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Triorganoindium Reagents in Selective Palladium-Catalyzed Cross-Coupling with Iodoimidazoles: Synthesis of Neurodazine

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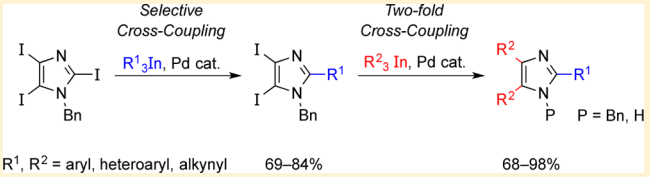
Supporting Information

ABSTRACT: Triorganoindium reagents (R_3In, R = aryl, heteroaryl, alkynyl) react selectively under palladium catalysis with *N*-benzyl-2,4,5-triiodoimidazole to afford the C-2 monocoupling products. The reaction proceeds efficiently for a variety of aryl- and heteroarylindium reagents with the transfer of all three organic groups attached to the metal. The coupling products can be used in a subsequent two-fold cross-coupling to give trisubstituted imidazoles in good yields. This approach was employed to synthesize neurodazine and analogues in good yields.



INTRODUCTION

Imidazole is an important structural motif in natural and synthetic organic compounds that are useful in pharmaceutical and industrial applications.[1] This unit is present in conjugated molecules and polymers for organic electronics such as sensors, lasers, and other semiconductor devices,[2] as ligands in metalloenzymes,[3] in coordination complexes,[4] and in environmentally friendly ionic solvents.[1c,5] Substituted imidazoles are also present in a number of highly significant biomolecules with interesting biological activities.[1d,6] Among them, 4,5-diarylimidazoles such as **1** (Figure 1) have been identified as a class of compounds that show antimicrobial activity against bacteria, yeast, and fungi.[7] Furthermore, triarylimidazole **2** is a potent nontoxic modulator of P-glycoprotein-mediated multidrug resistance (MDR),[8] and synthetic imidazole analogues such as fenflumizole (**3**) have shown anti-inflammatory activity.[9]

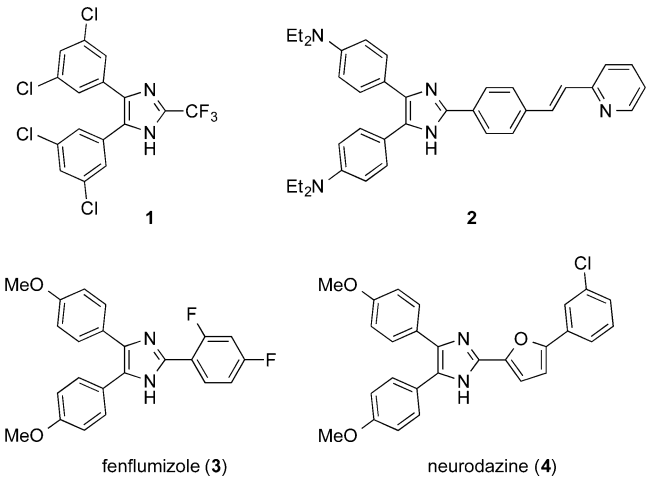


Figure 1. Biologically active imidazole compounds.

Another interesting example of the synthetic potential pharmacophore imidazole, which has attracted significant attention as a consequence of its potent biological activity, is neurodazine (**4**). This compound is able to specifically induce neurogenesis of nonpluripotent myoblasts and the cells derived from mature human skeletal muscle.[10] In fact, compounds such as neurodazine have been proposed as a more convenient and attractive approach to stem cell therapies in neurodegenerative diseases.

The synthesis of substituted imidazoles has been carried out by two main approaches: (a) a traditional linear synthetic sequence based on the formation of the imidazole ring in the final steps of the synthesis, which often provides limited access to target compounds in terms of substituents and substitution patterns,[1a−c,11] and (b) functionalization of imidazoles by successive metalation and reaction with electrophiles[12] or by transition metal-catalyzed cross-coupling reactions, a limited methodology due to the π-excessive character of the heterocycle. Nevertheless, the reactivity can be modulated by using the appropriate catalyst, imidazole halide, and/or highly reactive nucleophiles.[13,14]

In recent years we have shown that indium organometallics are useful reagents in metal-catalyzed cross-coupling reactions.[15,16] Besides their high efficiency, versatility, and selectivity in cross-coupling reactions, triorganoindium reagents (R_3In) are particularly effective for the synthesis of functionalized heterocyclic compounds,[17] and they exhibit high selectivity in coupling reactions with 3,4-dihalomaleimides, 2,5-dibromothiophenes, and 4,6-dichloropyrimidines.[18] As a continuation of our studies into the application of R_3In in organic synthesis, we report herein an efficient approach to trisubstituted imidazoles by selective and sequential palladium-

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catalyzed cross-coupling reactions of triorganoindium reagents with 2,4,5-trihaloimidazoles and the application of this approach to the synthesis of neurodazine and analogues.

RESULTS AND DISCUSSION

The relatively low reactivity of imidazole derivatives in coupling reactions and the high selectivity shown by indium organometallics led us to explore selective coupling processes. It was envisaged that 2,4,5-trisubstituted imidazoles could be synthesized by an initial C-2-selective palladium-catalyzed cross-coupling reaction between a 2,4,5-trihaloimidazole and a triorganoindium reagent, followed by a two-fold coupling reaction with other different R_3In species to provide the desired 2,4,5-trisubstituted imidazoles (Scheme 1).

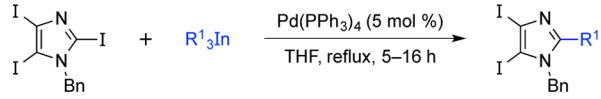
Scheme 1. Synthetic Route to 2,4,5-Trisubstituted Imidazoles

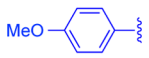
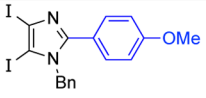
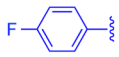
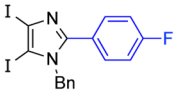
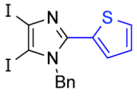
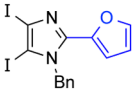
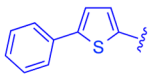
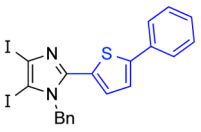
As stated above, the introduction of good leaving groups is a common approach to increase the reactivity of electron-rich heterocycles in coupling reactions.[13,14] Accordingly, for this study we selected *N*-benzyl-2,4,5-triiodoimidazole (**5**), which is readily prepared from imidazole.[19] We began by exploring the reactions of **5** with tri(4-methoxyphenyl)indium using different palladium sources and ligands such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, Pd_2dba_3, and $Pd(OAc)_2$ in the presence of SPhos or XPhos as ligands. The best results in terms of conversion and selectivity were obtained on using $Pd(PPh_3)_4$ (5 mol %) as catalyst and 50 mol % of the indium reagent (corresponding to 1.5 equiv of R^1) in THF under reflux to afford the monocoupling product *N*-benzyl-2-(4-methoxyphenyl)-4,5-diiodoimidazole (**6a**) in 78% yield (Table 1, entry 1) as the only regioisomer detected by ^1H NMR. Although the efficiency of the indium reagents in transferring the three groups attached to the metal in coupling reactions has been widely established, the use of lower amounts of indium reagents afforded lower yields of **6a**.

The methodology was extended to the synthesis of new biologically active compounds by studying the introduction of other functional groups. In this way, the reaction of **5** with tri(4-fluorophenyl)indium under the same conditions gave the fluorinated compound **6b** in 83% yield (entry 2). The monocoupling reaction with triheteroarylindium reagents such as tri(thiophen-2-yl)indium and tri(furan-2-yl)indium also gave the cross-coupling products **6c** and **6d** regioselectively and in high yield (entries 3 and 4). Analogously, the use of a substituted thiophenylindium compound such as tri(phenylthiophen-2-yl)indium with **5** under the standard conditions gave imidazole **6e** in 79% yield (entry 5).

