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Unexpected palladium catalyzed O-arylation occurring in 4-(4-fluoro-3-nitrophenyl)-1,2-dimethyl-5-nitro-1*H*-imidazole series

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ABSTRACT

We describe herein a new unexpected palladium-catalyzed O-arylation reaction in fluorinated nitro(*o*-nitrophenyl)imidazole series involving arylboronic acids under Suzuki–Miyaura cross-coupling reaction conditions.

During the course of our research on the chemistry of new safer antiprotozoal[1] agents in 5-nitroimidazole series,[2] we observed what appeared to be palladium-catalyzed O-arylation of an aryl fluoride.

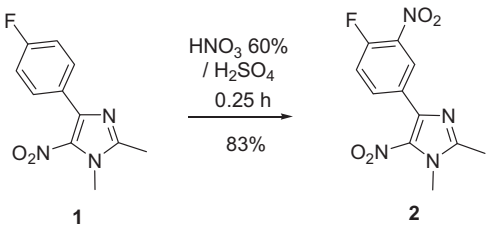
The development of mild conditions for the synthesis of diaryl ethers has attracted considerable attention, mainly due to their biological activity.[3] Reactions used to generate aryl ethers appear in the literature, for example the Cu-promoted arylation of alcohol derivatives with phenylboronic acids known as Chan–Lam coupling,[4] the Cu-mediated Ullmann condensation of phenols with aryl halides,[5] and the Buchwald's palladium-catalyzed C–O coupling of phenols with aryl halides.[6] However, to the best of our knowledge, no example of diaryl ether synthesis using arylboronic acid and aryl halides under the catalytic effects of palladium species has ever been described.

The Suzuki–Miyaura cross-coupling has proved to be extremely versatile and is extensively used in natural products and heterocyclic synthesis.[7] To our knowledge, only a few examples of Suzuki–Miyaura cross-coupling in haloimidazole series have been reported.[8] Bromides and chlorides are commonly used as leaving groups in Suzuki–Miyaura cross-coupling.[9] Although aryl fluorides have long been considered inert to palladium(0)-catalyzed coupling reactions, Yu and Kim described in 2003 an original palladium(0)-catalyzed Suzuki cross-coupling reactivity of highly electron-deficient aryl fluoride.[10]

Indeed, they demonstrated a possible mechanism for the oxidative addition step occurring via the palladium(0) species which, in the case of electron-deficient aryl fluoride, acts as a nucleophile and displaces the fluoride in an S_NAr manner to form the carbon–palladium bond, as suggested by Amatore and others.[11] Finally, a Nickel-catalyzed Suzuki–Miyaura reaction of aryl fluorides was recently described in the literature.[12]

This report focuses on the unexpected O-arylation of the aryl fluoride derivative **2** with boronic acids, giving diaryl ether derivatives instead of the expected C–C derivatives during the Suzuki–Miyaura cross-coupling study. The required starting material[13] was obtained by nitration using a mixture of HNO_3 60%/H_2SO_4 of compound **1**[8b] (Scheme 1).

Compound **2**, reacted with 4-methoxyphenylboronic acid under classical Suzuki–Miyaura reaction conditions using $Pd(OAc)_2$/xantphos catalyst, Cs_2CO_3 under inert atmosphere in DME at



Scheme 1. Preparation of starting material **2**.

