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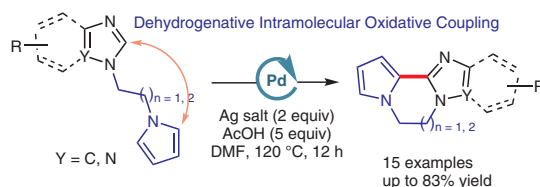# Palladium-Catalyzed Oxidative Annulation of Pyrrolylalkyl-1H-azoles: Towards the Synthesis of Polyheterocyclic Arenes

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Abstract A highly efficient and regioselective palladium-catalyzed annulation protocol for a series of linear and terminally substituted 1,2- and 1,3-di(heteroaryl)alkanes to the corresponding polyheterocyclic arenes is reported. Herein, intramolecular oxidative coupling involving double C(sp²)–H bond functionalization provides a feasible access to biheteroaryl systems annulated to a six-membered ring. The methodology is not restricted to six-membered annulations and was extended to the synthesis of compounds with a seven-membered ring and biheteroaryl core.

Key words C–H functionalization, pyrroles, oxidative coupling, palladium, imidazoles

Compounds containing pyrroloimidazoles,[1] pyrrolopyrazoles,[2] pyrrolopyrazines[3] and imidazopyrazoles[4] have garnered significant attention in the last two decades, not only because of their remarkable biological activities but also due to their use as essential synthons for natural and synthetic bioactive compounds through their isosterism with pyrrolizine and indolizine. Among these classes of compounds, pyrrolobis(imidazoles),[5] FM-381,[6] pyrrolo[1,2-c]imidazol-3(2H)-ones,[7] AG110[8] and related structures are the most extensively studied scaffolds (Figure 1). While many of the pyrazines and their analogues have potential antiarrhythmic,[9a] antiamnestic, antihypoxic,[9b] psychotropic,[9c] antihypersensitive[9d] and aldose reductase inhibition activities,[9e] interestingly most of them have received relatively little attention.

In this context, the development of novel types of polycyclic structures with a pyrrolopyrazine skeleton, which is of immense interest for biological screening, is becoming more expedient. In particular, for obtaining heterobiaryl-embedded rings, oxidative dehydrogenative coupling via transition-metal-catalyzed intramolecular cyclization has
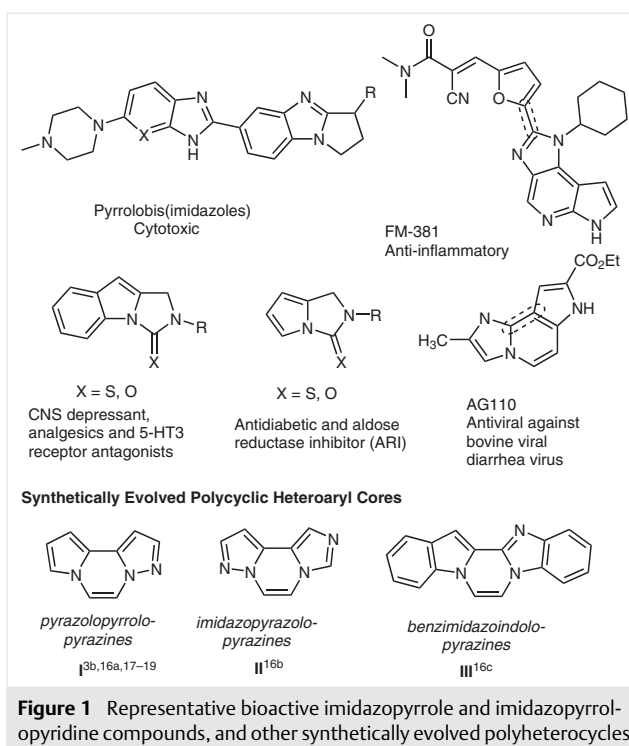

