG = SEM), respectively. Suzuki–Miyaura coupling with 3-chlorophenylboronic acid was performed using $Pd(PPh_3)_4$ as catalyst and cesium carbonate as base.

Table 4 Deprotection of 2,4,5-Triarylated Imidazoles

Entry	Substrate		Product		Yield (%)
1	**20**		**41**		25[a]
2	**21**		**42**		92[a]
3	**27**		**43**		30[a]
4	**32**		**44**		94[b]
5	**35**		**45**		90[b]

[a] Benzyl deprotection: DMSO, O_2, *t*-BuOK.
[b] SEM deprotection: 1 M Bu_4NF (5 equiv), THF, reflux.



Scheme 7 Synthesis of neurodazine. *Reagents and conditions*: a) benzyl deprotection: DMSO, oxygen, *t*-BuOK; b) SEM deprotection: 1 M Bu_4NF (5 equiv), THF, reflux.

While the SEM protected precursor gave only a moderate 37% yield (Scheme 7, **49**), satisfying results were obtained in the benzyl protecting series (Scheme 7, **48**, 69%). Deprotection of the imidazole ring led to neurodazine (**50**) in 74% yield (SEM deprotection) and 51% (benzyl cleavage). Comparing both protecting groups in the neurodazine total synthesis starting from tribromoimidazole (**1**), overall better results were obtained in the SEM series due to higher yields in the protection and deprotection steps as well as in the furyl coupling step (precursor **37**). Only the coupling step with 3-chlorophenylboronic acid gives a higher yield for the benzyl protecting group.

In conclusion tribromoimidazole (**1**) was used as a cheap and easily accessible starting material for three subsequent selective Suzuki–Miyaura cross-coupling steps. Three different protecting groups were investigated for their influence on the cross-coupling reaction. Selective cross-coupling at 2-position generally gave good yields and a broad range of arylboronic acids were tolerated (as long as boronic acid reaction partners are sufficiently stable under reaction conditions; see results with 2-furylboronic acid). Preparatively insufficient selectivity was observed for cross-coupling at 5-position even after an elaborate condition screening. On the other hand, the cross-couplings at 4- and 5-positions of the 4,5-dibromoimidazole substrates were performed simultaneously in good yields and with good substrate scope. An exception is the use of 2-tolylboronic acid as aryl donor, which is too sterically demanding. Deprotection of the SEM and benzyl groups was also realized. With this method, a critical neurodazine precursor could be obtained, which was converted into the bioactive target within three linear steps. Starting from N-protected 2,4,5-tribromoimidazole neurodazine (**50**) was synthesized in 8.9% overall yield using benzyl as protecting group and 5.1% in the case of SEM. In both cases, coupling with furanboronic acid is a low-yielding step due to the instability of this boronic acid.

Light petroleum (LP) used refers to the fraction boiling in the 40–65 °C range. Flash column chromatography was performed on silica gel 60 (Merck, 40–63 μm). Separations were carried out using a Büchi SepacoreTM MPLC system. Aluminum backed silica gel was used for TLC. TLC plates (20 × 20 cm, 1000 μm silica layer thickness) were used for preparative TLC; signals were visualized by UV light (254 nm). Melting points were determined using a Stanford Research Systems OptiMelt MPA100 or a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected. NMR spectra were recorded from either $CDCl_3$ (solvent peak referenced to 77.16 ppm), DMSO-d_6 (solvent peak referenced to 39.52 ppm), or CD_3OD (solvent peak referenced to 49.00 ppm) solutions on a Bruker AC 200 (200 MHz) or a Bruker Avance Ultrashield (400MHz) spectrometer (as indicated). Chemical shifts are reported in ppm relative to the nominal residual solvent signals. HRMS measurements were carried out by E. Rosenberg at the Vienna University of Technology, Institute for Chemical Technologies and Analytics. All samples were analyzed by LC-IT-TOF-MS in only positive ion detection mode upon recording of MS and MS/MS spectra. For the evaluation in the following, only positive ionization spectra were used (where the quasi-molecular ion is the one of $[M + H]^+$), and further data or information were not taken into consideration. Shimadzu Prominence HPLC: solvent degassing unit (DGU-20 A3), binary gradient Pump (2 × LC-20AD), auto-injector (SIL-20A), column oven (CTO-20AC), control module (CBM-20A), and diode array detector (SPD-M20A). MS System: Shimadzu IT-TOF-MS with electrospray interface. Column: Phenomenex Prodigy ODS (3), 30 mm × 4.6 mm, 3 μm particles, operated at 40 °C; Gradient: 0 min: 70% A, 30% B (1 min); linear gradient to 5 min to 10% A, 90% B (hold 2 min); at 7.01 min back to 70% A, 30% B, hold until 8.0 min). A: MeCN + 0.1% formic acid, B: H_2O + 0.1% formic acid. Column flow: 0.5 mL/min; injection volume: 2 μL. MS parameters as in autotune. Data recorded with detector voltage at autotune value. Scan range: 50–1000 amu for both, MS and MS/MS (PI) detection, ES ionization.

1-Benzyl-2,4,5-tribromo-1*H*-imidazole (2a)

A dry 500 mL three-necked flask equipped with a thermometer, a reflux condenser, a magnetic stir bar, and a septum was flushed with argon. Anhyd THF (200 mL) was placed in the flask and NaH (2.16

g, 90 mmol, 3 equiv) was added and suspended. The mixture was cooled to 0 °C. Then, 2,4,5-tribromoimidazole (**1**; 9.15 g, 30 mmol, 1 equiv) was added in portions. The solution was warmed to r.t. and stirred for 30 min. Benzyl bromide (3.92 mL, 33 mmol, 1.1 equiv, $\rho = 1.438$ g/cm^3) was added dropwise and then the reaction solution was heated to reflux for 5 h. Subsequently, the reaction mixture was poured into H_2O (100 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were washed with H_2O (70 mL) and dried (Na_2SO_4). The solvent was evaporated and the crude product was purified by flash column chromatography (100 g silica gel, LP–EtOAc, 30:1); yield: 6.83 g (58%, 17.30 mmol); colorless solid; mp 68–69 °C (Lit.[23] mp 58–59 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.22 (s, 2 H), 7.09–7.19 (m, 2 H), 7.31–7.41 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 51.2 (t), 105.6 (s), 117.0 (s), 118.6 (s), 126.7 (d), 128.3 (d), 128.9 (d), 133.9 (s).

2,4,5-Tribromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole (2b)[24]

A dry 500 mL three-necked flask equipped with a thermometer, a reflux condenser, a magnetic stirring bar, and a septum was flushed with argon. Anhyd THF (200 mL) was placed in the flask and NaH (0.72 g, 30 mmol, 2 equiv) was added and suspended. The mixture was cooled to 0 °C before 2,4,5-tribromoimidazole (**1**; 4.58 g, 15 mmol, 1 equiv) was added in portions. The mixture was warmed to r.t. and stirred for 2 h. 2-(Trimethylsilyl)ethoxymethyl chloride (2.93 mL, 17 mmol, 1.1 equiv) was added dropwise and the mixture was stirred at r.t. After 1 h, the reaction was complete according to TLC. The mixture was poured into H_2O (100 mL) and the aqueous solution was extracted with Et_2O (3 × 70 mL). The combined organic layers were washed with H_2O (70 mL) and dried (Na_2SO_4). The solvent was evaporated and the yellow oil obtained was purified by flash column chromatography (50 g silica gel, LP–EtOAc, 10:1); yield: 5.85 g (90%, 13.45 mmol); colorless solid; mp 58–60 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.00 (s, 9 H), 0.93 (t, ^3J = 8.2 Hz, 2 H), 3.61 (t, ^3J = 8.2 Hz, 2 H), 5.33 (s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 1.3 (q), 17.9 (t), 67.4 (t), 76.0 (t), 105.8 (s), 117.7 (s), 119.2 (s).

2,4,5-Tribromo-1-(4-methoxybenzyl)-1*H*-imidazole (2c)

A dry 50 mL three-necked flask equipped with a thermometer, a reflux condenser, a magnetic stir bar, and a septum was flushed with argon. Anhyd THF (12.5 mL) was placed in the flask and NaH (0.12 g, 4.8 mmol, 3 equiv) was added and suspended. The mixture was cooled to 0 °C before 2,4,5-tribromoimidazole (**1**; 0.5 g, 1.6 mmol, 1 equiv) was added in portions. The mixture was warmed to r.t. and stirred for 30 min. 4-Methoxybenzyl chloride (0.24 mL, 1.8 mmol, 1.1 equiv, $\rho = 1.154$ g/cm^3) was added dropwise and then the mixture was heated under reflux for 6 h. The mixture was poured into H_2O (20 mL) and the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O (15 mL) and dried (Na_2SO_4). The solvent was evaporated and the crude product was purified by flash column chromatography (50 g silica gel, LP–EtOAc, 30:1); yield: 0.37 g (53%, 0.87 mmol); colorless solid; mp 58–59 °C (Lit.[23] mp 69–70 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 5.14 (s, 2 H), 6.87 (d, ^3J = 8.6 Hz, 2 H), 7.14 (d, ^3J = 8.6 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 51.0 (t), 55.4 (q), 105.6 (s), 114.4 (d), 117.1 (s), 118.5 (s), 126.2 (s), 128.6 (d), 159.7 (s).

Suzuki–Miyaura Cross-Coupling Reaction

Cross-Coupling at Position 2 of 2a–c; General Procedure A

Protected 2,4,5-tribromo-1*H*-imidazole (1 equiv), boronic acid (1.1 equiv), 2 M aq K_2CO_3 (1 equiv), $Pd(PPh_3)_4$ (5 mol%), and MeOH–toluene (5:1) were placed in a 8 mL vial with a magnetic stirring bar and a screw cap with septum. The solution was purged with argon for 5 min. Then, the septum screw cap was exchanged for a closed cap under argon flow, since caps with septum did not withstand the pressure built up during the reaction. The mixture was heated to 120 °C in a heating block. The reaction was monitored by TLC and stopped when reaction control showed complete consumption of the starting material. If the reaction showed no further progress, additional equivalents of boronic acid were added until the reaction was complete. The reaction mixture was cooled to r.t., filtered through a pad of Celite, and the solvent was evaporated. The residue was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and dried (Na_2SO_4). The solvent was evaporated and the desired product was obtained by flash column chromatography.