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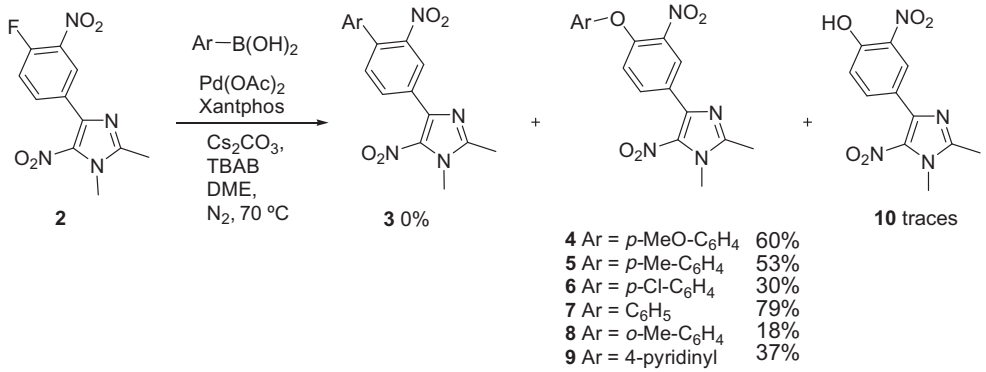


Scheme 2. Reaction of **2** and boronic acids.

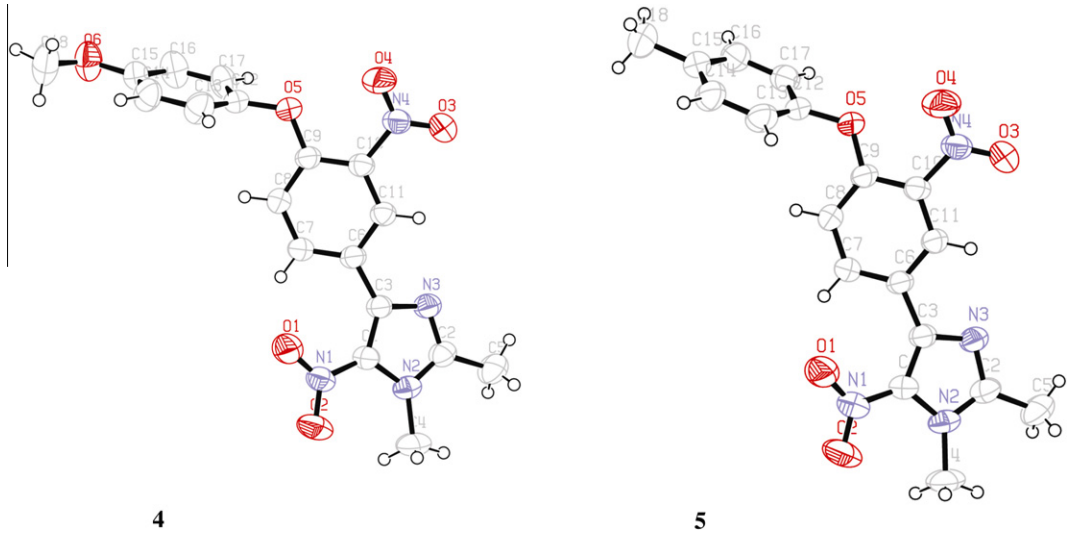
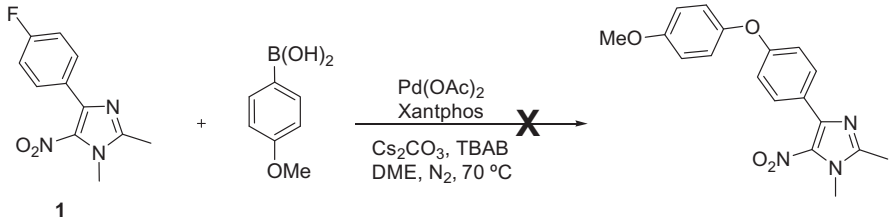


Figure 1. Ortep drawings of **4** and **5**.

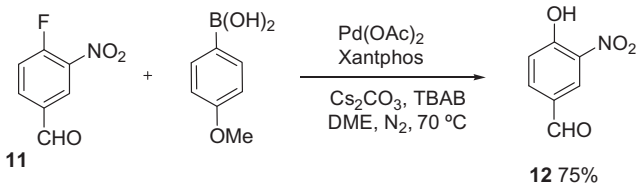


Scheme 3. Reaction using **1** and 4-methoxyphenylboronic acid.