Figure 1 Representative bioactive imidazopyrrole and imidazopyrrolopyridine compounds, and other synthetically evolved polyheterocycles

emerged as a potential route.[10] Interestingly, all the methodologies to date for obtaining six-membered rings utilize coupling reactions for joining two fragments followed by an addition or substitution reaction for the ring closure that usually requires prefunctionalized substrate.[11] Very few reports have described the formation of a six-membered ring via a direct cross-coupling reaction. Towards this, a more environmentally benign and sustainable alternative reaction can be a simple oxidative intramolecular dehydrogenative coupling (IDC) of two aryl/heteroaryl C(Ar)–H bonds

yielding biaryls/heterobiaryls. Using this strategy, the synthesis of biaryls and heterobiaryls embedded in a ring, including, but not limited to, the synthesis of phenanthridin-6-ones,[12] carbazoles,[13] N-fused heterocycles[14] and other related biaryls,[15] has proved the wide applicability of IDC.

Amongst synthetically evolved polycyclic heteroaryl cores (**I**[3b,16a,17–19], **II**[16b] and **III**[16c]; Figure 1), the significant approaches to pyrrolopyrazines include intramolecular aza-Friedel–Crafts reaction of N-aminoethylpyrroles with aldehydes catalyzed by a chiral phosphoric acid,[17] palladium-catalyzed intramolecular direct arylation of pyrrole-2-carboxamides,[18] AuCl$_3$-catalyzed intramolecular addition of pyrazoles to N-propargylpyrroles,[19] intramolecular oxidative C–H amination of an elaborated precursor to the corresponding polyheterocyclic arenes,[3b] and many other synthetic methodologies. Recently, some palladium-[20a] and copper-catalyzed[20b,c] syntheses of indole- and pyrrole-annulated heterocycles have been attempted. However, unactivated pyrrole annulation to a heterocycle remains a challenge. Herein, we describe a workable model for palladium-catalyzed dehydrogenative intramolecular oxidative coupling involving double C(sp^2)–H bonds resulting in the six- and seven-membered heterocyclic rings, dihydropyrazine and dihydrodiazepine, from terminal 1,2- and 1,3-diheteroaryl-substituted alkanes. We demonstrate that IDC can provide direct access to annulated heterobiaryl cyclic compounds (Scheme 1).
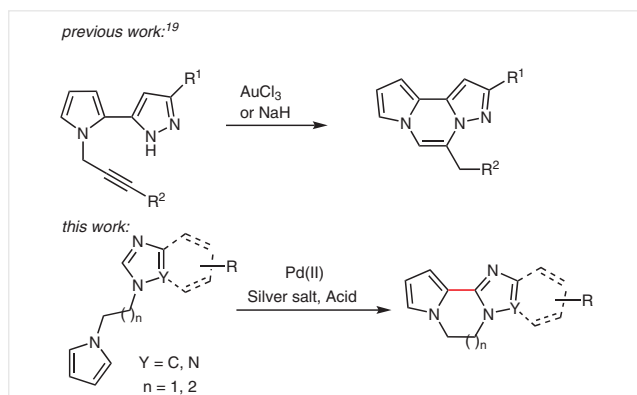
Scheme 1 Previous attempt and current dehydrogenative intramolecular oxidative coupling approach towards pyrrole-annulated heterocycles

Optimization of the reaction conditions commenced with an initial screening of the transition-metal catalyst under various reaction conditions (Table 1). At first, the reaction was explored under acidic conditions in the presence of excess oxidant to identify the optimal conditions. The substrate for the reaction was chosen keeping in mind that it should be easy to synthesize and can be easily diversified for the synthesis of related analogues. The reaction of **1a** (1 equiv), Cu(OAc)$_2$ (10 mol%), benzoic acid (5 equiv) and AgOAc (2 equiv) in DMF at 120 °C was found ineffective,