Cross-Coupling of 2a–c with 2-Furylboronic Acid; General Procedure B

Protected 2,4,5-tribromo-1*H*-imidazole (1 equiv), 2-furylboronic acid (1.1 equiv), $NaHCO_3$ (2.5 equiv), $Pd(PPh_3)_4$ (5 mol%), and DME–H_2O (3:1) were placed in a 8 mL vial with a magnetic stirring bar and a screw cap with septum. The solution was purged with argon for 5 min. Then the septum screw cap was exchanged for a closed cap under argon flow, since caps with septum did not withstand the pressure built up during the reaction. The mixture was heated to 100 °C in a heating block. If the reaction showed no further progress by TLC, additional equivalents of boronic acid were added. The addition of boronic acid was stopped when about 4 equiv were already added. The reaction mixture was cooled to r.t., filtered through a pad of Celite, and the solvent was evaporated. The residue was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and dried (Na_2SO_4). The solvent was evaporated and the desired product was obtained by flash column chromatography.

Cross-Coupling of Substrates 3–19 Towards Triarylated Imidazoles 20–40; General Procedure C

Protected 2-aryl-4,5-tribromo-1*H*-imidazole (1 equiv), boronic acid (3 equiv), 2 M aq K_2CO_3 (3 equiv), $Pd(PPh_3)_4$ (5 mol%), and MeOH–toluene (5:1) were placed in a 4 mL vial with a magnetic stirring bar and a screw cap with septum. The solution was purged with argon for 5 min. Then the septum screw cap was exchanged for a closed cap under argon flow, since caps with septum did not withstand the pressure built up during the reaction. The mixture was heated to 120 °C in a heating block. The reaction was monitored by TLC and stopped when reaction control showed complete consumption of the starting material. If the reaction showed no further progress, additional equivalents of boronic acid were added until the reaction was complete. The reaction mixture was cooled to r.t., filtered through a pad of Celite, and the solvent was evaporated. The residue was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and dried (Na_2SO_4). The solvent was evaporated and the desired product was obtained by flash column chromatography.

One-Pot Protocol for the Formation of 2,4,5-Triarylated Imidazoles; General Procedure D

Protected 2,4,5-tribromo-1*H*-imidazole (1 equiv), boronic acid (1.1 equiv), 2 M aq K_2CO_3 (4 equiv), $Pd(PPh_3)_4$ (5 mol%), and MeOH–toluene (5:1) were placed in a 4 mL vial with a magnetic stirring bar and a screw cap with septum. The solution was purged with argon for 5 min. Then the septum screw cap was exchanged for a closed cap under argon flow, since caps with septum did not withstand the pressure built up during the reaction. The mixture was heated to 120 °C in a heating block. The reaction was monitored by TLC. If the reaction showed no further progress, additional equivalents of boronic acid were added until the reaction was complete. After complete consumption of the starting material, the second boronic acid (3 equiv) was added, and the subsequent cross-coupling steps were carried out again at 120 °C. The reaction was stopped when reaction control showed complete consumption of the starting material. The reaction mixture was cooled to r.t., filtered through a pad of

Celite, and the solvent was evaporated. The residue was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and dried (Na_2SO_4). The solvent was evaporated and the desired product was obtained by flash column chromatography.

1-Benzyl-4,5-dibromo-2-phenyl-1*H*-imidazole (3)
Prepared according to general procedure A starting from compound **2a** (1 g, 2.53 mmol) and phenylboronic acid (0.37 g, 3.04 mmol, 1.2 equiv); 1.1 equiv added at the beginning, 0.1 equiv added after 4 h; toluene–MeOH (5:1, 6 mL); 5 h. Flash column chromatography (150 g silica gel, CH_2Cl_2–MeOH, 200:1); yield: 0.8 g (81%, 2.05 mmol); pale yellow solid; mp 91–92 °C (Lit.[25] mp 91–93 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.29 (s, 2 H), 6.97–7.07 (m, 2 H), 7.29–7.53 (m, 8 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 50.1 (t), 105.3 (s), 117.4 (s), 125.7 (d), 127.8 (d), 128.4 (d), 128.6 (d), 129.0 (d), 129.2 (s), 129.6 (d), 135.4 (s), 149.0 (s).

1-Benzyl-4,5-dibromo-2-(4-methoxyphenyl)-1*H*-imidazole (4)
Prepared according to general procedure A starting from compound **2a** (250 mg, 0.63 mmol) and 4-methoxyphenylboronic acid (105.8 mg, 0.70 mmol, 1.1 equiv) in toluene–MeOH (5:1, 1.5 mL) for 6 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 10:1); yield: 209 mg (78%, 0.50 mmol); colorless solid; mp 117–121 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 5.26 (s, 2 H), 6.82–6.92 (m, 2 H), 6.97–7.07 (m, 2 H), 7.29–7.45 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 50.3 (t), 55.4 (q), 105.1 (s), 114.2 (d), 117.1 (s), 121.7 (s), 125.9(d), 128.2 (d), 129.2 (d), 130.2 (d), 135.7 (s), 149.3 (s), 160.8 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 420.9546; found: 420.9553, difference = 1.66 ppm.

1-Benzyl-4,5-dibromo-2-(3-nitrophenyl)-1*H*-imidazole (5)
Prepared according to general procedure A starting from compound **2a** (592.5 mg, 1.5 mmol) and 3-nitrophenylboronic acid (275 mg, 1.65 mmol, 1.1 equiv) in toluene–MeOH (5:1, 3.6 mL) for 3.5 h. Flash column chromatography (100 g silica gel, CH_2Cl_2–MeOH, 200:1); yield: 357 mg (55%, 0.82 mmol); yellow solid; mp 96–100 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 5.44 (s, 2 H), 7.02 (d, ^3J = 6.4 Hz, 2 H), 7.24–7.43 (m, 3 H), 7.70–7.81 (m, 1 H), 7.99 (d, ^3J = 7.8 Hz, 1 H), 8.24–8.34 (m, 2 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 50.1 (t), 107.5 (s), 117.1 (s), 122.9 (d), 124.2 (d), 125.8 (d), 127.8 (d), 129.0 (d), 130.4 (s), 130.6 (d), 134.4 (d), 135.6 (s), 146.2 (s), 147.9 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 435.9291; found: 435.9301, difference = 2.29 ppm.

1-Benzyl-4,5-dibromo-2-(4-nitrophenyl)-1*H*-imidazole (6)
Prepared according to general procedure A starting from compound **2a** (250 mg, 0.63 mmol) and 4-nitrophenylboronic acid (116.3 mg, 0.70 mmol, 1.1 equiv) in toluene–MeOH (5:1, 1.5 mL) for 6 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 10:1); yield: 176.3 mg (64%, 0.40 mmol); yellow solid; mp 153–155 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.26 (s, 2 H), 6.88–7.04 (m, 2 H), 7.22–7.40 (m, 3 H), 7.60 (d, ^3J = 8.7 Hz, 2 H), 8.13 (d, ^3J = 8.7 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 50.7 (t), 107.9 (s), 118.7 (s), 124.1 (d), 125.7 (d), 128.5 (d), 129.2 (d), 129.6 (d), 134.9 (s), 135.2 (s), 146.7 (s), 148.2 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 435.9296; found: 435.9291, difference = 1.15 ppm.

1-Benzyl-4,5-dibromo-2-(2-tolyl)-1*H*-imidazole (7)
Prepared according to general procedure A starting from compound **2a** (500 mg, 1.27 mmol) and 2-tolylboronic acid (223 mg, 1.64 mmol, 1.3 equiv); 1.1 equiv added at the beginning, 0.2 equiv added after 4 h; toluene–MeOH (5:1, 3 mL); 6 h. Flash column chromatography (150 g silica gel, CH_2Cl_2–MeOH, 200:1); yield: 403 mg (79%, 0.99 mmol); yellow solid; mp 105–106 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.11 (s, 3 H), 5.06 (s, 2 H), 6.83–6.94 (m, 2 H), 7.13–7.42 (m, 7 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.7 (q), 50.0 (t), 104.1 (s), 116.8 (s), 125.8 (d), 126.8 (d), 128.1 (d), 128.8 (d), 129.3 (s), 130.2 (d), 130.3 (d), 130.7 (d), 135.4 (s), 138.7 (s), 148.5 (s).

1-Benzyl-4,5-dibromo-2-(2-furyl)-1*H*-imidazole (8)
Prepared according to general procedure B starting from compound **2a** (500 mg, 1.27 mmol) and 2-furylboronic acid (586 mg, 5.23 mmol, 4.1 equiv); 1.1 equiv added at the beginning, 1 equiv added after 0.5 h, 1 equiv after 2 h, 1 equiv after 1 h; toluene–MeOH (5:1, 4 mL); 4 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 6:1); yield: 210 mg (43%, 0.55 mmol); brown solid; mp 109–116 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.52 (s, 2 H), 6.63 (dd, ^3J = 3.3 Hz, ^4J = 1.7 Hz, 1 H), 6.85 (d, ^3J = 3.5 Hz, 1 H), 7.05 (d, ^3J = 6.5 Hz, 2 H), 7.23–7.43 (m, 3 H), 7.79–7.86 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 50.9 (t), 107.1 (s), 111.8 (d), 112.7 (d), 117.8 (s), 126.9 (d), 128.6 (d), 129.8 (d), 136.6 (s), 140.5 (s), 144.2 (s), 145.2 (d).

HRMS: *m*/*z* calcd for $[M + H]^+$: 380.9233; found: 380.9252, difference = 4.99 ppm.