70 °C in the presence of tetrabutylammonium bromide (TBAB), gave unexpected methoxyphenoxy derivative **4** in 60% yield, and traces of nitrophenol derivative **10** instead of the expected C–C coupled derivative **3**. Adding 10 equiv of water to the same reaction medium afforded compound **4** in similar yields (51% vs 60% without addition of water). Thus, the formation of compound **10** could result from a S_NAr reaction between compound **2** and, either carbonate or hydroxide anion as oxygen sources. Then, this reactivity was confirmed with other boronic acids, giving O-arylated compounds **5–9** in 30–79% yields (Scheme 2).[14]

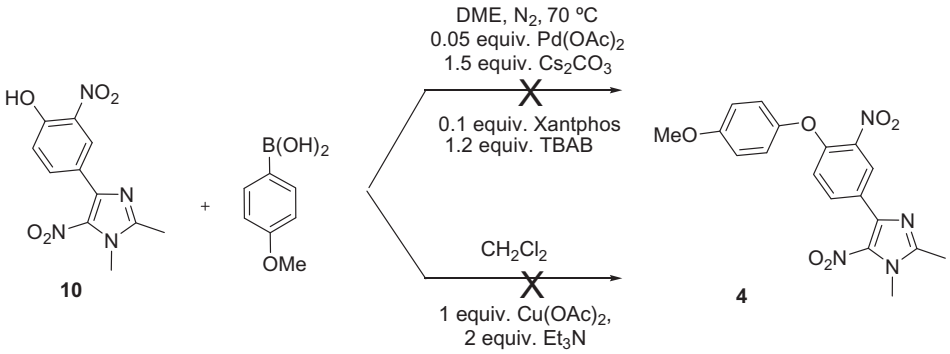
X-ray spectroscopy[15] of **4** and **5** (Fig. 1) and HRMS spectrum of these four compounds confirmed the C–O bond formation.

Since palladium-catalyzed O-arylation had never been described with arylboronic acids and electron-deficient aryl fluorides, additional experiments were performed to further understand the mechanism of the C–O bond formation.

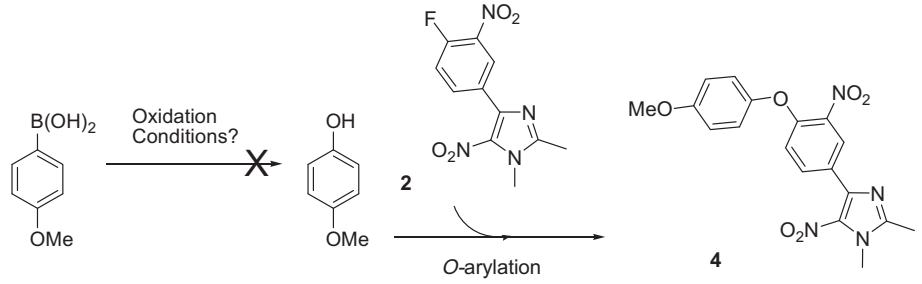


Scheme 4. Reaction using 4-fluoro-3-nitrobenzaldehyde **11** and 4-methoxyphenylboronic acid.

First, palladium catalysis was investigated by treating **2** and 4-methoxyphenylboronic acid under our experimental conditions



Scheme 5. Coupling assays of nitrophenol **10** and 4-methoxyphenylboronic acid.



Scheme 6. Formation hypothesis of 4-methoxyphenol.

but without palladium. After 5 days, this reaction did not produce any compound **4**, but only traces of the nitrophenol derivative **10**, which suggests that palladium plays a key catalytic role in the reaction.

As Kim and Yu[10] stated that a fluoride has to be activated by two withdrawing groups in order to react, the roles of the *o*-nitro and 5-nitroimidazole groups of substrate **2** were investigated. We found that the reaction of compound **1** (which does not bear the *o*-nitro group on the phenyl ring) and the 4-methoxyphenylboronic acid did not yield any expected product under our conditions (Scheme 3).