even after 12 hours, in affording the desired cyclized product (Table 1, entry 1). Next, we replaced Cu(OAc)$_2$ with PdCl$_2$, and found that with oxidant AgOAc and additive benzoic acid the reaction did not yield the desired product (Table 1, entry 2). Delightfully, variation in the protic acid additive, from benzoic acid to acetic acid, while keeping the loading of catalytic Pd and Ag salts the same as stated in entry 2, gave the desired cyclized product **2a** in 65% isolated yield (Table 1, entry 3). An increase in the yield (65% to 75%) was noticed when 10 mol% Pd(TFA)$_2$ was used with 2 equivalents of AgOAc and 5 equivalents of AcOH. A change in the Pd salt from Pd(TFA)$_2$ to Pd(OAc)$_2$ yielded 84% of desired product **2a** (Table 1, entry 5). These findings confirmed the efficacy of Pd(OAc)$_2$ over other Pd salts. Use of O$_2$ as an oxidant had no effect on the reactivity and there was no improvement in the yield (Table 1, entries 6 and 7). Oxidants other than AgOAc were tested; Ag$_2$CO$_3$ yielded 74% cyclized product whereas Cu(OAc)$_2$ afforded 51% isolated yield of **2a** (Table 1, entries 8 and 9).

Control experiments were performed to assess the importance of each reagent in the optimized reaction conditions. In the absence of either Pd catalyst or oxidant, the reaction failed to initiate (Table 1, entries 10 and 11); hence,

Table 1 Optimization of the Reaction Conditions[a]

Entry	Catalyst (equiv)	Oxidant (equiv)	Additive (equiv)	Yield[b] (%) of **2a**
1	Cu(OAc)$_2$ (0.1)	AgOAc (2)	C$_6$H$_5$COOH (5)	nd
2	PdCl$_2$ (0.1)	AgOAc (2)	C$_6$H$_5$COOH (5)	nd
3	PdCl$_2$ (0.1)	AgOAc (2)	AcOH (5)	65
4	Pd(TFA)$_2$ (0.1)	AgOAc (2)	AcOH (5)	75
5	Pd(OAc)$_2$ (0.1)	AgOAc (2)	AcOH (5)	84
6	Pd(OAc)$_2$ (0.1)	AgOAc (2)	AcOH (5) + O$_2$ (1 atm)	60
7	Pd(OAc)$_2$ (0.1)	AgOAc (2)	O$_2$ (1 atm)	71
8	Pd(OAc)$_2$ (0.1)	Ag$_2$CO$_3$ (2)	AcOH (5)	74
9	Pd(OAc)$_2$ (0.1)	Cu(OAc)$_2$ (2)	AcOH (5)	51
10	Pd(OAc)$_2$ (0.1)	–	AcOH (5)	nd
11	–	AgOAc (2)	AcOH (5)	nd
12	Pd(OAc)$_2$ (0.1)	AgOAc (2)	–	52
13	Pd(OAc)$_2$ (0.1)	AgOAc (1)	AcOH (5)	48
14	Pd(OAc)$_2$ (0.1)	AgOAc (2)	AcOH (2.5)	28
15	Pd(OAc)$_2$ (0.05)	AgOAc (2)	AcOH (5)	46

[a] Reaction conditions: **1a** (0.2 mmol), catalyst, oxidant, additive, DMF (1 mL), 120 °C, 12 h.
[b] Isolated yields; nd = not detected.

it was concluded that Pd catalyst and oxidant are essential for the reaction to proceed. A decreased yield of **2a** was observed when the entire set of optimized reaction conditions were imposed in the absence of acid additive AcOH (Table 1, entry 12).

To check stoichiometric dependency, we lowered the amount of Ag salt to half of its initial loading, which resulted in a decreased yield of **2a** (Table 1, entry 13). Further, reducing the amount of acid to 2.5 equivalents gave a poor yield (Table 1, entry 14). An attempt to reduce the catalytic loading of Pd(OAc)$_2$, to 5 mol%, gave **2a** in a lower 46% yield (Table 1, entry 15). Based on these studies, finally it was concluded that 10 mol% Pd(OAc)$_2$, 2 equivalents of AgOAc and 5 equivalents of protic additive AcOH in DMF at 120 °C for 12 hours were the best optimized reaction conditions for the synthesis of **2a**.

With these optimized reaction conditions in hand, we ventured into establishing a broad spectrum of substrate scope for this reaction and to get insight into the effect of various functionalities on this intramolecular C–H activation. We also studied the effect of the length of the alkyl loop linking the nitrogens of the azole and pyrrole on the yields. With these aims, we synthesized novel heterobiaryl systems with a six- or seven-membered ring, and the results are summarized in Table 2.