In general, these results show that the palladium-catalyzed coupling reactions of aryl- and heteroarylindium organometallics with trihalogenated imidazole **5** occurred with high efficiency and complete regioselectivity to give the corresponding C-2 monocoupling compounds in good yields. Alternatively, we found that coupling reactions with *N*-benzyltribromoimidazole also occur efficiently in the first selective C-2 coupling; however, coupling at C-4 and C-5 requires higher amounts of the triorganoindium and harsh reaction conditions to give moderate yields.

Table 1. Selective Cross-Coupling Reactions of Triorganoindium Reagents with *N*-Benzyl-2,4,5-triiodoimidazole (5)



Entry	R^1	Product	Yield (%)
1		 **6a**	78
2		 **6b**	83
3		 **6c**	84
4		 **6d**	83
5		 **6e**	79

According to our synthetic route, a two-fold cross-coupling reaction of monocoupled imidazoles (**6**) with R_3In should provide access to the desired analogues in a versatile and efficient manner. As a consequence, we proposed the synthesis of bioactive compound neurodazine.[20] The methods reported to date have involved the construction of the imidazole ring of neurodazine by multistep sequences.[10a]

The synthesis of neurodazine was planned by following a synthetic sequence of three sequential palladium-catalyzed coupling reactions using organoindium reagents. Starting from the commercially available 3-chloroiodobenzene, chemoselective cross-coupling using tri(furan-2-yl)indium (40 mol %) under reflux with $Pd(PPh_3)_4$ as catalyst (5 mol %) afforded the 2-(3-chlorophenyl)furan (**7**) in 86% yield (Scheme 2). Prior to the second coupling, lithiation of **7** with *n*-BuLi at low temperature and subsequent transmetalation with $InCl_3$ gave the corresponding indium reagent in solution (50 mol %). The reaction of this indium reagent with 2,4,5-triiodoimidazole **5** in the presence of $Pd(PPh_3)_4$ (5 mol %) as catalyst afforded **8** in 69% yield and with high regioselectivity.

Finally, the sequence was completed with a two-fold cross-coupling reaction of 4,5-diiodoimidazole **8** with 100 mol % of tri(4-methoxyphenyl)indium. On using the same catalytic system and after 16 h under reflux, trisubstituted imidazole **9** was obtained in 91% yield. The final step in the synthesis involved the removal of the benzyl group.[21] Treatment of **9**

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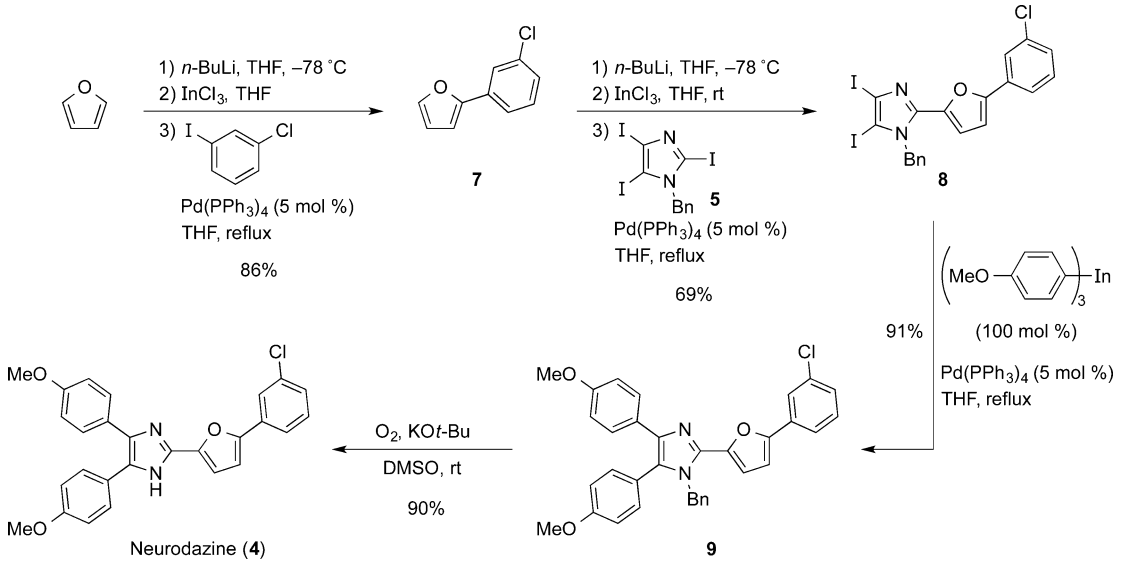
Scheme 2. Synthesis of Neurodazine



with DMSO and KO*t*-Bu in combination with oxygen at room temperature afforded neurodazine (**4**) in 90% yield (Scheme 2). It is remarkable that the synthesis of this biologically active compound has been achieved in 49% overall yield (four steps) by a sequential triple cross-coupling strategy using organoindium reagents.

Having established the efficiency of organoindium reagents in the second coupling for the substitutions at the C-4 and C-5 positions of imidazole, we proceeded to examine the scope and limitations of selected monocoupled products **6** in a new two-fold Pd-catalyzed cross-coupling reaction to obtain 2,4,5-trisusbtituted imidazoles of interest. On employing the previously described conditions, the reaction of tri(4-methoxyphenyl)indium (100 mol %) with **6b** gave **10a** in 87% yield after 12 h (Scheme 3). Interestingly, compound **10a** is structurally related to fenflumizole (**3**, Figure 1), which has been identified as an anti-inflammatory nonselective COX enzyme inhibitor.[9] In a similar manner, the aryl group was also efficiently transferred from the indium reagent as shown in the reaction of tri(4-methoxyphenyl)indium with imidazoles **6d** and **6e** to give the corresponding 4,5-diarylimidazoles **11a** and **12a** in 90% and 80% yield, respectively (Scheme 3). While the C-2 coupling reactions of triorganoindium reagents with **5** occur with complete regioselectivity, selective couplings at C-4 or C-5 in 2-substituted-4,5-diiodoimidazoles (**6a**−**e**) gave mixtures of isomers.

The versatility of this two-fold coupling reaction was also studied using heteroaryl indium organometallics. Thus, the reaction of tri(benzo[*b*]thiophen-2-yl)indium with imidazole **6e**, under standard conditions, afforded imidazole **13a** in 89% yield. Under the same conditions, the high efficiency of R_3In in this coupling was also evidenced by the reaction of tri(benzo[*b*]thiophen-2-yl)indium with the C-2 substituted imidazoles **6b** and **6d**, which provided derivatives **14a** and **15a** in good yields (98% and 87%, respectively).

Additionally, the reaction between tri(5-phenylthiophen-2-yl)indium and imidazole **6a** under the same conditions gave compound **16a** in a satisfactory 68% yield. We also found it of interest to study the two-fold cross-coupling reaction of the triorganoindium reagent derived from **7** (Scheme 2) with the C-2 substituted imidazole **6a**. Under the previously optimized conditions, the coupling product **17a** was obtained in 92% yield (Scheme 3), and this is an attractive derivative of biologically active neurodazine.[10] Overall, these results demonstrate the utility of R_3In in the synthesis of neurodazine and analogues through a two-fold coupling sequence.