In the same way, the reaction of the 4-fluoro-3-nitrobenzaldehyde **11**, bearing an aldehyde as electron-withdrawing group (instead of the 5-nitroimidazole group), only gave nitrophenol **12** under our experimental conditions (Scheme 4).

These two reactions suggest that both the *o*-nitro and the nitroimidazole groups are essential to the formation of the C–O bond.

Furthermore, as the nitrophenol derivative **10** was formed under these experimental conditions, we suggest that substrate **2** gives the nitrophenol derivative **10**, which could undergo a cross-coupling with the boronic acid derivatives.

Indeed, this coupling is known as the Chan–Lam reaction, but the reaction is copper-promoted. However, when the reactivity of nitrophenol **10** with 4-methoxyphenylboronic acid was examined under the previous experimental palladium-catalyzed conditions, no C–O coupled compound was detected. Another assay involving classic Chan–Lam copper-promoted conditions[4] was also ineffective (Scheme 5).

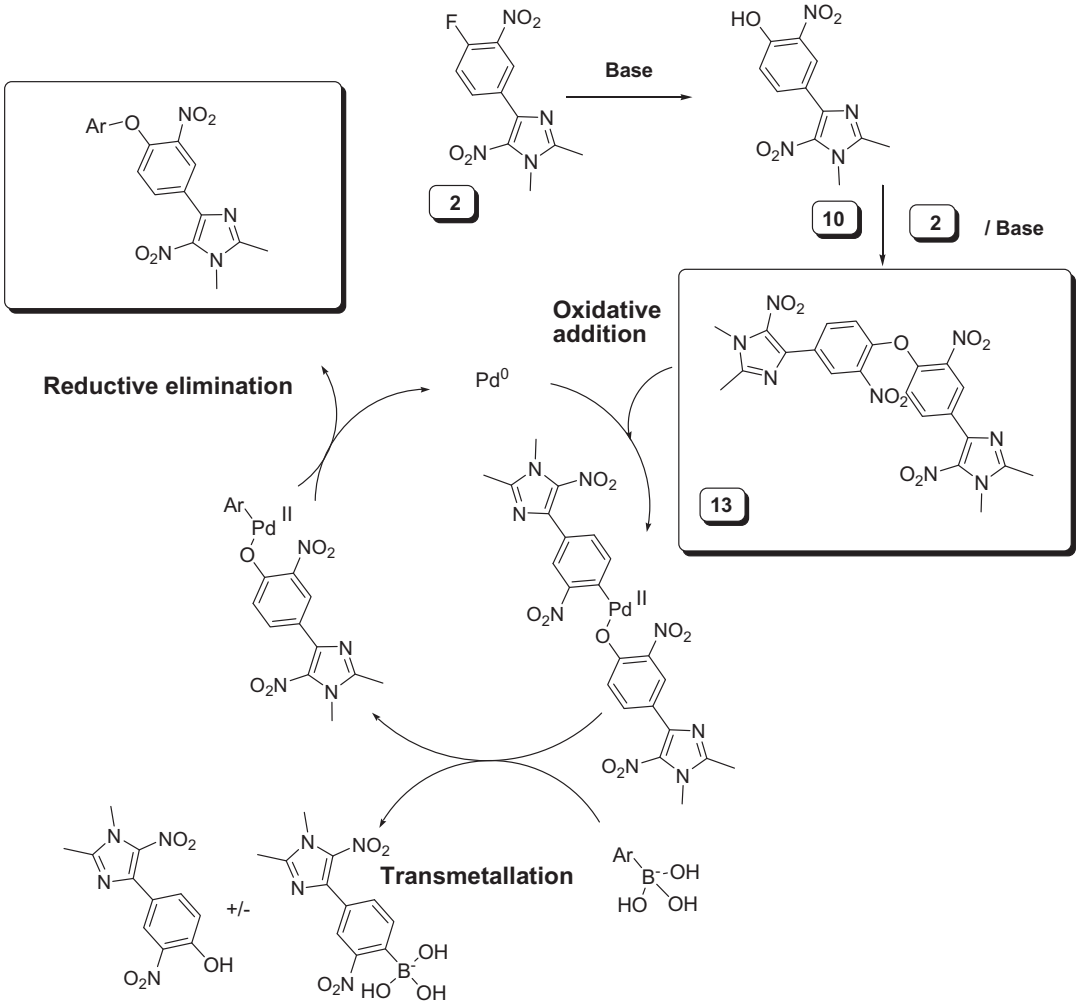
Next, we turned our attention to the boron species. Thus, by replacing arylboronic acids by a boronic ester (4,4,5,5-tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane) or potassium trifluoroborate (potassium 4-methoxyphenyltrifluoroborate), no reaction was observed. Furthermore, Lam and co-workers demonstrated that boronic acids can be oxidized into the corresponding phenol derivatives induced by copper- promoted conditions, or in the presence of 10 equiv water, and we therefore investigated the possibility of the 4-methoxyphenylboronic acid being converted into 4-methoxyphenol under the experimental conditions previously cited, subsequently reacting with substrate **2** via an O-arylation and S_NAr mechanism and leading to compound **4** (Scheme 6). However, no trace of methoxyphenol was produced (confirmed by LC/MS and TLC). Moreover, other oxidation assays were also performed, but no trace of 4-methoxyphenol was ever observed.