When the length of the linked alkyl chain was fixed at two carbons (n = 1), the desired imidazopyrrolodihydropyrazines **2a–2h** were successfully obtained in 48–83% isolated yield. Unsubstituted benzimidazole **1a** and benzimidazoles installed with electron-donating groups (**1b**) or electron-withdrawing groups (**1c** and **1d**) were successfully coupled at their C2 position with pyrrole, and resulted in the corresponding imidazopyrrolodihydropyrazines **2a–2d** in 83%, 76%, 77% and 72% isolated yield, respectively. Pyrrole N-ethyl-linked with imidazoles [imidazoles 4,5-disubstituted with Cl (**1e**), CN (**1f**) or Ph (**1g**) groups] and unsubstituted triazole **1h** were successfully coupled to give the six-membered cyclized products **2e–2h** in 48–73% isolated yield. Thus, the results were promising both when electron-donating groups or electron-withdrawing groups were installed on benzimidazoles and imidazoles. Next, we extended the linked alkyl chain between pyrrole and the azoles to three carbons (n = 2). Using our reaction conditions, we successfully synthesized imidazopyrrolodiazepines **2i–2o** from the corresponding lengthened pyrrolopropylazoles **1i–1o**. Unsubstituted (**1i**) and electron-donating (Me, **1j**) or electron-withdrawing [Cl (**1k**), Br (**1l**)] functional groups on the benzimidazole of pyrrolopropylbenzimidazoles were well tolerated under these reaction conditions, giving diazepines **2i–2l** in 62–71% isolated yield. Pyrrolopropylimidazoles substituted with electron-withdrawing substituents [Cl (**1m**), CN (**1n**), Ph (**1o**)] at the imidazole also led to the corresponding imidazopyrrolodiazepines **2m–2o** in good yields (52%, 58% and 46%, respectively).

Table 2 Substrate Scope for the Cross-Coupling Reaction[a]
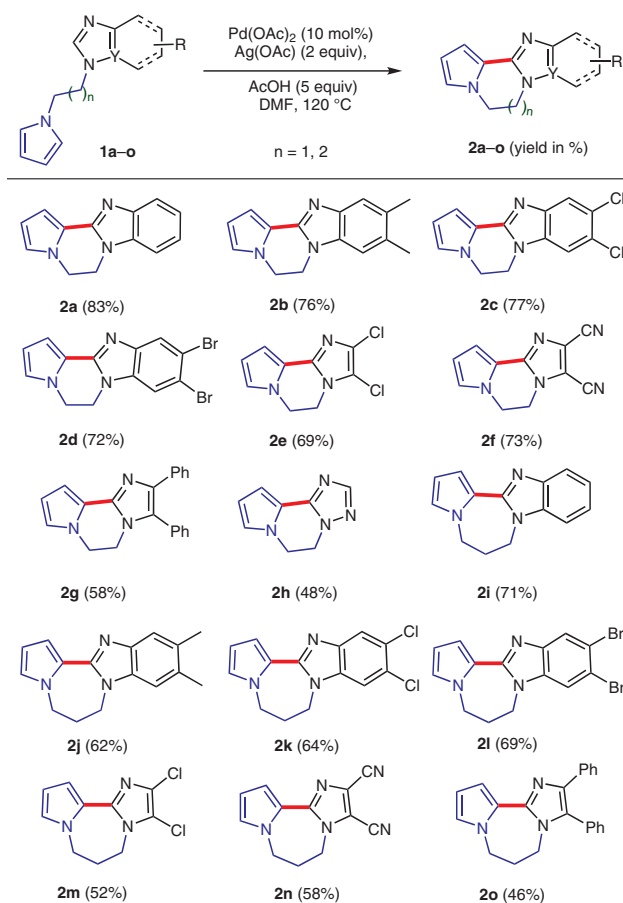

[a] Reaction conditions: **1** (0.2 mmol), Pd(OAc)$_2$ (10 mol%), AgOAc (2.0 equiv), AcOH (5.0 equiv), DMF (1 mL), 120 °C, 12 h.