Removal of the benzyl group from some *N*-benzyl-2,4,5-trisusbtituted imidazoles **10a**−**17a** was also carried out under the previously described conditions to afford the corresponding imidazoles **10b**, **11b**, **12b**, **16b**, and **17b** in yields ranging from 84% to 96%. Interestingly, **11b** has shown antiproliferative activities against the growth of some cell lines.[22]

Finally, the synthetic utility of our strategy was expanded by the introduction of different substituents in a one-pot procedure via sequential reactions with various R_3In reagents. The reaction of **5** with tri(furan-2-yl)indium (50 mol %) under the standard conditions followed by addition of tri(4-methoxyphenyl)indium (100 mol %) afforded coupling product **11a** in 74% yield (Scheme 4). We also tested our protocol preparing 2-alkynyl-4,5-diarylimidazoles, which are of interest in materials science.[23] In this case, the same sequence was performed with tris(trimethylsilylethynyl)indium (50 mol %) and tri(4-methoxyphenyl)indium (100 mol %), and this proved to be satisfactory in providing the trisubstituted product **18a** in 40% yield.

■ CONCLUSIONS

It has been demonstrated that triorganoindium reagents react selectively with *N*-benzyl-2,4,5-triiodoimidazole under palladium catalysis to afford monocoupling products at C-2 in good yields. All three organic groups attached to the metal are efficiently transferred. The reaction can be performed using triaryl- or triheteroarylindium reagents. The monocoupling products were subsequently used in a two-fold cross-coupling process to afford a series of trisubstituted imidazoles. This methodology was applied to the synthesis of the bioactive compound neurodazine by three sequential palladium-catalyzed cross-coupling reactions using organoindium compounds to give the target compound in good yield. The biological activities of the novel imidazoles are currently being evaluated, and further applications of this method to other targets are now underway.

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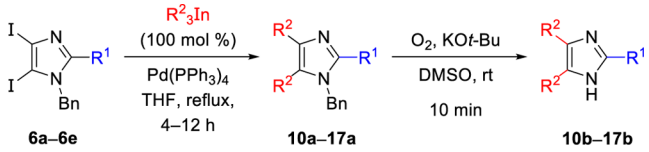
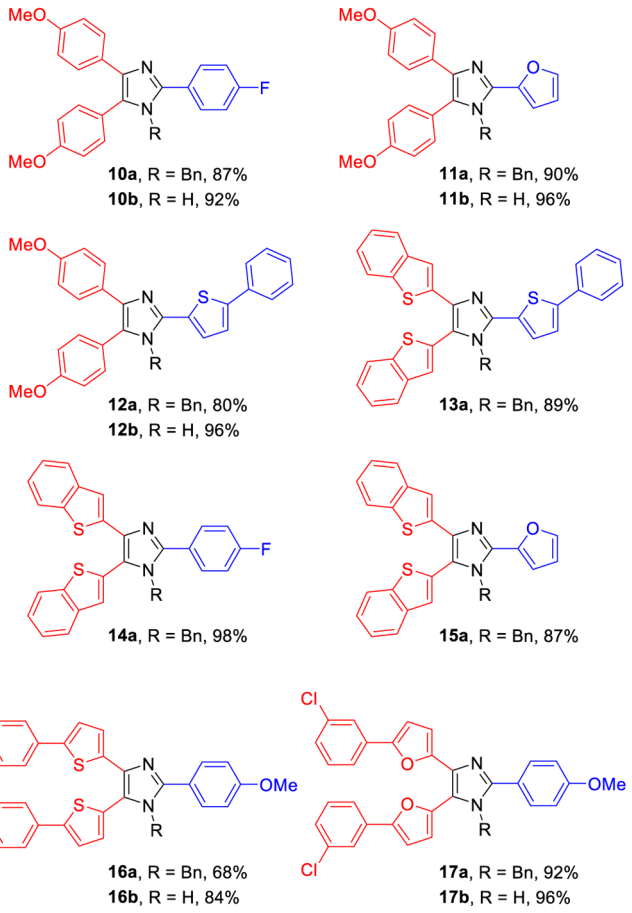
Scheme 3. Synthesis of 2,4,5-Trisubtituted Imidazoles by Two-Fold Cross-Coupling Reactions of *N*-Benzyl-2-substituted-4,5-diiodoimidazoles with Triorganoindium Reagents Followed by Deprotection

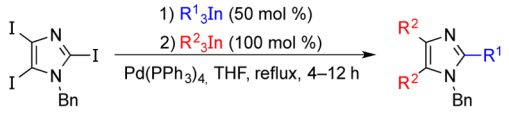




EXPERIMENTAL SECTION

General Methods. All reactions were carried out in flame-dried glassware under an argon atmosphere using standard gas-tight syringes, cannulae, and septa. Tetrahydrofuran (THF) was dried by distillation from the sodium ketyl of benzophenone. Reaction temperatures refer to external bath temperatures. Butyllithium and 4-methoxyphenylmagnesium bromide were titrated prior to use. Furan was lithiated according to a previously reported method.[24] All other commercially available reagents were used as received. Organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated using a rotary evaporator at aspirator pressure. Reactions were monitored by TLC using precoated silica gel plates (Alugram Xtra SIL G/UV_{254}, 0.20 mm thick) with UV light as a visualizing agent and ethanolic phosphomolybdic acid as a developing agent. Flash column chromatography was performed using 230−400 mesh silica gel packed in glass columns. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 at 300 MHz for ^1H and 75 MHz for ^{13}C, at 300 K, and calibrated to the solvent peak. DEPT data were used to assign carbon types. Mass spectra were obtained with EI ionization at 70 eV. Melting points are uncorrected.

Scheme 4. One-Pot Cross-Coupling of 5 with Different R_3In



Preparation of Triorganoindium Reagents. Triorganoindium compounds were prepared according to previously published methods[15−18] by treatment of the corresponding organolithium reagents (3 equiv., ∼0.5 M in dry THF) with a solution of $InCl_3$ (1.1 equiv., ∼0.05 M in dry THF) at −78 or −20 °C and warming to room temperature.

Synthesis of 1-Benzyl-2,4,5-triiodo-1*H*-imidazole (5). To a solution of imidazole (1.80 g, 26.4 mmol) in aqueous NaOH (160 mL, 2 M) was added a solution of I_2 (25.0 g, 98.5 mmol) and KI (35.0 g, 210.8 mmol) in water (75 mL). The mixture was stirred overnight and then neutralized by the addition of HOAc. The resulting precipitate was filtered off and dried in vacuo over P_2O_5 to give 7.1 g of a gray crude solid, which was dissolved in dry THF (25 mL) and slowly added to a mixture of NaH (0.45 g, 18.84 mmol) in dry THF (15 mL) at 0 °C. After 30 min, BnBr (2.24 mL, 18.84 mmol) was added dropwise and the mixture was stirred overnight at rt. Water (30 mL) was added, and the mixture was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine (20 mL), dried, and concentrated. The residue was purified by flash chromatography (20% EtOAc/hexanes), to provide 1-benzyl-2,4,5-triiodoimidazole (**5**) as a white solid (6.80 g, 48%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.37 (m, 3H), 7.08 (d, J = 6.8 Hz, 2H), 5.31 (s, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 134.4 (C), 128.9 (2 × CH), 128.2 (CH), 126.6 (2 × CH), 97.9 (C), 90.5 (C), 85.0 (C), 55.2 (CH_2); IR (ATR) ν_{max} 2922, 1438, 1377, 1348, 1175 cm^{-1}; MS (EI) m/z 537 $[M + H]^+$ (12), 536 $[M]^+$ (100); HRMS (EI-ion trap) calcd for $C_{10}H_7N_2I_3$ $[M]^+$ 535.7743, found 535.7765.