These unsuccessful results led us to re-examine LC/MS spectra previously observed under Pd-catalyzed reactions. A mass peak (*m/z* 539 $[M+H]^+$) was chosen because of its occurrence throughout the reactions using different arylboronic acids. Complementary spectral analysis confirmed the formation of 4,4′-[4,4′-oxybis(3-nitro-4,1-phenylene)]bis(1,2-dimethyl-5-nitro-1*H*-imidazole) **13**.

We hypothesized that a possible mechanism for the O-arylation could be via intermediate **13** after a palladium oxidative addition and a cross-coupling with arylboronic acids, even though, to the best of our knowledge, no such palladium addition had ever been described.

In order to propose a mechanism, supposing the in situ formation of compound **13**, we realized a particular assay using the same reaction conditions and 1 equiv of compound **10**. Thus, with *p*-chlorophenylboronic acid, the desired product **6** was formed in 30% yield. In order to reinforce the proposed mechanism, compound **13** was synthesized by reaction with aryl fluoride derivative **2** and nitrophenol derivative **10** under base-mediated conditions.[16] Then, compound **13** was tested with 4-methoxyphenylboronic acid under the above experimental conditions. After 48 h, a conversion of **13** in O-arylated compound **4** (39%), nitrophenol **10** (60%), and *C*-arylated compound **3** (traces) were observed, suggesting the possible mechanism depicted in Scheme 7.

The present work is the first example of a palladium-catalyzed C–O bond formed from a reaction between an activated phenylfluoride derivative and aryl or heteroaryl boronic acids. Initial mechanistic studies indicate that the reaction may occur via the formation of a nitrophenol derivative **10** and a diphenyl ether



Scheme 7. Proposed mechanism of C–O bond formation.

derivative **13** obtained via S_NAr reaction, which could have a key role in the reactivity. Further investigations of the scope and mechanism involved here, as well as potential synthetic applications, are currently in progress and will be reported in due course. We hope these data will provide useful input for further mechanistic and computational studies, as well as fueling additional studies of this mechanism.

Acknowledgments

This work is supported by the CNRS and the Universities of Aix-Marseille. The authors thank the Spectropole team for various analytical measurements, and M. Giorgi for the X-ray crystal-structure determinations. We express our thanks to V. Remusat for ^1H and ^{13}C NMR spectra recording.