4,5-Dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-2-phenyl-1*H*-imidazole (9)[17]
Prepared according to general procedure A starting from compound **2b** (500 mg, 1.15 mmol) and phenylboronic acid (154 mg, 1.26 mmol, 1.1 equiv) in toluene–MeOH (5:1, 3 mL) for 5 h. Flash column chromatography (75 g silica gel, LP–EtOAc, 20:1); yield: 409 mg (82%, 0.94 mmol); colorless solid: mp 76–79 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.08 (s, 9 H), 0.95 (t, ^3J = 8.2 Hz, 2 H), 3.65 (t, ^3J = 8.2 Hz, 2 H), 5.31 (s, 2 H), 7.41–7.51 (m, 3 H), 7.72–7.83 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –1.3 (q), 18.0 (t), 67.1 (t), 74.8 (t), 105.4 (s), 117.9 (s), 128.8 (d), 129.1 (d), 129.3 (s), 130.0 (d), 149.9 (s).

LCMS: *m*/*z* (%) = 455 (12), 433 (82, MH^+), 403 (17), 375 (100).

4,5-Dibromo-2-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole (10)[26]
Prepared according to general procedure A starting from compound **2b** (500 mg, 1.15 mmol) and 4-methoxyphenylboronic acid (192 mg, 1.26 mmol, 1.1 equiv) in toluene–MeOH (5:1, 3 mL) for 6.5 h. Flash column chromatography (100 g silica gel, LP–EtOAc, 7:1); yield: 393 mg (74%, 0.85 mmol); red brown solid; mp 95–97 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.00 (s, 9 H), 0.94 (t, ^3J = 8.3 Hz, 2 H), 3.65 (t, ^3J = 8.3 Hz, 2 H), 3.83 (s, 3 H), 5.26 (s, 2 H), 6.94 (d, ^3J = 8.7 Hz, 2 H), 7.79 (d, ^3J = 8.7 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –1.6 (q), 17.7 (t), 55.2 (q), 66.8 (t), 74.5 (t), 104.7 (s), 114.0 (s), 116.7 (d), 120.9 (s), 130.3 (d), 149.6 (s), 160.8 (s).

4,5-Dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-2-(3-nitrophenyl)-1*H*-imidazole (11)
Prepared according to general procedure A starting from compound **2b** (500 mg, 1.15 mmol) and 3-nitrophenylboronic acid (230 mg, 1.38 mmol, 1.2 equiv.); 1.1 equiv added at the beginning, 0.1 equiv added after 5 h; toluene–MeOH (5:1, 3 mL); 6.5 h. Flash column chromatography (100 g silica gel, LP–EtOAc, 10:1); yield: 355 mg (65%, 0.74 mmol); yellow solid; mp 102–105 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.03 (s, 9 H), 1.05 (t, ^3J = 8.3 Hz, 2 H), 3.78 (t, ^3J = 8.3 Hz, 2 H), 5.33 (s, 2 H), 7.65 (t, ^3J = 8.0 Hz, 1 H), 8.17–8.33 (m, 2 H), 8.77 (t, ^3J = 1.8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –1.6 (q), 17.8 (t), 67.1 (t), 74.4 (t), 106.6 (s), 118.1 (s), 123.3 (d), 124.2 (d), 129.7 (d), 130.5 (s), 134.3 (d), 147.0 (s), 148.2 (s).

4,5-Dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-2-(4-nitrophenyl)-1*H*-imidazole (12)

Prepared according to general procedure A starting from compound **2b** (250 mg, 0.58 mmol) and 4-nitrophenylboronic acid (106 mg, 0.63 mmol, 1.1 equiv) in toluene–MeOH (5:1, 1.5 mL) for 5 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 15:1); yield: 188 mg (68%, 0.39 mmol); yellow solid; mp 133–136 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.04 (s, 9 H), 1.00 (t, ^3J = 8.3 Hz, 2 H), 3.79 (t, ^3J = 8.3 Hz, 2 H), 5.34 (s, 2 H), 8.08 (d, ^3J = 8.9 Hz, 2 H), 8.31 (d, ^3J = 8.9 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –1.2 (q), 18.2 (t), 67.7 (t), 74.8 (t), 107.5 (s), 118.9 (s), 124.1 (d), 129.6 (d), 135.0 (s), 147.4 (s), 148.4 (s)

HRMS: *m*/*z* calcd for $[M + H]^+$: 475.9635; found: 475.9645, difference = 2.10 ppm.

4,5-Dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-2-(2-tolyl)-1*H*-imidazole (13)

Prepared according to general procedure A starting from compound **2b** (250 mg, 0.58 mmol) and 2-tolylboronic acid (86 mg, 0.63 mmol, 1.1 equiv) in toluene–MeOH (5:1, 1.5 mL) for 5 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 15:1); yield: 190 mg (74%, 0.43 mmol); beige oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.00 (s, 9 H), 0.85 (t, ^3J = 8.3 Hz, 2 H), 2.29 (s, 3 H), 3.41 (t, ^3J = 8.3 Hz, 2 H), 5.16 (s, 2 H), 7.24–7.48 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –1.7 (q), 17.5 (t), 19.6 (q), 66.4 (t), 74.2 (t), 103.6 (s), 117.0 (s), 125.4 (d), 128.5 (s), 129.9 (d), 130.34 (d), 130.38 (d), 138.2 (s), 148.5 (s)

HRMS: *m*/*z* calcd for $[M + H]^+$: 444.9941; found: 444.9956, difference = 2.10 ppm.

4,5-Dibromo-2-(2-furyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole (14)

Prepared according to general procedure B starting from compound **2b** (500 mg, 1.15 mmol) and 2-furylboronic acid (463 mg, 4.14 mmol, 3.6 equiv); 1.1 equiv added at the beginning, 0.5 equiv added after 1 h, 1 equiv after 30 min, 1 equiv after 15 min; toluene–MeOH (5:1, 3 mL); 2 h. Flash column chromatography (100 g silica gel, LP–EtOAc, 10:1); yield: 149 mg (31%, 0.35 mmol); brown solid; mp 73–76 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = –0.04 (s, 9 H), 0.90 (t, ^3J = 8.2 Hz, 2 H), 3.60 (t, ^3J = 8.2 Hz, 2 H), 5.56 (s, 2 H), 6.53 (dd, ^3J = 3.5 Hz, ^4J = 1.8 Hz, 1 H), 7.02 (d, ^3J = 3.5 Hz, 1 H), 7.53 (d, ^3J = 1.8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –1.3 (q), 17.9 (t), 66.9 (t), 75.0 (t), 105.4 (s), 111.8 (d), 111.9 (d), 118.2 (s), 140.9 (s), 143.7 (d), 144.0 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 420.9577; found: 420.9579, difference = 0.48 ppm.

4,5-Dibromo-1-(4-methoxybenzyl)-2-phenyl-1*H*-imidazole (15)

Prepared according to general procedure A starting from compound **2c** (100 mg, 0.24 mmol) and phenylboronic acid (32 mg, 0.26 mmol, 1.1 equiv) in toluene–MeOH (5:1, 0.6 mL) for 5 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 10:1); yield: 74 mg (74%, 0.17 mmol); pale yellow solid; mp 98–102 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 5.22 (s, 2 H), 6.81–6.99 (m, 4 H), 7.31–7.54 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 49.8 (t), 55.3 (q), 105.3 (s), 114.4 (d), 117.4 (s), 127.3 (d), 127.5 (s), 128.6 (d), 128.7 (d), 129.5 (s), 129.7 (d), 149.1 (s), 159.2 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 420.9546; found: 420.9547, difference = 0.24 ppm.

4,5-Dibromo-2-(4-methoxyphenyl)-1-(4-methoxybenzyl)-1*H*-imidazole (16)

Prepared according to general procedure A starting from compound **2c** (100 mg, 0.24 mmol) and 4-methoxyphenylboronic acid (39 mg, 0.26 mmol, 1.1 equiv) in toluene–MeOH (5:1, 0.6 mL) for 5 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 10:1); yield: 82 mg (77%, 0.18 mmol); yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 3.80 (s, 3 H), 5.18 (s, 2 H), 6.79–7.00 (m, 6 H), 7.33–7.45 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 49.6 (t), 55.18 (q), 55.22 (q), 104.6 (s), 114.0 (d), 114.3 (d), 117.0 (s), 121.8 (s), 127.1 (d), 127.6 (s), 130.0 (d), 149.0 (s), 159.1 (s), 160.5 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 450.9651; found: 450.9670, difference = 4.21 ppm.

4,5-Dibromo-1-(4-methoxybenzyl)-2-(3-nitrophenyl)-1*H*-imidazole (17)

Prepared according to general procedure A starting from compound **2c** (200 mg, 0.47 mmol) and 3-nitrophenylboronic acid (86 mg, 0.52 mmol, 1.1 equiv) in toluene–MeOH (5:1, 1.2 mL) for 6 h. Flash column chromatography (75 g silica gel, LP–EtOAc, 10:1); yield: 138 mg (63%, 0.29 mmol); beige oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 5.27 (s, 2 H), 6.82–7.01 (m, 4 H), 7.57 (t, ^3J = 8.2 Hz, 1 H), 7.85 (d, ^3J = 7.7 Hz, 1 H), 8.25 (d, ^3J = 8.2 Hz, 1 H), 8.32–8.39 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 50.1 (t), 55.3 (q), 107.1 (s), 114.6 (d), 118.1 (s), 123.3 (d), 124.2 (d), 126.6 (s), 127.1 (d), 129.9 (d), 130.9 (s), 134.2 (d), 146.3 (s), 148.2 (s), 159.5 (s).

HRMS: *m*/*z* calcd for $[M + Na]^+$: 487.9216; found: 487.9229, difference = 2.66 ppm.

4,5-Dibromo-1-(4-methoxybenzyl)-2-(2-tolyl)-1*H*-imidazole (18)

Prepared according to general procedure A starting from compound **2c** (200 mg, 0.47 mmol) and 2-tolylboronic acid (70 mg, 0.52 mmol, 1.1 equiv) in toluene–MeOH (5:1, 1.2 mL) for 6 h. Flash column chromatography (75 g silica gel, LP–EtOAc, 10:1); yield: 121 mg (59%, 0.28 mmol); beige oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.97 (s, 3 H), 3.73 (s, 3 H), 5.03 (s, 2 H), 6.72–6.79 (m, 4 H), 7.14–7.49 (m).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.3 (q), 51.3 (t), 56.5 (q), 106.6 (s), 115.9 (d), 117.4 (s), 127.8 (d), 129.4 (s), 130.2 (d), 131.1 (s), 132.2 (d), 132.4 (d), 132.5 (d), 140.7 (s), 150.7 (s), 161.7 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 434.9702; found: 434.9707, difference = 1.15 ppm.