General Procedure for the C-2 Selective Palladium-Catalyzed Cross-Coupling Reactions. A solution of R_3In (0.25 mmol, 0.05 M in dry THF) was added to a solution of **5** (0.5 mmol) and $Pd(PPh_3)_4$ (0.025 mmol) in dry THF (2 mL) in a Schlenk tube filled with argon. The reaction mixture was heated to 80 °C until the starting material had been consumed (5−16 h). The mixture was allowed to cool to rt and quenched by the addition of a few drops of MeOH, and the solvent was removed. The residue was diluted with EtOAc (25 mL), and the organic phase was washed with brine (20 mL), dried, and concentrated. The residue was purified by flash chromatography (EtOAc/hexanes) to afford, after concentration and high-vacuum drying, the corresponding cross-coupling products.

1-Benzyl-2-(4-methoxyphenyl)-4,5-diiodo-1*H*-imidazole (6a). According to the general procedure, the reaction of **5** with tri(4-methoxyphenyl)indium afforded, after purification by column chromatography (50% EtOAc/hexanes), compound **6a** as a pale brown solid (201 mg, 78%): mp 129−131 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.39 (m, 3H), 7.31−7.34 (m, 2H), 6.98−7.01 (m, 2H), 6.84−6.89 (m, 2H), 5.30 (s, 2H), 3.80 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.7 (C), 153.3 (C), 135.9 (C), 130.1 (2 × CH), 129.0 (2 × CH), 127.9 (CH), 126.0 (2 × CH), 122.0 (C), 114.0 (2 × CH), 96.3 (C), 83.9 (C), 55.3 (CH_3), 52.4 (CH_2); IR (ATR) ν_{max} 2931, 1610, 1468, 1254 cm^{-1}; MS (EI) m/z 517 $[M + H]^+$ (17), 516 $[M]^+$ (98), 425 $[M - C_7H_7]^+$ (100); HRMS (EI-ion trap) calcd for $C_{17}H_{14}N_2I_2O$ $[M]^+$ 515.9190, found 515.9180.

1-Benzyl-2-(4-fluorophenyl)-4,5-diiodo-1*H*-imidazole (6b). According to the general procedure, the reaction of **5** with tri(4-fluorophenyl)indium afforded, after purification by column chromatography (30% EtOAc/hexanes), compound **6b** as a pale brown solid (193 mg, 83%): mp 96−98 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.49 (m, 3H), 7.32−7.37 (m, 2H), 7.09−7.05 (m, 2H), 6.97−7.02 (m, 2H), 5.30 (s, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2 (C), 161.9 (C), 152.2 (C), 135.7 (C), 130.7 (CH), 130.6 (CH), 129.1 (2 × CH), 128.0 (CH), 125.9 (2 × CH), 115.9 (CH), 115.6 (CH), 96.5

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(C), 84.8 (C), 52.5 (CH_2); IR (ATR) ν_{max} 3033, 2926, 1468, 1224 cm^{-1}; MS (EI) m/z 505 $[M + H]^+$ (24), 504 $[M]^+$ (87), 413 $[M - C_7H_7]^+$ (12); HRMS (EI-ion trap) calcd for $C_{16}H_{11}N_2I_2F$ $[M]^+$ 503.8990, found 503.8980.

1-Benzyl-2-(thiopen-2-yl)-4,5-diiodo-1*H*-imidazole (6c). According to the general procedure, the reaction of **5** with tri(thiophen-2-yl)indium afforded, after purification by column chromatography (30% EtOAc/hexanes), compound **6c** as a pale brown oil (170 mg, 84%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−7.40 (m, 4H), 6.96−7.11 (m, 4H), 5.45 (s, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 135.3 (2 × C), 131.0 (C), 129.1 (2 × CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 127.1 (CH), 125.9 (2 × CH), 125.9 (2 × CH), 96.7 (C), 85.1 (C), 52.7 (CH_2); IR (ATR) ν_{max} 2924, 1443, 1156 cm^{-1}; MS (EI) m/z 493 $[M + H]^+$ (10), 492 $[M]^+$ (65), 401 $[M - C_7H_7]^+$ (18); HRMS (EI-ion trap) calcd for $C_{14}H_{10}N_2I_2S$ $[M]^+$ 491.8654, found 491.8647.

1-Benzyl-2-(furan-2-yl)-4,5-diiodo-1*H*-imidazole (6d). According to the general procedure, the reaction of **5** with tri(furan-2-yl) indium afforded, after purification by column chromatography (40% EtOAc/hexanes), compound **6d** as a white solid (197 mg, 83%): mp 154−156 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.27−7.34 (m, 3H), 7.04 (d, J = 7.4 Hz, 2H), 6.78 (d, J = 2.7 Hz, 1H), 6.44−6.47 (m, 1H), 5.54 (s, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 144.0 (C), 143.3 (CH), 135.5 (2 × C), 128.9 (2 × CH), 127.9 (CH), 126.3 (2 × CH), 111.6 (CH), 110.9 (CH), 96.9 (C), 85.0 (C), 52.9 (CH_2); IR (ATR) ν_{max} 3030, 2362, 1446, 1387, 1224 cm^{-1}; MS (EI) m/z 477 $[M + H]^+$ (27), 476 $[M]^+$ (100), 385 $[M - C_7H_7]^+$ (25); HRMS (EI-ion trap) calcd for $C_{14}H_{10}N_2I_2O$ $[M]^+$ 475.8882, found 475.8863.

1-Benzyl-2-(5-phenylthiophen-2-yl)-4,5-diiodo-1*H*-imidazole (6e). According to the general procedure, the reaction of **5** with tri(5-phenylthiophen-2-yl)indium afforded, after purification by column chromatography (30% EtOAc/hexanes), compound **6e** as a yellow solid (224 mg, 79%): mp 126−128 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 7.1 Hz, 2H), 7.35−7.41 (m, 4H), 7.29−7.32 (m, 2H), 7.16 (d, J = 3.9 Hz, 1H), 7.06 (d, J = 7.0 Hz, 2H), 7.00 (d, J = 3.9 Hz, 1H), 5.49 (s, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 147.0 (C), 146.6 (C), 135.3 (C), 133.5 (C), 130.1 (C), 129.2 (2 × CH), 129.0 (2 × CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 126.0 (2 × CH), 125.9 (2 × CH), 123.4 (CH), 96.8 (C), 85.2 (C), 52.8 (CH_2); IR (ATR) ν_{max} 3063, 2925, 1496, 1478, 1207 cm^{-1}; MS (EI) m/z 569 $[M + H]^+$ (6), 568 $[M]^+$ (20), 477 $[M - C_7H_7]^+$ (42); HRMS (EI-ion trap) calcd for $C_{20}H_{14}N_2I_2S$ 567.8962, found 567.8954.

2-(3-Chlorophenyl)furan (7).[25] A solution of tri(2-furyl)indium (6.7 mL, 1.01 mmol, 0.15 M in dry THF) was added to a solution of 3-chloroiodobenzene (600 mg, 2.52 mmol) and $Pd(PPh_3)_2Cl_2$ (88 mg, 0.13 mmol) in dry THF (2 mL) in a Schlenk tube filled with argon. The reaction mixture was heated to 80 °C for 20 h. The mixture was allowed to cool to rt and quenched by the addition of a few drops of MeOH, and the solvent was removed. The residue was diluted with EtOAc (40 mL), and the organic phase was washed with brine (30 mL), dried, and concentrated. The residue was purified by flash chromatography (10% EtOAc/hexanes) to afford, after concentration and high-vacuum drying, compound **7** as a yellowish oil (387 mg, 86%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (t, J = 1.7 Hz, 1H), 7.56 (dt, J = 6.3, 1.4 Hz, 1H), 7.49 (d, J = 1.7 Hz, 1H), 7.34−7.21 (m, 2H), 6.68 (d, J = 3.4 Hz, 1H), 6.48 (dd, J = 3.4, 1.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 152.5 (C), 142.6 (CH), 134.7 (C), 132.5 (C), 129.9 (CH), 127.2 (CH), 123.8 (CH), 121.8 (CH), 111.8 (CH), 106.1 (CH); IR (ATR) ν_{max} 2925, 1727, 1603, 1582, 1563, 1499, 1471 cm^{-1}.