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13. *Synthesis and data of compound **2**:* 1.83 mL of nitric acid 60% was added dropwise to a two neck flask placed on a cold water bath and containing **1** (4.25 mmol, 1 equiv) solubilized in concentrated sulphuric acid (18.3 mL). The reaction progress was monitored by TLC analysis. After 45 min at room temperature, the mixture is poured into cold H_2O. The precipitate was filtered off, washed with a solution of Na_2CO_3 1 M, H_2O, and dried with EtOH and petroleum ether. The filtrate was extracted by $CHCl_3$ after neutralization by Na_2CO_3, and the organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Compound **2** was isolated in 83% yield. *4-(4-Fluoro-3-nitrophenyl)-1,2-dimethyl-5-nitro-1H-imidazole* (**2**): Yellow powder, mp 179 °C (*i*-PrOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.54 (s, 3H), 3.94 (s, 3H), 7.26–7.39 (m, 1H), 8.05–8.13 (m, 1H), 8.53–8.58 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2 (CH_3), 34.3 (CH_3), 118.0 (d, J = 21.2 Hz, CH), 127.6 (d, J = 2.2 Hz, CH), 128.9 (d, J = 4.4 Hz, C), 136.6 (d, J = 9.2 Hz, CH), 139.8 (C), 148.8 (C), 153.1 (C), 158.4 (C). A C–NO_2 group did not appear in these conditions. Anal. Calcd for $C_{11}H_9FN_4O_4$: C, 47.15; H, 3.24; N, 19.99. Found C, 47.34; H, 3.33; N, 19.79.
14. *General synthesis and data of compounds **4**, **5**, **6**, **7**, **8**, **9**, **10**:* To a two neck flask, 0.36 mmol (1 equiv) of **2** was dissolved in DME (15 mL). 0.43 mmol, (1.2 equiv) of the appropriate arylboronic acid was added with 0.54 mmol (1.5 equiv) of Cs_2CO_3, 0.018 mmol (0.05 equiv) of $Pd(OAc)_2$, 0.036 mmol (0.1 equiv) of Xantphos, and 0.43 mmol (1.2 equiv) of TBAB. The mixture was stirred under inert atmosphere at 70 °C during 48 h until disappearance of the starting material. After cooling, the DME was evaporated under reduced pressure and the residue was purified by column chromatography with a mixture of CH_2Cl_2–MeCN (95–5) as eluent. *4-[4-(4-Methoxyphenoxy)-3-nitrophenyl]-1,2-dimethyl-5-nitro-1H-imidazole* (**4**): Yellow crystals, mp 109 °C (*i*-PrOH).^{1}H NMR (200 MHz, $CDCl_3$): δ 2.52 (s, 3H), 3.83 (s, 3H), 3.92 (s, 3H, 6.99–6.95 m, 3H), 7.07 (d, J = 9.2 Hz, 2H), 7.90 (dd, J = 2.2 Hz, 8.8 Hz, 1H), 8.43 (d, J = 2.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (CH_3), 34.3 (CH_3), 55.6 (CH_3), 115.2 (2 × CH), 117.9 (CH), 121.4 (2 × CH), 121.6 (C), 126.1 (C), 127.2 (CH), 135.1 (CH), 139.8 (C), 140.6 (C), 148.0 (C), 148.7 (C), 152.6 (C), 157.0 (C). HRMS calcd for $C_{18}H_{16}N_4O_6$ $[M+H]^+$: 385.1143, found 385.1144.