4,5-Dibromo-2-(2-furyl)-1-(4-methoxybenzyl)-1*H*-imidazole (19)

Prepared according to general procedure B starting from compound **2c** (400 mg, 0.94 mmol) and 2-furylboronic acid (379 mg, 3.39 mmol, 3.6 equiv); 1.1 equiv added at the beginning, 0.5 equiv added after 1 h, 1 equiv after 30 min, 1 equiv after 15 min; toluene–MeOH (5:1, 2.4 mL); 2 h. Flash column chromatography (200 g silica gel, LP–EtOAc, 9:1); yield: 136 mg (35%, 0.33 mmol); dark beige oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.75 (s, 3H), 5.42 (s, 2 H), 6.42–6.52 (m, 1 H), 6.77–6.87 (m, 3 H), 7.02 (d, ^3J = 8.7 Hz, 2 H), 7.42–7.52 (m, 1 H).

^{13}C NMR (50 MHz $CDCl_3$,): δ = 49.9 (t), 55.1 (q), 105.4 (s), 110.8 (d), 111.6 (d), 114.1 (d), 117.6 (s), 127.2 (s), 127.8 (d), 139.9 (s), 143.1 (d), 144.1 (s), 159.2 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 410.9338; found: 410.9326, difference = –2.92 ppm.

1-Benzyl-2,4,5-triphenyl-1*H*-imidazole (20)[27]
Prepared according to general procedure C starting from compound **3** (100 mg, 0.26 mmol) and phenylboronic acid (93 mg, 0.77 mmol, 3 equiv) in toluene–MeOH (5:1, 0.6 mL) for 3 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 5:1); yield: 79 mg (79%, 0.20 mmol); colorless solid; mp 157–160 °C (Lit.[27] mp 157–159 °C).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 5.15 (s, 2 H), 6.63–6.85 (m, 2 H), 6.97–7.94 (m, 18 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 47.6 (t), 125.6 (d), 126.1 (d), 126.2 (d), 126.4 (d), 127.1 (d), 128.1 (d), 128.48 (d), 128.53 (d), 128.8 (d), 128.9 (d), 130.1 (s), 130.5 (s), 130.7 (s), 130.8 (d), 134.5 (s), 136.8 (s), 137.3 (s), 147.0 (s).

1-Benzyl-4,5-di(4-methoxyphenyl)-2-phenyl-1*H*-imidazole (21)
Prepared according to general procedure C starting from compound **3** (100 mg, 0.26 mmol) and 4-methoxyphenylboronic acid (116 mg, 0.77 mmol, 3 equiv) in toluene–MeOH (5:1, 0.6 mL) for 4 h. Flash column chromatography (50 g silica gel, LP–EtOAc, = 4:1); yield: 97 mg (85%, 0.22 mmol).

Alternatively prepared according to general procedure D starting from compound **2a** (100 mg, 0.26 mmol); boronic acid 1: phenylboronic acid (34 mg, 0.28 mmol, 1.1 equiv); boronic acid 2: 4-methoxyphenylboronic acid (115 mg, 0.76 mmol, 3 equiv); toluene–MeOH (5:1, 0.6 mL); 3 h for the first coupling step, 4.5 h for the second coupling step. Flash column chromatography (50 g silica gel, LP–EtOAc, 7:1); yield: 102 mg (89%, 0.23 mmol); beige oil.

^{1}H NMR (200 MHz, CD_3OD): δ = 3.65 (s, 3 H), 3.69 (s, 3 H), 5.05 (s, 2 H), 6.60–7.65 (m, 18 H).

^{13}C NMR (50 MHz, CD_3OD): δ = 49.1 (t), 55.6 (q), 55.7 (q), 114.6 (d), 115.3 (d), 123.7 (s), 127.0 (d), 128.0 (s), 128.4 (d), 129.4 (d), 129.6 (d), 129.7 (d), 130.3 (d), 130.4 (d), 130.7 (s), 131.8 (s), 133.5 (d), 138.8 (s), 138.9 (s), 149.2 (s), 160.0 (s), 161.4 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 447.2067; found: 447.2085, difference = 4.02 ppm.

1-Benzyl-4,5-di(3-nitrophenyl)-2-phenyl-1*H*-imidazole (22)
Prepared according to general procedure C starting from compound **3** (100 mg, 0.26 mmol) and 3-nitrophenylboronic acid (128 mg, 0.77 mmol, 3. equiv) in toluene–MeOH (5:1, 0.6 mL) for 3 h. Flash column chromatography (15 g silica gel, CH_2Cl_2–MeOH, 200:1); yield: 68 mg (56%, 0.14 mmol); yellow solid; mp 159–161 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 5.23 (s, 2 H), 6.68–6.87 (m, 2 H), 7.08–7.27 (m, 3 H), 7.43–7.61 (m, 4 H), 7.64–7.84 (m, 5 H), 8.03 (d, ^3J = 8.10 Hz, 1 H), 8.15 (s, 1 H), 8.26–8.41 (m, 2 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 48.2 (t), 120.3 (d), 121.2 (d), 124.0 (d), 125.4 (d), 125.9 (d), 127.4 (d), 128.6 (d), 128.8 (d), 128.9 (s), 129.3 (d), 129.9 (d), 130.0 (s), 130.8 (d), 131.4 (s), 131.9 (d), 135.5 (s), 135.6 (s), 136.7 (s), 137.5 (d), 148.1 (s), 148.5 (s).

HRMS: *m*/*z* calcd for $[M + Na]^+$: 499.1377; found: 499.1398, difference = 4.21 ppm.

1-Benzyl-2-phenyl-4,5-di(2-tolyl)-1*H*-imidazole (23)
Prepared according to general procedure C starting from compound **3** (100 mg, 0.26 mmol) and 2-tolylboronic acid (104.1 mg, 0.77 mmol, 3 equiv) in toluene–MeOH (5:1, 0.6 mL) for 4 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 4:1), followed by preparative HPLC; yield: 39 mg (37%, 0.09 mmol); beige oil.

^{1}H NMR (200 MHz, CD_3OD): δ = 1.73 (s, 3 H), 2.30 (s, 3 H), 5.21 (d, ^3J = 16.0 Hz, 1 H), 5.11 (d, ^3J = 16.0 Hz, 1 H), 6.51–6.70 (m, 2 H), 6.90–7.32 (m, 11 H), 7.39–7.58 (m, 3 H), 7.61–7.79 (m, 2 H).

^{13}C NMR (50 MHz CD_3OD): δ = 19.8 (q), 20.7 (q), 49.7 (t), 126.3 (d), 126.8 (d), 127.5 (d), 128.5 (d), 128.7 (d), 129.4 (d), 129.9 (d), 130.0 (d), 130.4 (d), 130.5 (s), 131.3 (d), 131.4 (d), 131.6 (d), 131.7 (s), 131.8 (s), 132.8 (d), 135.1 (s), 139.8 (s), 140.3 (s), 149.6 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 415.2169; found: 415.2176, difference = 1.69 ppm.

1-Benzyl-2-(4-methoxyphenyl)-4,5-di(3-nitrophenyl)-1*H*-imidazole (24)
Prepared according to general procedure C starting from compound **4** (100 mg, 0.24 mmol) and 3-nitrophenylboronic acid (119 mg, 0.71 mmol, 3 equiv) in toluene–MeOH (5:1, 0.6 mL) for 5 h. Flash column chromatography (20 g silica gel, LP–EtOAc, 5:1); yield: 73 mg (60%, 0.14 mmol).

Alternatively prepared according to general procedure D starting from compound **2a** (100 mg, 0.26 mmol); boronic acid 1: 4-methoxyphenylboronic acid (42 mg, 0.28 mmol, 1.1 equiv); boronic acid 2: 3-nitrophenylboronic acid (254 mg, 1.52 mmol, 6 equiv); toluene–MeOH (5:1, 0.6 mL); 6 h for the first coupling step, 3 h for the second coupling step. Flash column chromatography (50 g silica gel, LP–EtOAc, 10:1); yield: 94 mg (73%, 0.18 mmol); yellow solid; mp 149–151 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.80 (s, 3 H), 5.20 (s, 2 H), 6.71–6.84 (m, 2 H), 7.06 (d, ^3J = 8.7 Hz, 2 H), 7.12–7.28 (m, 3 H), 7.50 (t, ^3J = 8.1 Hz, 1 H), 7.59–7.81 (m, 5 H), 8.01 (dd, ^3J = 7.83 Hz, ^4J = 1.76 Hz, 1 H), 8.13 (s, 1 H), 8.23–8.38 (m, 2 H).

^{13}C NMR (50 MHz DMSO-d_6): δ = 48.2 (t), 55.3 (q), 114.2 (d), 120.3 (d), 121.1 (d), 122.3 (s), 124.0 (d), 125.4 (d), 125.8 (d), 127.4 (d), 128.6 (d), 130.0 (d), 130.2 (d), 130.8 (d), 131.6 (s), 131.9 (d), 135.4 (d), 135.7 (s), 136.8 (s), 137.5 (d), 148.0 (s), 148.1 (s), 148.5 (s), 160.0 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 507.1663; found: 507.1686, difference = 4.53 ppm.

1-Benzyl-2-(4-methoxyphenyl)-4,5-di(2-tolyl)-1*H*-imidazole (25)
Prepared according to general procedure C starting from compound **4** (100 mg, 0.24 mmol) and 2-tolylboronic acid (97 mg, 0.71 mmol, 3 equiv) in toluene–MeOH (5:1, 0.6 mL) for 4 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 4:1), followed by preparative HPLC; yield: 66 mg (63%, 0.15 mmol); colorless oil.