1-Benzyl-2-(5-(3-chlorophenyl)furan-2-yl)-4,5-diiodo-1*H*-imidazole (8). According to the general procedure, the reaction of **5** with tri(2-(3-chlorophenyl)furan-2-yl)indium afforded, after purification by column chromatography (30% EtOAc/hexanes), compound **8** as a dark yellow solid (202 mg, 69%): mp 135−137 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.41 (m, 4H), 7.20−7.24 (m, 3H), 7.09 (d, J = 6.8 Hz, 2H), 6.96 (d, J = 3.6 Hz, 1H), 6.73 (d, J = 3.6 Hz, 1H), 5.62 (s, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 153.2 (C), 143.9 (C), 143.8 (C), 135.6 (C), 134.8 (C), 131.4 (C), 130.0 (CH), 129.1 (2 × CH), 127.9 (2 × CH), 125.8 (2 × CH), 123.8 (CH), 122.0 (CH), 113.0 (CH), 108.0 (CH), 97.1 (C), 85.6 (C), 53.2 (CH_2); IR (ATR) ν_{max} 2921, 1412, 1304, 1257 cm^{-1}; MS (EI) m/z 587 $[M + H]^+$ (23), 586 $[M]^+$ (100), 495 $[M - C_7H_7]^+$ (100); HRMS (EI-ion trap) calcd for $C_{20}H_{13}N_2OI_2Cl$ $[M]^+$ 585.8806, found 585.8816.

General Procedure for the Multiple Palladium-Catalyzed Cross-Coupling Reactions. A solution of R_3In (0.5 mmol, 0.05 M in dry THF) was added to a solution of protected 2-substituted 4,5-diiodo-1*H*-imidazole (0.5 mmol) and $Pd(PPh_3)_4$ (0.025 mmol) in dry THF (2 mL) in a Schlenk tube filled with argon. The reaction mixture was heated to 80 °C until the starting material had been consumed (4−12 h). The mixture was allowed to cool to rt and quenched by the addition of a few drops of MeOH, and the solvent was removed. The residue was diluted with EtOAc (25 mL), and the organic phase was washed with brine (20 mL), dried, and concentrated. The residue was purified by flash chromatography (EtOAc/hexanes) to afford, after concentration and high-vacuum drying, the corresponding cross-coupling products.

1-Benzyl-2-(5-(3-chlorophenyl)furan-2-yl)-4,5-bis(4-methoxyphenyl)-1*H*-imidazole (9).[20] According to the general procedure, the reaction of **8** with tri(4-methoxyphenyl)indium afforded, after purification by column chromatography (50% EtOAc/hexanes), compound **9** as a yellow solid (249 mg, 91%): mp 68−70 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (dt, J = 8.9, 2.5 Hz, 2H), 7.27−7.35 (m, 4H), 7.22−7.25 (m, 2H), 7.13−7.20 (m, 3H), 6.99−7.05 (m, 3H), 6.87 (dt, J = 8.8, 2.5 Hz, 2H), 6.79 (dt, J = 8.9, 2.5 Hz, 2H), 6.73 (d, J = 3.6 Hz, 1H), 5.32 (s, 2H), 3.83 (s, 3H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.9 (C), 158.4 (C), 152.4 (C), 145.7 (C), 138.6 (C), 138.5 (C), 137.9 (C), 134.7 (C), 132.3 (2 × CH), 131.8 (C), 129.9 (CH), 129.5 (C), 128.8 (2 × CH), 128.1 (2 × CH), 127.4 (CH), 127.3 (CH), 127.1 (C), 125.6 (2 × CH), 123.6 (CH), 122.4 (C), 121.8 (CH), 114.4 (2 × CH), 113.6 (2 × CH), 112.1 (CH), 108.0 (CH), 55.2 (2 × CH_3), 48.5 (CH_2); IR (ATR) ν_{max} 2933, 1519, 1494, 1249 cm^{-1}; MS (EI) m/z 547 $[M + H]^+$ (6), 546 $[M]^+$ (19), 455 $[M - C_7H_7]^+$ (49); HRMS (EI-ion trap) calcd for $C_{34}H_{27}N_2O_3Cl$ $[M]^+$ 546.1705, found 546.1702.

1-Benzyl-2-(4-fluorophenyl)-4,5-bis(4-methoxyphenyl)-1*H*-imidazole (10a). According to the general procedure, the reaction of **6b** with tri(4-methoxyphenyl)indium afforded, after purification by column chromatography (30% EtOAc/hexanes), compound **10a** as a pale yellow solid (202 mg, 87%): mp 53−56 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58−7.62 (m, 2H), 7.52 (dt, J = 8.9, 2.4 Hz, 2H), 7.20−7.23 (m, 3H), 7.13 (dt, J = 8.7, 2.4 Hz, 2H), 7.03−7.09 (m, 2H), 6.82−6.86 (m, 4H), 6.78 (dt, J = 8.9, 2.5 Hz, 2H), 5.05 (s, 2H), 3.81 (s, 3H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 164.7 (C), 161.4 (C), 159.8 (C), 158.3 (C), 146.6 (C), 137.9 (C), 137.6 (C), 132.4 (2 × CH), 130.9 (CH), 130.8 (CH), 128.9 (C), 128.7 (2 × CH), 127.9 (2 × CH), 127.4 (CH), 127.3 (C), 125.9 (2 × CH), 123.1 (C), 115.7 (CH), 115.4 (CH), 114.3 (2 × CH), 113.6 (2 × CH), 55.2 (2 × CH_3), 48.1 (CH_2); IR (ATR) ν_{max} 2933, 1518, 1494, 1247 cm^{-1}; MS (EI) m/z 465 $[M + H]^+$ (59), 464 $[M]^+$ (93), 373 $[M - C_7H_7]^+$ (100); HRMS (EI-ion trap) calcd for $C_{30}H_{25}N_2O_2F$ $[M]^+$ 464.1895, found 464.1881.

1-Benzyl-2-(furan-2-yl)-4,5-(4-methoxyphenyl)-1*H*-imidazole (11a).[20] According to the general procedure, the reaction of **6d** with tri(4-methoxyphenyl)indium afforded, after purification by column chromatography (50% EtOAc/hexanes), compound **11a** as a yellow solid (196 mg, 90%): mp 66−68 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (dt, J = 8.9, 2.5 Hz, 2H), 7.45 (d, J = 1.2 Hz, 1H), 7.21−7.26 (m, 3H), 7.11 (dt, J = 8.8, 2.4 Hz, 2H), 6.93 (m, 2H), 6.86 (dt, J = 8.8, 2.4 Hz, 2H), 6.76 (dt, J = 8.9, 2.5 Hz, 2H), 6.71 (d, J = 3.4 Hz, 1H), 6.43 (dd, J = 1.8, 3.4 Hz, 1H), 5.23 (s, 2H), 3.82 (s, 3H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.9 (C), 158.3 (C), 145.5 (C), 142.7 (CH), 138.9 (C), 138.3 (C), 137.6 (C), 132.4 (2 × CH), 129.1 (C), 128.6 (2 × CH), 128.0 (2 × CH), 127.2 (CH), 127.3 (C), 126.0 (2 × CH), 122.6 (C), 114.3 (2 × CH), 113.5 (2 × CH), 111.4 (CH), 109.7 (CH), 55.2 (2 × CH_3), 48.2 (CH_2); IR (ATR) ν_{max} 2933, 1517, 1493, 1245 cm^{-1}; MS (EI) m/z 437 $[M + H]^+$ (54), 436 $[M]^+$ (100), 345 $[M - C_7H_7]^+$ (100); HRMS (IE) calcd for $C_{28}H_{24}N_2O_3$ $[M]^+$ 436.1781, found 436.1778.