*1,2-Dimethyl-5-nitro-4-[3-nitro-4-(p-tolyloxy)phenyl]-1H-imidazole (**5**):* Yellow crystals, mp 94 °C (*i*-PrOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.36 s, 3H, 2.52 s, 3H, 3.92 s, 3H, 6.95–7.02 m, 3H), 7.20 (d, J = 8.5 Hz, 2H), 7.91 (dd, J = 2.1 Hz, 8.5 Hz, 1H), 8.43 (d, J = 2.1 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (CH_3), 20.8 (CH_3), 34.3 (CH_3), 118.7 (CH), 119.8 (2 × CH), 126.4 (C), 127.2 (CH), 130.6 (2 × CH), 134.9 (CH), 135.1 (C), 140.2 (C), 140.6 (C), 148.7 (C), 152.1 (C), 152.7 (C). A C–NO_2 group did not appear in these conditions. HRMS calcd for $C_{18}H_{16}N_4O_5$ $[M+H]^+$: 369.1193, found 369.1191.
*4-[4-(4-Chlorophenoxy)-3-nitrophenyl]-1,2-dimethyl-5-nitro-1H-imidazole (**6**):* Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.53 (s, 3H), 3.94 (s, 3H), 7.00–7.06 (m, 3H), 7.33–7.39 (m, 2H), 7.97 (dd, J = 2.1 Hz, 8.8 Hz, 1H), 8.45 (d, J = 2.1 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (CH_3), 34.3 (CH_3), 119.6 (CH), 120.8 (2 × CH), 127.4 (CH), 127.5 (C), 130.2 (2 × CH), 135.3 (CH), 140.2 (C), 140.8 (C), 148.7 (C), 150.9 (C), 154.1 (C). The two C–NO_2 groups did not appear in these conditions. HRMS calcd for $C_{17}H_{13}ClN_4O_5$ $[M+H]^+$: 389.0647, found 389.0650.
*1,2-Dimethyl-5-nitro-4-(3-nitro-4-phenoxyphenyl)-1H-imidazole (**7**):* Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.52 (s, 3H), 3.93 (s, 3H), 6.99–7.22 (m, 3H), 7.37–7.45 (m, 3H), 7.94 (dd, J = 2.2 Hz, 8.8 Hz, 1H), 8.45 (d, J = 2.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2 (CH_3), 34.3 (CH_3), 119.2 (CH), 119.7 (2 × CH), 125.0 (CH), 126.9 (C), 127.2 (CH), 127.9 (C), 128.7 (C), 130.2 (2 × CH), 135.1 (CH), 140.5 (C), 148.7 (C), 151.6 (C), 155.2 (C). HRMS calcd for $C_{17}H_{14}N_4O_5$ $[M+H]^+$: 355.1036, found 355.1031.
*1,2-dimethyl-5-nitro-4-[3-nitro-4-(o-tolyloxy)phenyl]-1H-imidazole (**8**):* Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.52 (s, 3H), 3.93 (s, 3H), 6.81 (d, J = 8.8 Hz, 1H), 7.01 (dd, J = 1.7 Hz, 7.3 Hz, 1H), 7.15–7.32 (m, 3H), 7.90 (dd, J = 2.2 Hz, 8.8 Hz, 1H), 8.46 (d, J = 2.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2 (CH_3), 16.0 (CH_3), 34.3 (CH_3), 117.3 (CH), 120.4 (CH), 125.7 (CH), 126.1 (C), 127.4 (CH), 127.6 (CH), 130.4 (C), 131.9 (CH), 135.2 (CH), 139.6 (C), 140.7 (C), 148.7 (C), 152.0 (C), 152.6 (C), a C–NO_2 group did not found. HRMS calcd for $C_{18}H_{16}N_4O_5$ $[M+H]^+$: 369.1193, found 369.1190.
*4-[4-(1,2-dimethyl-5-nitro-1H-imidazol-4-yl)-2-nitrophenoxy]pyridine (**9**):* Brown powder, mp 235 °C (*i-PrOH*). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.55 (s, 3H), 3.96 (s, 3H), 6.48 (d, J = 7.8 Hz, 2H), 7.34 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 8.3 Hz, 1H), 8.22 (dd, J = 2.0 Hz, 8.3 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2 (CH_3), 34.4 (CH_3), 119.1 (2 × CH), 127.4 (CH), 128.3 (CH), 134.1 (C), 135.4 (CH), 136.1 (C), 138.7 (C), 139.4 (2 × CH), 144.1 (C), 149.1 (C), 178.7 (C), a C–NO_2 group did not found. HRMS calcd for $C_{16}H_{13}N_5O_5$ $[M+H]^+$: 356.0989, found 356.0990.