^{1}H NMR (200 MHz, CD_3OD): δ = 1.72 (s, 3 H), 2.29 (s, 3 H), 3.82 (s, 3 H), 5.08 (d, ^3J = 16.1 Hz, 1 H), 5.18 (d, ^3J = 16.1 Hz, 1 H), 6.55–6.68 (m, 2 H), 6.91–7.23 (m, 13 H), 7.62 (d, ^3J = 8.9 Hz, 2 H).

^{13}C NMR (50 MHz, CD_3OD): δ = 19.8 (q), 20.7 (q), 49.6 (t), 55.8 (q), 115.3 (d), 124.0 (s), 126.3 (d), 126.8 (d), 127.5 (d), 128.5 (d), 128.6 (d), 129.4 (d), 123.0 (d), 130.7 (s), 131.26 (d), 131.30 (s), 131.4 (d), 131.6 (d), 131.8 (d), 132.8 (d), 135.3 (s), 138.2 (s), 138.4 (s), 139.8 (s), 140.1 (s), 149.6 (s), 162.0 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 445.2274; found: 445.2282, difference = 1.80 ppm.

1-Benzyl-2-(3-nitrophenyl)-4,5-diphenyl-1*H*-imidazole (26)[27]
Prepared according to general procedure C starting from compound **5** (100 mg, 0.23 equiv) and phenylboronic acid (84 mg, 0.69 mmol, 3 equiv) in toluene–MeOH (5:1, 0.6 mL) for 3 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 4:1); yield: 84 mg (85%, 0.20 mmol); yellow solid; mp 126–128 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 5.23 (s, 2 H), 6.73–6.89 (m, 2 H), 7.07–7.54 (m, 13 H), 7.71 (t, ^3J = 8.0 Hz, 1 H), 8.13 (d, ^3J = 8.0 Hz, 1 H), 8.23 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1 H), 8.42–8.53 (m, 1 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 47.9 (t), 122.8 (d), 123.4 (d), 125.7 (d), 126.2 (d), 126.5 (d), 127.3 (d), 128.2 (d), 128.6 (d), 129.0 (d), 130.1 (s), 130.3 (d), 130.8 (d), 131.3 (s), 132.0 (s), 134.1 (s), 134.4 (d), 136.9 (s), 137.4 (s), 144.7 (s), 147.8 (s).

1-Benzyl-2-(4-nitrophenyl)-4,5-diphenyl-1*H*-imidazole (27)[28]
Prepared according to general procedure C starting from compound **6** (135 mg, 0.31 equiv) and phenylboronic acid (126 mg, 1.03 mmol, 3 equiv) in toluene–MeOH (5:1, 0.9 mL) for 1.5 h. Flash column chromatography (75 g silica gel, LP–EtOAc, 4:1); yield: 106 mg (79%, 0.25 mmol); yellow solid: mp 171–173 °C (Lit.[28] mp 168–171 °C).

^{1}H NMR (200 MHz DMSO-d_6): δ = 5.25 (s, 2 H), 6.68–6.87 (m, 2 H), 7.04–7.57 (m, 13 H), 7.98 (d, ^3J = 8.8 Hz, 2 H), 8.27 (d, ^3J = 8.8 Hz, 2 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 47.9 (t), 123.8 (d), 125.7 (d), 126.2 (d), 126.6 (d), 127.4 (d), 128.2 (d), 128.7 (d), 129.1 (d), 129.3 (d), 130.0 (s), 130.8 (d), 131.9 (s), 134.0 (s), 136.7 (s), 136.8 (s), 137.8 (s), 144.8 (s), 147.0 (s).

HRMS: *m*/*z* [M + H]$^+$: 432.1707; found: 432.1711, difference = 0.93 ppm.

1-Benzyl-4,5-di(4-methoxyphenyl)- 2-(2-tolyl)-1*H*-imidazole (28)
Prepared according to general procedure C starting from compound **7** (115 mg, 0.28 mmol) and 4-methoxyphenylboronic acid (169 mg, 1.11 mmol, 3 equiv) in toluene–MeOH (5:1, 0.9 mL) for 1.5 h. Flash column chromatography (75 g silica gel, LP–EtOAc, 2:1); yield: 89 mg (68%, 0.19 mmol); beige oil.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.18 (s, 3 H), 3.68 (s, 3 H), 3.75 (s, 3 H), 4.91 (s, 2 H), 6.55–6.67 (m, 2 H), 6.69–6.80 (m, 2 H), 6.86–6.97 (m, 2 H), 7.02–7.13 (m, 3 H), 7.14–7.45 (m, 8 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 19.9 (q), 48.9 (t), 55.6 (q), 55.7 (q), 114.6 (d), 115.5 (d), 123.9 (s), 126.8 (d), 127.6 (d), 128.1 (s), 128.4 (d), 129.3 (d), 129.4 (d), 129.6 (s), 130.9 (d), 131.5 (d), 131.6 (d), 133.6 (d), 138.2 (s), 139.9 (s), 148.5 (s), 159.9 (s), 161.5 (s).

HRMS: *m*/*z* calcd for [M + H]$^+$: 461.2224; found: 461.2237, difference = 2.82 ppm.

1-Benzyl-4,5-di(3-nitrophenyl)-2-(2-tolyl)-1*H*-imidazole (29)
Prepared according to general procedure C starting from compound **7** (100 mg, 0.25 mmol) and 3-nitrophenylboronic acid (144 mg, 0.86 mmol, 3.5 equiv); 3 equiv added at the beginning, 0.5 equiv added after 4 h; toluene–MeOH (5:1, 0.6 mL) for 7 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 5:1); yield: 48 mg (39%, 0.10 mmol); yellow oil.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.29 (s, 3 H), 5.01 (s, 2 H), 6.59–6.72 (m, 2 H), 7.02–7.18 (m, 3 H), 7.23–7.82 (m, 8 H), 7.97–8.07 (m, 1 H), 8.10–8.15 (m, 1 H), 8.22–8.34 (m, 2 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 20.0 (q), 49.6 (t), 122.5 (d), 122.6 (d), 125.1 (d), 126.9 (d), 127.1 (d), 127.7 (d), 128.8 (d), 129.6 (d), 130.6 (s), 130.8 (d), 131.4 (d), 131.68 (d), 131.74 (d), 131.8 (d), 133.0 (s), 133.8 (d), 136.6 (s), 137.4 (s), 138.5 (d), 139.9 (s), 149.7 (s), 150.0 (s), 150.6 (s).

HRMS: *m*/*z* calcd for [M + H]$^+$: 491.1714; found: 491.1731, difference = 3.46 ppm.

1-Benzyl-2-(2-furyl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole (30)
Prepared according to general procedure C starting from compound **8** (200 mg, 0.52 mmol) and 4-methoxyphenylboronic acid (238 mg, 1.57 mmol, 3 equiv) in toluene–MeOH (5:1, 1.2 mL) for 4 h. Flash column chromatography (100 g silica gel, LP–EtOAc, 2:1); yield: 184 mg (81%, 0.42 mmol); brown solid; mp 67–70 °C.

^{1}H NMR (200 MHz, CD_3OD): δ = 3.70 (s, 3 H), 3.75 (s, 3 H), 5.26 (s, 2 H), 6.47–6.54 (m, 1 H), 6.65–7.45 (m, 14 H), 7.54–7.61 (m, 1 H).

^{13}C NMR (50 MHz, CD_3OD): δ = 49.2 (t), 55.6 (q), 55.7 (q), 111.5 (d), 112.6 (d), 114.6 (d), 115.4 (d), 123.0 (s), 126.9 (d), 127.7 (s), 128.4 (d), 129.5 (d), 129.7 (d), 130.9 (s), 133.5 (d), 138.6 (s), 139.3 (s), 140.2 (s), 144.5 (d), 145.9 (s), 160.1 (s), 161.5 (s).

1-{[2-(Trimethylsilyl)ethoxy]methyl}-2,4,5-triphenyl-1*H*-imidazole (31)
Prepared according to general procedure C starting from compound **9** (100 mg, 0.23 mmol) and phenylboronic acid (85 mg, 0.69 mmol, 3 equiv) in toluene–MeOH (5:1, 0.6 mL) for 4 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 6:1); yield: 90 mg (91%, 0.21 mmol); colorless solid, mp 67–70 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = –0.10 (s, 9 H), 0.73 (t, ^3J = 8.2 Hz, 2 H), 3.20 (t, ^3J = 8.2 Hz, 2 H), 5.06 (s, 2 H), 7.12–7.28 (m, 3 H), 7.36–7.65 (m, 10 H), 7.79–7.93 (m, 2 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = –1.4 (q), 18.7 (t), 67.0 (t), 74.3 (t), 128.0 (d), 128.6 (d), 129.2 (d), 129.8 (d), 130.0 (d), 130.5 (d), 130.7 (d), 131.3 (s), 131.5 (s), 131.7 (s), 132.4 (d), 135.2 (s), 138.9 (s), 150.2 (s).

HRMS: *m*/*z* calcd for [M + H]$^+$: 427.2202; found: 427.2209, difference = –0.54 ppm.

2-(4-Methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-4,5-diphenyl-1*H*-imidazole (32)
Prepared according to general procedure C starting from compound **10** (150 mg, 0.33 mmol) and phenylboronic acid (119 mg, 0.97 mmol, 3 equiv) in toluene–MeOH (5:1, 0.9 mL) for 2.5 h. Flash column chromatography (75 g silica gel, LP–EtOAc, 3:1); yield: 119 mg (80%, 0.26 mmol); colorless oil.

^{1}H NMR (200 MHz, CD_3OD): δ = –0.04 (s, 9 H), 0.81 (t, ^3J = 8.3 Hz, 2 H), 3.25 (t, ^3J = 8.3 Hz, 2 H), 3.83 (s, 3 H), 4.97 (s, 2 H) 6.97–7.11 (m, 2 H), 7.12–7.25 (m, 3 H), 7.30–7.48 (m, 7 H), 7.75 (d, ^3J = 8.8 Hz, 2 H).