1-Benzyl-2-(5-phenylthiophen-2-yl)-4,5-bis(4-methoxyphenyl)-1*H*-imidazole (12a). According to the general procedure,

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the reaction of **6e** with tri(4-methoxyphenyl)indium afforded, after purification by column chromatography (30% EtOAc/hexanes), compound **12a** as a pale yellow solid (211 mg, 80%): mp 206−208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 7.2 Hz, 2H), 7.52 (dt, J = 8.8, 2.5 Hz, 2H), 7.37−7.40 (m, 2H), 7.30 (dd, J = 7.4 Hz, 4H), 7.10−7.17 (m, 3H), 6.99−7.04 (m, 3H), 6.85 (dt, J = 8.8, 2.3 Hz, 2H), 6.78 (dt, J = 8.8, 2.5 Hz, 2H), 5.21 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.9 (C), 158.3 (C), 145.2 (C), 141.6 (C), 138.2 (C), 137.4 (2 × C), 134.0 (C), 132.3 (2 × CH), 129.6 (C), 129.0 (2 × CH), 128.9 (2 × CH), 128.0 (2 × CH), 127.7 (CH), 127.5 (CH), 127.2 (C), 126.3 (CH), 125.8 (2 × CH), 125.7 (2 × CH), 123.4 (CH), 122.7 (C), 114.3 (2 × CH), 113.6 (2 × CH), 55.2 (2 × CH_3), 48.2 (CH_2); IR (ATR) ν_{max} 2932, 1518, 1493, 1249 cm^{-1}; MS (EI) m/z 529 [M + H]$^+$ (32), 528 [M]$^+$ (71), 437 [M − C_7H_7]$^+$ (100); HRMS (EI-ion trap) calcd for $C_{34}H_{28}N_2O_2S$ [M]$^+$ 528.1866, found 528.1857.

1-Benzyl-2-(5-phenylthiophen-2-yl)-4,5-bis(benzo[*b*]-thiophen-2-yl)-1*H*-imidazole (13a). According to the general procedure, the reaction of **6e** with tri(benzo[*b*]thiophen-2-yl)indium afforded, after purification by column chromatography (20% EtOAc/hexanes), compound **13a** as a lemon-yellow solid (261 mg, 89%): mp 225−227 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.87 (m, 1H), 7.76−7.80 (m, 1H), 7.70−7.73 (m, 1H), 7.62 (d, J = 7.6 Hz, 4H), 7.47 (s, 1H), 7.37−7.43 (m, 4H), 7.23−7.33 (m, 6H), 7.19 (d, J = 3.9 Hz, 1H), 7.11 (d, J = 3.9 Hz, 1H), 7.04 (d, J = 6.3 Hz, 2H), 5.35 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 146.3 (C), 143.5 (C), 141.7 (C), 140.2 (C), 139.6 (C), 139.4 (C), 137.0 (C), 136.8 (C), 136.6 (C), 133.8 (C), 131.0 (C), 129.6 (C), 129.1 (2 × CH), 129.0 (2 × CH), 128.8 (CH), 128.0 (CH), 127.8 (CH), 127.4 (CH), 125.9 (2 × CH), 125.7 (2 × CH), 125.3 (CH), 124.6 (CH), 124.3 (CH), 124.1 (CH), 123.9 (CH), 123.5 (CH), 123.4 (CH), 123.0 (C), 122.4 (CH), 122.1 (CH), 120.3 (CH), 48.7 (CH_2); IR (ATR) ν_{max} 2921, 1594, 1479 cm^{-1}; MS (EI) m/z 581 [M + H]$^+$ (18), 580 [M]$^+$ (48), 489 [M − C_7H_7]$^+$ (100); HRMS (EI-ion trap) calcd for $C_{36}H_{24}N_2S_3$ [M]$^+$ 580.1096, found 580.1090.

1-Benzyl-2-(4-fluorophenyl)-4,5-bis(benzo[*b*]thiophen-2-yl)-1*H*-imidazole (14a). According to the general procedure, the reaction of **6b** with tri(benzo[*b*]thiophen-2-yl)indium afforded, after purification by column chromatography (30% EtOAc/hexanes), compound **14a** as a pale yellow solid (253 mg, 98%): mp 202−205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81−7.88 (m, 1H), 7.76−7.79 (m, 1H), 7.69−7.72 (m, 1H), 7.59−7.64 (m, 3H), 7.36−7.43 (m, 3H), 7.20−7.28 (m, 6H), 7.09 (t, J = 8.6 Hz, 2H), 6.90−6.93 (m, 2H), 5.19 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.0 (C), 161.6 (C), 148.5 (C), 141.7 (C), 140.2 (C), 139.5 (C), 139.5 (C), 137.2 (C), 137.1 (C), 136.4 (C), 131.1 (CH), 131.0 (CH), 129.9 (C), 128.9 (2 × CH), 128.7 (CH), 127.7 (CH), 125.8 (2 × CH), 125.2 (CH), 124.6 (CH), 124.3 (CH), 123.9 (CH), 123.4 (CH), 122.6 (C), 122.4 (CH), 122.1 (CH), 120.0 (CH), 115.9 (CH), 115.6 (CH), 48.6 (CH_2); IR (ATR) ν_{max} 2922, 1454, 1225 cm^{-1}; MS (EI) m/z 517 [M + H]$^+$ (30), 516 [M]$^+$ (90), 425 [M − C_7H_7]$^+$ (100); HRMS (EI-ion trap) calcd for $C_{32}H_{21}N_2S_2F$ [M]$^+$ 516.1125, found 516.1121.

1-Benzyl-2-(furan-2-yl)-4,5-bis(benzo[*b*]thiophen-2-yl)-1*H*-imidazole (15a). According to the general procedure, the reaction of **6d** with tri(benzo[*b*]thiophen-2-yl)indium afforded, after purification by column chromatography (30% EtOAc/hexanes), compound **15a** as a pale yellow solid (211 mg, 87%): mp 192−194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−7.88 (m, 1H), 7.78−7.82 (m, 1H), 7.69−7.72 (m, 1H), 7.59−7.62 (m, 1H), 7.48−7.49 (m, 4H), 7.46 (d, J = 1.0 Hz, 1H), 7.39−7.45 (m, 2H), 7.29 (d, J = 1.0 Hz, 1H), 7.20−7.27 (m, 5H), 6.84 (dd, J = 1.0, 3.5 Hz, 1H), 6.48 (q, J = 3.5, 1.8 Hz, 1H), 5.39 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 144.6 (C), 143.3 (CH), 141.8 (C), 140.6 (C), 140.2 (C), 139.5 (C), 139.4 (C), 137.0 (2 × C), 136.7 (C), 129.5 (C), 128.9 (CH), 128.8 (2 × CH), 127.6 (CH), 125.9 (2 × CH), 125.3 (CH), 124.6 (CH), 124.3 (CH), 124.1 (CH), 123.9 (CH), 123.4 (CH), 122.6 (C), 122.5 (CH), 122.0 (CH), 120.3 (CH), 111.6 (CH), 111.0 (CH), 48.7 (CH_2); IR (ATR) ν_{max} 2921, 1454, 1354, 1155 cm^{-1}; MS (EI) m/z 489 [M + H]$^+$ (34), 488 [M]$^+$ (100), 397 [M − C_7H_7]$^+$ (100), 331 [M − C_4H_3O]$^+$ (33); HRMS (EI-ion trap) calcd for $C_{30}H_{20}N_2OS_2$ [M]$^+$ 488.1012, found 488.1003.