*4-(1,2-Dimethyl-5-nitro-1H-imidazol-4-yl)-2-nitrophenol (**10**):* Orange oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.53 (s, 3H), 3.93 (s, 3H), 7.22 (d, J = 8.8 Hz, 1H), 8.05 (dd, J = 2.2 Hz, 8.8 Hz, 1H), 8.63 (d, J = 2.2 Hz, 1H), 10.75 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2 (CH_3), 34.3 (CH_3), 119.6 (CH), 124.5 (C), 126.6 (CH), 127.6 (C), 133.2 (C), 138.6 (CH), 140.8 (C), 148.7 (C), 155.6 (C). HRMS calcd for $C_{11}H_{10}N_4O_5$ $[M+H]^+$: 279.0724, found 279.0725.
15. *Crystal data for compound **4**:* $C_{18}H_{16}N_4O_6$, M = 384.35, triclinic, a = 7.3800(2) Å, b = 9.2849(2) Å, c = 13.6130(4) Å, α = 90.672(1)°, β = 105.679(1)°, γ = 94.599(1)°, V = 894.66(4) Å^3, T = 293(2) K, space group $P\bar{1}$, Z = 2, 14055 reflections measured, 4399 independent reflections (R_{int} = 0.04). The final R_1 values were 0.066 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.2022 ($I > 2\sigma(I)$). The final R_1 values were 0.1023 (all data). The final $wR(F^2)$ values were 0.2494 (all data). CCDC 877509 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.cdcc.cam.ac.uk/data_request/cif of from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223) 336033; email: deposit@ccdc.cam.ac.uk.
*Crystal data for compound **5**:* $C_{18}H_{16}N_4O_5$, M = 368.35, triclinic, a = 7.4586(2) Å, b = 9.5297(2) Å, c = 12.8344(4) Å, α = 83.826(1)°, β = 75.061(1)°, γ = 86.635(1)°, V = 875.85(4) Å^3, T = 293(2) K, space group $P\bar{1}$, Z = 2, 10098 reflections measured, 4275 independent reflections (R_{int} = 0.042). The final R_1 values were 0.0682 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.1831 ($I > 2\sigma(I)$). The final R_1 values were 0.0983 (all data). The final $wR(F^2)$ values were 0.2232 (all data). CCDC 877510 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.cdcc.cam.ac.uk/data_request/cif of from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: + 44 (1223) 336033; email: deposit@ccdc.cam.ac.uk.
16. *Synthesis and data of compound **13**:* A mixture of compound **10** (0.23 mmol) in DMSO in the presence of KOH (0.23 mmol, 1 equiv) was added slowly to an excess of **2** (0.46 mmol, 2 equiv) and heated at 80 °C by conventional oil-bath heating. Appearance of compound **13** was monitored by LC/MS. After 7 days, the mixture was poured into cold H_2O and extracted with $CHCl_3$. The organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The compound was isolated (34% yield) after purification by column chromatography using a mixture of acetone–$CHCl_3$ (50–50) as eluent. *4,4′-[4,4′-Oxybis(3-nitro-4,1-phenylene)]bis(1,2-dimethyl-5-nitro-1H-imidazole)* (**13**): Orange oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.54 (s, 6H), 3.94 (s, 6H), 7.15 (d, J = 8.7 Hz, 2H), 8.06 (dd, J = 2.2 Hz, 8.7 Hz, 2H), 8.56 (d, J = 2.2 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (2 × CH_3), 34.3 (2 × CH_3), 120.5 (2 × CH), 127.6 (2 × CH), 129.1 (2 × C), 135.0 (2 × C), 135.7 (2 × CH), 139.8 (2 × C), 140.6 (2 × C), 148.8 (2 × C), 149.3 (2 × C). HRMS calcd for $C_{22}H_{18}N_8O_9$ $[M+H]^+$: 539.1270, found 539.1270.