^{13}C NMR (50 MHz, CD_3OD): δ = –1.3 (q), 18.8 (t), 55.9 (q), 67.0 (t), 74.2 (t), 115.2 (d), 123.4 (s), 127.9 (d), 128.6 (d), 129.2 (d), 130.0 (d), 131.3 (s), 131.5 (s), 131.8 (d), 132.3 (d), 135.2 (s), 138.6 (s), 150.2 (s), 162.2 (s).

HRMS: *m*/*z* calcd for [M + H]$^+$: 457.2306; found: 457.2319, difference = 2.84 ppm.

2-(4-Methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-4,5-di(2-tolyl)-1*H*-imidazole (33)
Prepared according to general procedure C starting from compound **10** (100 mg, 0.22 mmol) and 2-tolylboronic acid (147 mg, 1.08 mmol, 5 equiv); 3 equiv added at the beginning, 2 equiv added after 4 h; toluene–MeOH (5:1, 0.6 mL); 6 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 5:1), followed by preparative HPLC; yield: 28 mg (11%, 0.04 mmol); yellow-beige oil.

^{1}H NMR (200 MHz, CD_3OD): δ = –0.07 (s, 9 H), 0.76 (t, ^3J = 8.2 Hz, 2 H), 1.99 (s, 3 H), 2.28 (s, 3 H), 3.20 (t, ^3J = 8.2 Hz, 2 H), 3.86 (s, 3 H), 5.00 (d, ^3J = 10.5 Hz, 1 H), 5.19 (d, ^3J = 10.5 Hz, 1 H), 6.93–7.45 (m, 10 H), 7.71–7.83 (m, 2 H).

^{13}C NMR (50 MHz, CD_3OD): δ = –1.4 (q), 18.7 (t), 20.2 (q), 20.7 (q), 55.9 (q), 67.0 (t), 74.6 (t), 115.2 (d), 123.6 (s), 126.3 (d), 126.8 (d), 128.8 (d), 130.2 (d), 130.5 (s), 131.2 (s), 131.3 (d), 131.4 (d), 131.6 (d), 131.8 (d), 133.3 (d), 135.1 (s), 138.3 (s), 139.8 (s), 140.0 (s), 150.0 (s), 162.2 (s).

HRMS: *m*/*z* calcd for [M + H]$^+$: 485.2619; found: 485.2641, difference = 4.53 ppm.

4,5-Di(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2-(3-nitrophenyl)-1*H*-imidazole (34)
Prepared according to general procedure C starting from compound **11** (50 mg, 0.11 mmol) and 4-methoxyphenylboronic acid (48 mg, 0.31 mmol, 3 equiv) in toluene–MeOH (5:1, 0.3 mL) for 4 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 5:1); yield: 30 mg (53%, 0.07 mmol).

Alternatively prepared according to general procedure D starting from compound **2b** (100 mg, 0.23 mmol); boronic acid 1: 3-nitrophenylboronic acid (42 mg, 0.25 mmol, 1.1 equiv), boronic acid 2: 4-methoxyphenylboronic acid (105 mg, 0.69 mmol, 3 equiv); tolu-

ene–MeOH (5:1, 0.6 mL); 6 h for the first coupling step, 2 h for the second coupling step. Flash column chromatography (50 g silica gel, LP–EtOAc, 4:1); yield: 71 mg (58%, 0.13 mmol); yellow-beige oil.

^{1}H NMR (200 MHz, CD_3OD): δ = –0.01 (s, 9 H), 0.96 (t, ^3J = 8.3 Hz, 2 H), 3.41 (t, ^3J = 8.3 Hz, 2 H), 3.74 (s, 3 H), 3.84 (s, 3 H), 5.01 (s, 2 H), 6.74 (d, ^3J = 8.6 Hz, 2 H), 7.01 (d, ^3J = 8.6 Hz, 2 H), 7.28–7.40 (m, 4 H), 7.76 (t, ^3J = 8.1 Hz, 1 H), 8.20–8.39 (m, 2 H), 8.74–8.81 (m, 1 H).

^{13}C NMR (50 MHz, CD_3OD): δ = –1.4 (q), 18.8 (t), 55.6 (q), 55.8 (q), 67.0 (t), 74.2 (t), 114.7 (d), 115.5 (d), 123.0 (s), 124.4 (d), 124.9 (d), 127.5 (s), 129.7 (d), 131.2 (d), 131.7 (s), 132.9 (s), 133.6 (d), 136.0 (d), 139.1 (s), 147.1 (s), 149.8 (s), 160.3 (s), 161.8 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 532.2262; found: 532.2284, difference = 4.13 ppm.

4,5-Di(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-2-(4-nitrophenyl)-1*H*-imidazole (35)

Prepared according to general procedure C starting from compound **12** (100 mg, 0.21 mmol) and 4-methoxyphenylboronic acid (96 mg, 0.63 mmol, 3 equiv) in toluene–MeOH (5:1, 0.6 mL) for 5 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 4:1); yield: 24 mg (21%, 0.04 mmol); yellow oil.

^{1}H NMR (200 MHz, DMSO-d_6): δ = –0.08 (s, 9 H), 0.76 (t, ^3J = 8.3 Hz, 2 H), 3.27 (t, ^3J = 8.3 Hz, 2 H), 3.71 (s, 3 H), 3.83 (s, 3 H), 5.10 (s, 2 H), 6.83 (d, ^3J = 8.5 Hz, 2 H), 7.10 (d, ^3J = 9.0 Hz, 2 H), 7.30–7.45 (m, 4 H), 8.15 (d, ^3J = 9.0 Hz, 2 H), 8.38 (d, ^3J = 9.0 Hz, 2 H).

^{13}C NMR (50 MHz DMSO-d_6): δ = –1.5 (q), 17.3 (t), 55.0 (q), 55.2 (q), 65.5 (t), 72.6 (t), 113.7 (d), 114.5 (d), 121.7 (s), 124.0 (d), 126.6 (s), 127.6 (d), 129.1 (d), 130.5 (s), 132.4 (d), 136.5 (s), 137.5 (s), 144.8 (s), 147.1 (s), 158.2 (s), 159.8 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 532.2262; found: 532.2298, difference = 6.76 ppm.

1-{[2-(Trimethylsilyl)ethoxy]methyl}-4,5-di(3-nitrophenyl)-2-(2-tolyl)-1*H*-imidazole (36)

Prepared according to general procedure C starting from compound **13** (50 mg, 0.11 mmol) and 3-nitrophenylboronic acid (112 mg, 0.67 mmol, 6 equiv); 3 equiv added at the beginning, 3 equiv added after 4 h in toluene–MeOH (5:1, 0.3 mL) for 5 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 7:1); yield: 44 mg (74%, 0.08 mmol); yellow oil.

^{1}H NMR (200 MHz, CD_3OD): δ = –0.08 (s, 9 H), 0.78 (t, ^3J = 8.3 Hz, 2 H), 2.38 (s, 3 H), 3.25 (t, ^3J = 8.3 Hz, 2 H), 5.01 (s, 2 H), 7.27–7.59 (m, 5 H), 7.70–7.82 (m, 2 H), 7.85–7.94 (m, 1 H), 7.99–8.12 (m, 1 H), 8.21–8.31 (m, 1 H), 8.32–8.43 (m, 1 H), 8.44–8.53 (m, 1 H).

^{13}C NMR (50 MHz, CD_3OD): δ = –1.5 (q), 18.6 (t), 20.2 (q), 67.2 (t), 74.5 (t), 122.9 (d), 123.0 (s), 125.1 (d), 126.9 (d), 127.0 (d), 129.6 (s), 130.2 (d), 130.8 (d), 131.5 (d), 131.7 (d), 131.8 (d), 132.6 (d), 134.2 (d), 136.5 (s), 137.5 (s), 138.5 (d), 140.1 (s), 149.8 (s), 150.1 (s), 150.7 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 531.2058; found: 531.2071, difference = 2.45 ppm.

2-(2-Furyl)-4,5-di(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole (37)

Prepared according to general procedure C starting from compound **14** (300 mg, 0.71 mmol) and 4-methoxyphenylboronic acid (324 mg, 2.13 mmol, 3 equiv) in toluene–MeOH (5:1, 1.8 mL) for 4 h. Flash column chromatography (80 g silica gel, LP–EtOAc, 3:1); yield: 325 mg (96%, 0.68 mmol); yellow beige oil.

Alternatively prepared according to general procedure D starting from compound **2b** (200 mg, 0.46 mmol); boronic acid 1: 2-furylboronic acid (160 mg, 1.43 mmol, 3.1 equiv); boronic acid 2: 4-methoxyphenylboronic acid (210 mg, 1.38 mmol, 3 equiv); toluene–MeOH (5:1, 1.2 mL); 6 h for the first coupling step, 2 h for the second coupling step. Flash column chromatography (50 g silica gel, LP–EtOAc, 4:1); yield: 54 mg (58 %, 0.11 mmol); yellow beige oil.

^{1}H NMR (200 MHz, CD_3OD): δ = –0.07 (s, 9 H), 0.78 (t, ^3J = 8.1 Hz, 2 H), 3.35 (t, ^3J = 8.1 Hz, 2 H), 3.75 (s, 3 H), 3.85 (s, 3 H), 5.34 (s, 2 H), 6.61–6.67 (m, 1 H), 6.74–6.83 (m, 2 H), 6.97–6.06 (m, 3 H), 7.26–7.38 (m, 4 H, ArH), 7.70–7.75 (m, 1 H).

^{13}C NMR (50 MHz, CD_3OD): δ = –1.4 (q), 18.6 (t), 55.6 (q), 55.8 (q), 67.1 (t), 74.1 (t), 112.2 (d), 112.7 (d), 114.6 (d), 115.5 (d), 122.9 (s), 127.5 (s), 129.8 (d), 130.7 (s), 133.9 (d), 139.0 (s), 140.6 (s), 144.8 (s), 145.8 (d), 160.2 (s), 161.7 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 477.2204; found: 477.2223, difference = 3.98 ppm.