1-Benzyl-2-(4-methoxyphenyl)-4,5-bis(5-phenylthiophen-2-yl)-1*H*-imidazole (16a). According to the general procedure, the reaction of **6a** with tri(5-phenylthiophen-2-yl)indium afforded, after purification by column chromatography (20% EtOAc/hexanes), compound **16a** as a pale green solid (197 mg, 68%): mp 83−86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.60 (m, 7H), 7.35−7.41 (m, 2H), 7.24−7.33 (m, 6H), 7.13 (dd, J = 3.8, 10.4 Hz, 2H), 6.90−6.96 (m, 6H), 5.18 (s, 2H), 3.82 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 160.4 (C), 149.0 (C), 147.7 (C), 142.5 (C), 137.6 (2 × C), 137.1 (C), 136.3 (C), 134.7 (C), 133.9 (C), 132.3 (CH), 130.4 (2 × CH), 129.0 (2 × CH), 128.8 (4 × CH), 128.0 (CH), 127.5 (CH), 127.0 (CH), 126.0 (2 × CH), 125.8 (2 × CH), 125.5 (2 × CH), 124.3 (CH), 123.4 (CH), 123.3 (CH), 122.8 (C), 120.7 (C), 114.1 (2 × CH), 55.3 (CH_3), 48.4 (CH_2); IR (ATR) ν_{max} 2929, 1610, 1476, 1251 cm^{-1}; MS (EI) m/z 581 [M + H]$^+$ (23), 580 [M]$^+$ (60), 489 [M − C_7H_7]$^+$ (100); HRMS (EI-ion trap) calcd for $C_{37}H_{28}N_2S_2O$ [M]$^+$ 580.1638, found 580.1615.

1-Benzyl-2-(4-methoxyphenyl)-4,5-bis(5-(3-chlorophenyl)-furan-2-yl)-1*H*-imidazole (17a). According to the general procedure, the reaction of **6a** with tri(5-(3-chlorophenyl)furan-2-yl)indium afforded, after purification by column chromatography (40% EtOAc/hexanes), compound **17a** as a yellow-orange solid (284 mg, 92%): mp 64−66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.57 (m, 3H), 7.26−7.42 (m, 7H), 7.04−7.20 (m, 4H), 6.90−6.94 (m, 4H), 6.79 (d, J = 3.4 Hz, 1H), 6.72 (dd, J = 3.5, 8.0 Hz, 2H), 5.28 (s, 2H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 160.6 (C), 153.1 (C), 151.3 (C), 150.1 (C), 149.8 (C), 143.2 (C), 137.6 (C), 134.7 (C), 134.6 (C), 133.0 (C), 132.3 (C), 131.9 (C), 130.5 (2 × CH), 129.9 (CH), 129.7 (CH), 128.9 (2 × CH), 127.7 (CH), 127.5 (CH), 126.8 (CH), 125.8 (2 × CH), 123.7 (CH), 123.5 (CH), 122.4 (C), 121.8 (CH), 121.5 (CH), 119.9 (C), 115.0 (CH), 114.2 (2 × CH), 109.1 (CH), 107.9 (CH), 107.4 (CH), 55.3 (CH_3), 49.3 (CH_2); IR (ATR) ν_{max} 2933, 2836, 1594, 1480, 1250 cm^{-1}; MS (EI) m/z 617 [M + H]$^+$ (19), 616 [M]$^+$ (50), 525 [M − C_7H_7]$^+$ (100); HRMS (EI-ion trap) calcd for $C_{37}H_{26}N_2O_3Cl_2$ [M]$^+$ 616.1315, found 616.1306.

Benzyl-2-((trimethylsilyl)ethynyl)-4,5-bis(4-methoxyphenyl)-1*H*-imidazole (18a). Compound **18a** was prepared by sequential cross-coupling reactions in a one-pot procedure: a solution of tris(trimethylsilylethynyl)indium (5 mL, 0.05 M in THF, 0.3 mmol) was added slowly to a solution of **5** (268 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) in dry THF (2 mL) in an argon-filled Schlenk tube. The mixture was heated at 80 °C for 20 h, and the starting material was consumed (TLC monitoring). A solution of tri(4-methoxyphenyl)indium (5 mL, 0.05 M in THF, 0.5 mmol) was added, and the mixture was heated at 80 °C until the intermediate monocoupling product had been consumed (21 h). The reaction mixture was quenched and treated according to the general procedure to afford, after purification by column chromatography (20% EtOAc/hexanes), compound **18a** as a pale yellow oil (70 mg, 40%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dt, J = 8.9, 2.3 Hz, 2H), 7.22−7.25 (m, 3H), 7.06 (dt, J = 8.7, 2.2 Hz, 2H), 6.95−6.99 (m, 2H), 6.88 (dt, J = 8.9, 2.3 Hz, 2H), 6.74 (dt, J = 8.9, 2.5 Hz, 2H), 5.08 (s, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 0.19 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 160.0 (C), 158.4 (C), 138.4 (C), 136.1 (C), 132.2 (2 × CH), 131.2 (C), 128.9 (C), 128.5 (2 × CH), 128.0 (2 × CH), 127.6 (CH), 127.1 (2 × CH), 126.7 (C), 122.4 (C), 114.4 (2 × CH), 113.5 (2 × CH), 100.1 (C), 94.2 (C), 55.1 (2 × CH_3), 48.5 (CH_2), −0.4 (3 × CH_3); IR (ATR) ν_{max} 2964, 2164, 1495, 1248 cm^{-1}; MS (EI) m/z 467 [M + H]$^+$ (38), 466 [M]$^+$ (100), 375 [M − C_7H_7]$^+$ (30); HRMS (EI-ion trap) m/z calcd for $C_{29}H_{30}N_2O_2Si$ [M]$^+$ 466.2071, found 466.2070.

General Procedure for Deprotection of the Benzyl Group.[21] 1-Benzyl-2,4,5-trisubstituted-1*H*-imidazole (0.06 mmol) and anhydrous DMSO (5 mL) were placed in a dry 25 mL two-necked flask. KO*t*-Bu (1.0 M in THF, 0.47 mmol) was slowly added, and O_2 was bubbled through the solution for 10 min. The reaction mixture was stirred at rt, and the reaction was monitored by TLC. After completion of the reaction, the solution was poured into sat. aq NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL), dried, and concentrated. The residue was purified by flash chromatography (50% EtOAc/hexanes) to afford,

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after concentration and high-vacuum drying, the corresponding N-debenzylation products.

2-(5-(3-Chlorophenyl)furan-2-yl)-4,5-bis(4-methoxyphenyl)-1*H*-imidazole (Neurodazine, 4).[20] According to the general procedure, the reaction of **9** with KO*t*-Bu afforded, after purification by column chromatography (20% EtOAc/hexanes), compound **4** as a yellow solid (24 mg, 90%): mp 86−88 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.79 (s, 1H), 7.98 (t, J = 1.7 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.41−7.49 (m, 5H), 7.32−7.37 (m, 1H), 7.23 (d, J = 3.4 Hz, 1H), 7.03 (dd, J = 2.4, 6.0 Hz, 3H), 6.87 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 3.75 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 159.4 (C), 158.5 (C), 151.4 (C), 146.3 (C), 138.0 (C), 137.3 (C), 134.3 (C), 132.4 (C), 131.2 (CH), 130.4 (2 × CH), 128.7 (2 × CH), 127.9 (C), 127.7 (CH), 127.4 (C), 123.7 (C), 123.5 (CH), 122.7 (CH), 114.6 (2 × CH), 114.1 (2 × CH), 109.9 (CH), 109.4 (CH), 55.7 (CH_3), 55.5 (CH_3); IR (ATR) ν_{max} 2921, 2835, 1500, 1244 cm^{-1}; MS (EI) m/z 457 [M + H]$^+$ (32), 456 [M]$^+$ (100), 441 [M − CH_3]$^+$ (27); HRMS (EI-ion trap) calcd for $C_{27}H_{21}N_2O_3Cl$ [M]$^+$ 456.1235, found 456.1232.