4,5-Di(4-methoxyphenyl)-1-(4-methoxybenzyl)-2-(3-nitrophenyl)-1*H*-imidazole (38)

Prepared according to general procedure C starting from compound **17** (130 mg, 0.28 mmol) and 4-methoxyphenylboronic acid (127 mg, 0.84 mmol, 3 equiv) in toluene–MeOH (5:1, 0.6 mL) for 3.5 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 5:1); yield: 62 mg (43%, 0.12 mmol); yellow oil.

^{1}H NMR (200 MHz, CD_3OD): δ = 3.68 (s, 3 H), 3.72 (s, 3 H), 3.78 (s, 3 H), 5.08 (s, 2 H), 6.63–6.84 (m, 6 H), 6.91 (d, ^3J = 8.7 Hz, 2 H), 7.18 (d, ^3J = 8.7 Hz, 2 H), 7.38 (d, ^3J = 8.8 Hz, 2 H), 7.64 (t, ^3J = 8.0 Hz, 1 H), 7.94–8.04 (m, 1 H), 8.18–8.32 (m, 1 H), 8.43 (t, ^3J = 1.8 Hz, 1 H).

^{13}C NMR (50 MHz, CD_3OD): δ = 48.8 (t), 55.6 (q), 55.7 (q), 55.8 (q), 114.6 (d), 115.2 (d), 115.5 (d), 123.4 (s), 124.7 (d), 124.8 (d), 127.8 (s), 128.3 (d), 129.5 (d), 130.2 (s), 131.1 (d), 131.8 (s), 133.5 (s), 133.6 (d), 135.9 (d), 139.5 (s), 146.6 (s), 149.6 (s), 160.2 (s), 160.5 (s), 161.7 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 522.2023; found: 522.2043, difference = 3.83 ppm.

1-(4-Methoxybenzyl)-4,5-di(3-nitrophenyl)-2-(2-tolyl)-1*H*-imidazole (39)

Prepared according to general procedure C starting from compound **18** (30 mg, 0.07 mmol) and 3-nitrophenylboronic acid (35 mg, 0.21 mmol, 3 equiv) in toluene–MeOH (5:1, 0.3 mL) for 5 h. Purification via preparative TLC (LP–EtOAc, 3:1); yield: 33 mg (92%, 0.06 mmol); beige oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.27 (s, 3 H), 3.62 (s, 3 H), 4.89 (s, 2 H), 6.51 (d, ^3J = 8.5 Hz, 2 H), 6.66 (d, ^3J = 8.5 Hz, 2 H), 7.26–7.57 (m, 5 H), 7.65–7.85 (m, 3 H), 7.97–8.05 (m, 1 H), 8.16 (s, 1 H), 8.27–8.37 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.5 (q), 47.4 (t), 55.0 (q), 113.8 (d), 120.2 (d), 121.0 (d), 123.9 (d), 125.4 (d), 125.8 (d), 127.6 (d), 127.8 (s), 128.2 (s), 129.6 (d), 129.8 (s), 130.0 (d), 130.3 (d), 130.5 (d), 130.8 (d), 131.7 (s), 131.8 (d), 135.0 (s), 135.8 (s), 137.5 (d), 138.0 (s), 148.0 (s), 148.1 (s), 158.4 (s).

2-(2-Furyl)-4,5-di(4-methoxyphenyl)-1-(4-methoxybenzyl)-1*H*-imidazole (40)

Prepared according to general procedure C starting from compound **19** (40 mg, 0.11 mmol) and 4-methoxyphenylboronic acid (88 mg, 0.58 mmol, 6 equiv); 3 equiv added at the beginning, 3 equiv added after 6 h; toluene–MeOH (5:1, 0.3 mL); 7 h. Flash column chromatography (25 g silica gel, LP–EtOAc, 2:1); yield: 24 mg (53%, 0.05 mmol); yellow oil.

^{1}H NMR (200 MHz, CD_3OD): δ = 3.71 (s, 3 H), 3.73 (s, 3 H), 3.80 (s, 3 H), 5.22 (s, 2 H), 6.50–6.60 (m, 1 H), 6.69–6.83 (m, 7 H), 6.92 (d, ^3J = 8.7 Hz, 2 H), 7.11 (d, ^3J = 8.7 Hz, 2 H), 7.34 (d, ^3J = 8.7 Hz, 2 H), 7.58–7.62 (m, 1 H).

^{13}C NMR (50 MHz, CD_3OD): δ = 48.8 (t), 55.6 (q), 55.8 (q), 111.6 (d), 112.6 (d), 114.6 (d), 115.0 (d), 115.4 (d), 123.2 (s), 127.8 (s),

128.4 (d), 129.6 (d), 130.5 (s), 133.5 (d), 133.6 (d), 144.6 (d), 146.0 (s), 160.2 (s), 160.5 (s), 161.7 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 467.1965; found: 467.1977, difference = 2.57 ppm.

Cleavage of the Benzyl Group; General Procedure E

1-Benzyl-2,4,5-triaryl-1*H*-imidazole (1 equiv) was dissolved in DMSO in a 8 mL vial with stir bar and a screw cap with septum. A 1 M *t*-BuOK solution in THF (7 equiv) was added with a syringe. The solution changed the color immediately. O_2 was bubbled through the solution for 10 min. The reaction mixture was stirred at r.t. and the reaction was monitored by TLC. After the completion of the reaction, the solution was poured into sat. aq NH_4Cl and extracted with EtOAc (3 ×). The combined organic layers were washed with H_2O and dried (Na_2SO_4). The solvent was evaporated and the desired product was obtained by flash column chromatography.

2,4,5-Triphenyl-1*H*-imidazole (41)[29]

Prepared according to general procedure E starting from compound **20** (91 mg, 0.24 mmol) using *t*-BuOK (1.6 mL, 1 M solution in THF, 1.6 mmol) in THF (2 mL) for 16 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 6:1); yield: 17 mg (25%, 0.06 mmol); colorless solid; mp 270–272 °C (Lit.[29] mp 269 °C).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.14–7.60 (m, 13 H), 8.01–8.13 (m, 2 H), 12.69 (s, 1 H).

^{13}C NMR (50 MHz DMSO-d_6): δ = 125.2 (d), 126.5 (d), 127.1 (d), 127.8 (d), 128.2 (d), 128.3 (d), 128.5 (d), 128.69 (d), 128.71 (d), 130.3 (s), 131.1 (s), 135.2 (s), 137.1 (s), 145.5 (s).

4,5-Di(4-methoxyphenyl)-2-phenyl-1*H*-imidazole (42)[30]

Prepared according to general procedure E starting from compound **21** (99 mg, 0.22 mmol) using *t*-BuOK (1.5 mL, 1 M solution in THF, 1.5 mmol) in THF (2 mL) for 16 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 3:1); yield: 72 mg (92%, 0.20 mmol); yellow oil.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.77 (s, 6 H), 6.95 (d, ^3J = 8.4 Hz, 4 H), 7.33–7.53 (m, 7 H), 8.08 (d, ^3J = 7.6 Hz, 2 H), 12.53 (s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 55.1 (q), 113.9 (d), 125.1 (d), 128.0 (d), 128.7 (d), 128.9 (d), 130.6 (s), 144.8 (s), 158.4 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 357.1598, found: 357.1592, difference = –1.68 ppm.

2-(4-Nitrophenyl)-4,5-diphenyl-1*H*-imidazole (43)[31]

Prepared according to general procedure E starting from compound **27** (109 mg, 0.25 mmol) using *t*-BuOK (1.7 mL, 1 M solution in THF, 1.7 mmol) in THF (3 mL) for 16 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 4:1); yield: 26 mg (30%, 0.08 mmol); yellow solid; mp 233–236 °C (Lit.[31] mp 235–237 °C).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.21–7.63 (m, 10 H), 8.34 (s, 4 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 124.3 (d), 125.8 (d), 126.9 (d), 127.2 (d), 128.3 (d), 128.6 (d), 128.8 (d), 130.1 (s), 130.5 (s), 134.6 (s), 136.1 (s), 138.5 (s), 143.4 (s), 146.6 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 342.1237; found: 342.1227, difference = –2.92 ppm.

Cleavage of the SEM Group; General Procedure F

The corresponding 1-SEM-2,4,5-triaryl-1*H*-imidazole was dissolved in 1 M Bu_4NF (5 equiv) in THF in a 4 mL vial with stirring bar and a screw cap. The reaction was heated to reflux and monitored by TLC. After workup and purification by preparative TLC, the pure product was obtained.

2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazole (44)[32]

Prepared according to general procedure F starting from compound **32** (140 mg, 0.31 mmol). TBAF: (2.0 mL, 1 M solution in THF, 2.0 mmol); 7 equiv added at the beginning, 1.5 equiv added after 6 h. The overall reaction time was 24 h. Flash column chromatography (50 g silica gel, LP–EtOAc, 3:1); yield: 94 mg (94%, 0.29 mmol); colorless solid; mp 229–230 °C (Lit.[32] mp 226–227 °C).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.81 (s, 3 H), 7.05 (d, ^3J = 8.7 Hz, 2 H), 7.14–7.63 (m, 10 H), 8.04 (d, ^3J = 8.7 Hz, 2 H), 12.53 (s, 1 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 55.2 (q), 114.1 (d), 123.1 (s), 126.4 (d), 126.7 (d), 127.1 (d), 127.6 (d), 127.7 (s), 128.1 (d), 128.4 (d), 128.6 (d), 131.2 (s), 135.3 (s), 136.8 (s), 145.7 (s), 159.4 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 327.1492; found: 327.1482, difference = –3.06 ppm.

4,5-Di(4-methoxyphenyl)-2-(4-nitrophenyl)-1*H*-imidazole (45)[33]

Prepared according to general procedure F starting from compound **35** (33 mg, 0.06 mmol). TBAF: (0.31 mL, 1 M solution in THF, 0.31 mmol), 6 h reaction time. Flash column chromatography (50 g silica gel, LP–EtOAc, 3:1); yield: 22 mg (90%, 0.06 mmol); orange solid; mp 119–121 °C (Lit.[33] mp 217–219 °C).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.75 (s, 3 H), 3.81 (s, 3 H), 6.90 (d, ^3J = 8.5 Hz, 2 H), 7.03 (d, ^3J = 8.4 Hz, 2 H), 7.35–7.57 (m, 4 H), 8.21–8.40 (m, 4 H), 12.97 (s, 1 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 55.1 (q), 55.2 (q), 113.7 (d), 114.2 (d), 122.9 (s), 124.3 (d), 125.5 (d), 127.3 (s), 128.3 (d), 129.2 (s), 129.8 (d), 136.3 (s), 137.9 (s), 142.7 (s), 146.3 (s), 158.2 (s), 159.2 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 532.2302; found: 532.2298, difference = –3.06 ppm.

1-Benzyl-2-(5-bromofuran-2-yl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole (46)

Substrate **30** (110 mg, 0.25 mmol, 1 equiv) was dissolved in DMF (6 mL) in a 8 mL vial with a magnetic stirring bar and a screw cap. The solution was cooled to 0 °C. *N*-Bromosuccinimide (49 mg, 0.28 mmol, 1.1 equiv) was added in portions and the reaction was warmed to r.t. The reaction mixture was stirred for 4 h at r.t. The mixture was poured into sat. aq NH_4Cl (10 mL) and was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with H_2O (5 mL) and dried (Na_2SO_4). The solvent was evaporated and the pure product was obtained by flash column chromatography (130 g silica gel, LP–EtOAc, 3:1); yield: 95 mg (73%, 0.18 mmol); yellow solid; mp 95–99 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.70 (s, 3 H), 3.77 (s, 3 H), 5.18 (s, 2 H), 6.60–7.05 (m, 8 H), 7.13–7.48 (m, 7 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 47.4 (t), 55.9 (q), 56.1 (q), 112.8 (d), 114.5 (d), 115.5 (d), 122.6 (s), 122.9 (s), 126.5 (d), 127.6 (s), 128.2 (d), 128.3 (d), 129.6 (d), 130.3 (s), 133.2 (d), 137.8 (s), 138.1 (s), 147.7 (s), 158.9 (s), 160.6 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 515.0965; found: 515.0974, difference = 1.75 ppm.

2-(5-Bromofuran-2-yl)-4,5-di(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole (47)

Substrate **37** (288 mg, 0.61 mmol, 1 equiv) was dissolved in DMF (15 mL) in a 25 mL flask with a thermometer, a condenser, and a magnetic stirring bar. The solution was cooled to 0 °C. *N*-Bromosuccinimide (118 mg, 0.67 mmol, 1.1 equiv) was added in portions and the reaction was warmed to r.t. and stirred for 24 h. The mixture was poured into sat. aq NH_4Cl (30 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with H_2O (15 mL) and dried (Na_2SO_4). The solvent was evaporated and the product was obtained by flash column chromatography (150 g silica gel, LP–EtOAc, 5:1); yield: 254 mg (75%, 0.46 mmol); orange oil.

^{1}H NMR (200 MHz, CD_3OD): δ = –0.06 (s, 9 H), 0.81 (t, ^3J = 8.2 Hz, 2 H), 3.38 (t, ^3J = 8.2 Hz, 2 H), 3.74 (s, 3 H), 3.85 (s, 3 H), 5.29

(s, 2 H), 6.63 (d, ^3J = 3.6 Hz, 1 H), 6.78 (d, ^3J = 8.8 Hz, 2 H), 6.97–7.11 (m, 3 H), 7.22–7.39 (m, 4 H).

^{13}C NMR (50 MHz, CD_3OD): δ = –1.4 (q), 18.6 (t), 55.6 (q), 55.8 (q), 67.2 (t), 74.1 (t), 114.57 (d), 114.61 (d), 114.8 (d), 115.5 (d), 122.7 (s), 124.4 (s), 127.3 (s), 129.8 (d), 131.1 (s), 133.8 (d), 139.2 (s), 139.5 (s), 147.7 (s), 160.3 (s), 161.8 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 555.1309; found: 555.1355, difference = 8.29 ppm.

1-Benzyl-2-[5-(3-chlorophenyl)furan-2-yl]-4,5-di(4-methoxyphenyl)-1*H*-imidazole (48)

Substrate **46** (60 mg, 0.12 mmol, 1 equiv), 3-chlorphenylboronic acid (20 mg, 0.13 mmol, 1.1 equiv), Cs_2CO_3 (76 mg, 0.23 mmol, 2 equiv), $Pd(PPh_3)_4$ (6.7 mg, 5 mol%), and anhyd toluene (1.5 mL) were placed in a 4 ml vial with a magnetic stirring bar and a screw cap with septum. The solution was purged with argon for 5 min. Then, the septum screw cap was exchanged for a closed cap under argon flow. The mixture was heated to 120 °C and the reaction was monitored by TLC (LP–EtOAc, 3:1) and stopped after 4 h when the reaction control showed complete consumption of the starting material. The reaction mixture was cooled to r.t., filtered through a pad of Celite, and the solvent was evaporated. The residue was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with H_2O (5 mL) and dried (Na_2SO_4). The solvent was evaporated and the desired product was obtained by flash column chromatography (50 g silica gel, LP–EtOAc, 3:1); yield: 44 mg (69%, 0.08 mmol); yellow solid, mp 67–69 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.70 (s, 3 H), 3.77 (s, 3 H), 5.33 (s, 2 H), 6.76–7.05 (m, 8 H), 7.13–7.53 (m, 11 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 47.8 (t), 55.0 (q), 55.2 (q), 109.2 (d), 111.8 (d), 113.6 (d), 114.6 (d), 121.7 (s), 122.0 (d), 122.8 (d), 125.2 (d), 126.8 (s), 127.1 (d), 127.4 (d), 128.7 (d), 129.4 (s), 130.7 (d), 131.5 (s), 132.2 (d), 133.8 (s), 137.4 (s), 137.6 (s), 137.9 (s), 145.4 (s), 151.4 (s), 158.0 (s), 159.7 (s).

HRMS: *m*/*z* $[M + H]^+$: 547.1783; found: 547.1809, difference = 4.75 ppm.

2-[5-(3-Chlorophenyl)furan-2-yl]-4,5-di(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazole (49)

Substrate **47** (170 mg, 0.31 mmol, 1 equiv), 3-chlorphenylboronic acid (53 mg, 0.34 mmol, 1.1 equiv), Cs_2CO_3 (200 mg, 0.61 mmol, 2 equiv), $Pd(PPh_3)_4$ (17.7 mg, 5 mol%), and anhyd toluene (4 mL) were placed in a 8 ml vial with a magnetic stirring bar and a screw cap with septum. The solution was purged with argon for 5 min. Then, the septum screw cap was exchanged for a closed cap under argon flow. The reaction mixture was heated to 120 °C for 4 h, subsequently cooled to r.t., filtered through a pad of Celite, and the solvent was evaporated. The residue was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O (15 mL) and dried (Na_2SO_4). The solvent was evaporated and the product was obtained by flash column chromatography (50 g silica gel, LP–EtOAc, 5:1); yield: 67 mg (37%, 0.11 mmol); orange oil.

^{1}H NMR (200 MHz, CD_3OD): δ = –0.11 (s, 9 H), 0.78 (t, ^3J = 8.0 Hz, 2 H), 3.35 (t, ^3J = 8.0 Hz, 2 H), 3.74 (s, 3 H), 3.83 (s, 3 H), 5.32 (s, 2 H), 6.78 (d, ^3J = 9.0 Hz, 1 H), 6.94–7.05 (m, 3 H), 7.10 (d, ^3J = 3.5 Hz, 1 H), 7.21–7.43 (m, 7 H), 7.72 (d, ^3J = 7.5 Hz, 1 H), 7.87 (s, 1 H).

^{13}C NMR (50 MHz, CD_3OD): δ = –1.4 (q), 18.7 (t), 55.6 (q), 55.8 (q), 67.2 (t), 74.2 (t), 109.4 (d), 114.1 (d), 114.6 (d), 115.5 (d), 122.7 (s), 123.4 (d), 124.9 (d), 127.5 (s), 128.8 (d), 129.8 (d), 131.0 (s), 131.5 (d), 133.3 (s), 133.9 (d), 136.0 (s), 139.3 (s), 140.2 (s), 145.7 (s), 154.4 (s), 160.3 (s), 161.7 (s).

HRMS: *m*/*z* calcd for $[M + H]^+$: 587.2127; found: 587.2178; difference = 8.69 ppm.

2-[5-(3-Chlorophenyl)furan-2-yl]-4,5-di(4-methoxyphenyl)-1*H*-imidazole (Neurodazine, 50)[6]

Substrate **49** (62 mg, 0.11 mmol, 1 equiv) was dissolved in 1 M Bu_4NF in THF (0.53 mL, 0.53 mmol, 5 equiv) in a 4 mL vial with stir bar and a screw cap with septum. The mixture was heated to 80 °C and the reaction progress was monitored by TLC (LP–EtOAc, 3:1). After completion of the reaction (4 h), the mixture was poured into H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O (15 mL) and dried (Na_2SO_4). The solvent was evaporated and the product was obtained by flash column chromatography (50 g silica gel, LP–EtOAc, 3:1); yield: 36 mg (74%, 0.08 mmol); yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.75 (s, 3 H), 3.81 (s, 3 H), 6.88 (d, ^3J = 8.9 Hz, 2 H), 7.00–7.07 (m, 3 H), 7.25 (d, ^3J = 3.7 Hz, 1 H), 7.35–7.52 (m, 6 H), 7.85 (d, ^3J = 8.2 Hz, 1 H), 7.98–8.01 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.5 (q), 55.7 (q), 109.4 (d), 109.9 (d), 114.1 (d), 114.6 (d), 122.7 (d), 123.5 (d), 123.6 (s), 127.3 (s), 127.7 (d), 127.9 (s), 128.6 (d), 130.4 (d), 131.2 (d), 132.6 (s), 134.3 (s), 137.2 (s), 137.9 (s), 146.4 (s), 151.3 (s), 158.5 (s), 159.4 (s).

Acknowledgment

The authors would like to thank Vienna University of Technology for supporting this work via the innovative project grant BACARA.

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