2-(4-Fluorophenyl)-4,5-bis(4-methoxyphenyl)-1*H*-imidazole (10b).[26] According to the general procedure, the reaction of **10a** with KO*t*-Bu afforded, after purification by column chromatography (30% EtOAc/hexanes), compound **10b** as a yellow solid (20 mg, 92%): mp 194−197 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.82 (m, 2H), 7.41 (d, J = 8.7 Hz, 4H), 7.01−7.07 (m, 2H), 6.83 (d, J = 8.7 Hz, 4H), 3.80 (s, 6H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 164.6 (C), 164.0 (C), 161.3 (C), 159.0 (2 × C), 144.7 (C), 129.1 (4 × CH), 127.3 (CH), 127.2 (CH), 126.3 (C), 126.2 (C), 115.9 (CH), 115.6 (CH), 114.0 (4 × CH), 55.2 (2 × CH_3); IR (ATR) ν_{max} 2927, 2837, 1498, 1243 cm^{-1}; MS (EI) m/z 375 [M + H]$^+$ (25), 374 [M]$^+$ (100), 359 [M − CH_3]$^+$ (29); HRMS (EI-ion trap) calcd for $C_{23}H_{19}N_2O_2F$ [M]$^+$ 374.1425, found 374.1415.

2-(Furan-2-yl)-4,5-bis(4-methoxyphenyl)-1*H*-imidazole (11b).[22] According to the general procedure, the reaction of **11a** with KO*t*-Bu afforded, after purification by column chromatography (30% EtOAc/hexanes), compound **11b** as a pale brown solid (20 mg, 96%): mp 169−172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.43 (m, 5H), 6.95 (d, J = 3.3 Hz, 1H), 6.85 (dt, J = 8.8, 2.4 Hz, 4H), 6.48 (dd, J = 3.4, 1.8 Hz, 1H), 3.82 (s, 6H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 159.0 (4 × C), 145.5 (2 × C), 142.2 (CH), 138.3 (2 × C), 129.1 (4 × CH), 114.0 (4 × CH), 112.0 (CH), 107.4 (CH), 55.3 (2 × CH_3); IR (ATR) ν_{max} 2956, 2835, 1518, 1497, 1248 cm^{-1}; MS(EI) m/z 347 [M + H]$^+$ (20), 346 [M]$^+$ (100), 331 [M − CH_3]$^+$ (29); HRMS (EI-ion trap) calcd for $C_{21}H_{18}N_2O_3$ [M]$^+$ 346.1312, found 346.1307.

2-(5-Phenylthiophen-2-yl)-4,5-bis(4-methoxyphenyl)-1*H*-imidazole (12b). According to the general procedure, the reaction of **12a** with KO*t*-Bu afforded, after purification by column chromatography (30% EtOAc/hexanes), compound **12b** as a lemon-yellow solid (24 mg, 92%): mp 58−60 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.66 (s, 1H), 7.72 (d, J = 6.5 Hz, 2H), 7.65 (d, J = 3.9 Hz, 1H), 7.54 (d, J = 3.8 Hz, 1H), 7.40−7.46 (m, 8H), 7.32 (t, J = 7.3 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 159.3 (C), 158.5 (C), 143.0 (C), 141.1 (C), 136.8 (C), 134.0 (C), 133.9 (C), 130.1 (2 × CH), 129.6 (2 × CH), 128.6 (2 × CH), 128.2 (CH), 127.9 (C), 127.4 (C), 125.7 (2 × CH), 125.3 (CH), 124.9 (CH), 123.7 (C), 114.7 (2 × CH), 114.1 (2 × CH), 55.7 (CH_3), 55.5 (CH_3); IR (ATR) ν_{max} 2924, 1495, 1248 cm^{-1}; MS (EI) m/z 439 [M + H]$^+$ (35), 438 [M]$^+$ (100), 423 [M − CH_3]$^+$ (30); HRMS (EI-ion trap) calcd for $C_{27}H_{22}N_2O_2S$ [M]$^+$ 438.1397, found 438.1391.

2-(4-Methoxyphenyl)-4,5-bis(5-phenylthiophen-2-yl)-1*H*-imidazole (16b). According to the general procedure, the reaction of **16a** with KO*t*-Bu afforded, after purification by column chromatography (20% EtOAc/hexanes), compound **16b** as a lemon-yellow solid (24 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dt, J = 8.9, 2.4 Hz, 2H), 7.68 (d, J = 7.2 Hz, 4H), 7.56 (s_a, 2H), 7.29−7.45 (m, 8H), 7.08 (dt, J = 8.9, 2.3 Hz, 2H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 160.3 (2 × C), 147.0 (C), 144.4 (C), 142.1 (C), 137.7 (C), 134.3 (C), 133.7 (C), 133.6 (C), 130.7 (C), 130.0 (CH), 129.7 (2 × CH), 129.6 (2 × CH), 128.4 (CH), 127.9 (CH), 127.4 (2 × CH), 125.8 (2 × CH), 125.5 (2 × CH), 124.9 (CH), 124.6 (CH), 124.4 (CH), 122.7 (C), 120.8 (C), 114.7 (2 × CH), 55.7 (CH_3); IR (ATR) ν_{max} 2924, 2854, 1599, 1440, 1254 cm^1; MS (EI) m/z 491 [M + H]$^+$ (35), 490 [M]$^+$ (100); HRMS (EI-ion trap) calcd for $C_{30}H_{22}N_2OS_2$ [M]$^+$ 490.1168, found 490.1157.

2-(4-Methoxyphenyl)-4,5-bis(5-(3-chlorophenyl)furan-2-yl)-1*H*-imidazole (17b). According to the general procedure, the reaction of **17a** with KO*t*-Bu afforded, after purification by column chromatography (20% EtOAc/hexanes), compound **17b** as an orange oil (30 mg, 96%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.78 (s, 1H), 8.06 (d, J = 8.7 Hz, 2H), 7.90 (s, 1H), 7.65−7.80 (m, 3H), 7.27−7.43 (m, 5H), 7.23 (d, J = 3.4 Hz, 1H), 7.14 (d, J = 3.5 Hz, 1H), 7.10 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 3.4 Hz, 1H), 3.84 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 160.4 (C), 151.5 (C), 150.9 (C), 150.5 (C), 147.6 (C), 145.3 (C), 134.3 (2 × C), 132.6 (C), 132.3 (C), 131.2 (CH), 131.1 (C), 130.1 (C), 127.9 (2 × CH), 127.7 (CH), 127.4 (CH), 123.5 (CH), 123.1 (CH), 122.7 (C), 122.6 (CH), 122.0 (CH), 119.5 (CH), 114.7 (2 × CH), 110.9 (CH), 109.9 (CH), 109.8 (2 × CH), 55.8 (CH_3); IR (ATR) ν_{max} 2923, 2852, 1595, 1500, 1252 cm^{-1}; MS (EI) m/z 527 [M + H]$^+$ (34), 526 [M]$^+$ (100); HRMS (EI-ion trap) calcd for $C_{30}H_{20}N_2O_3Cl_2$ [M]$^+$ 526.0845, found 526.0836.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C{^{1}H} NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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