To gain mechanistic insight into this intramolecular oxidative cross-coupling, we explored the optimized cyclization in the presence of TEMPO (Scheme 2). While no TEMPO-coupled side product was observed, a slight loss in product yield was noted. This observation rules out the possibility of a radical pathway for the cyclization. Also, intermolecular coupling of ethyl acrylate in a mixture of N-methylbenzimidazole and **1a** was studied (Scheme 2). Here, the intramolecular cyclization appeared to predominate over the intermolecular, leaving the added other coupling partners intact in the reaction mixture. The quest was to identify the preferred activation site for the intermolecular reactions and then extend the insight into the developed intramolecular oxidative C–C bond formation. Based on our recent reports,[20] we expected the C-2 position of benzimidazole to be more reactive than the C-2 of pyrrole. This was indeed observed in our competition studies, too. Thus, it indicates that the reaction is probably initiated by metalation at the azole. Palladation of the benzimidazole at C-2 forms complex **A** with the loss of one molecule of AcOH (Scheme
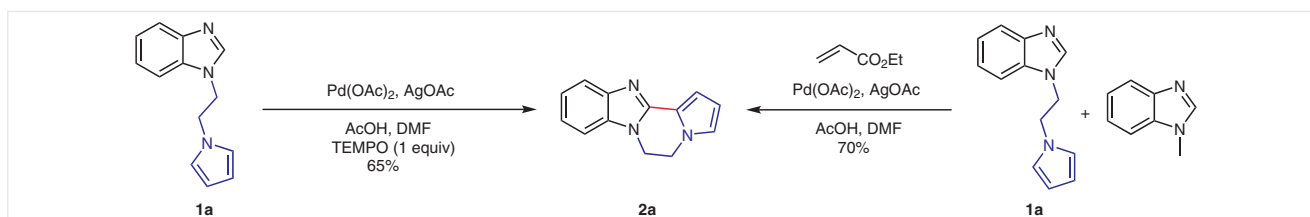
Scheme 2 Cyclization in the presence of TEMPO and other controlled conditions

3). Further, electrophilic C-2 carbometalation of pyrrole proceeds via transition state **B** in a concerted metalation–deprotonation (CMD) step to form complex **C**. Finally, the desired product is formed along with expulsion of Pd(0) from complex **C** through a reductive elimination process. The Pd(0) is re-oxidized to Pd(II) with the Ag(I) oxidant and re-enters the catalytic cycle.
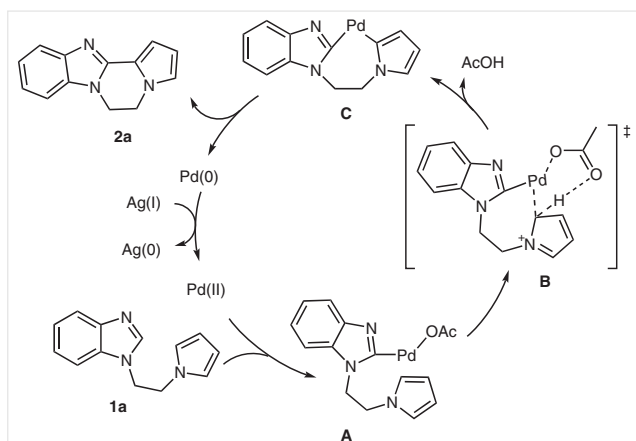
Scheme 3 Proposed mechanism for the intramolecular dehydrogenative coupling

In accordance with the information obtained from ^{1}H and ^{13}C NMR spectroscopy, the structure of cyclized product **2a** was also unequivocally confirmed by X-ray crystallography (Figure 2).
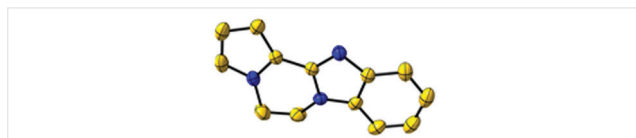

Figure 2 X-ray crystal structure of **2a**[21]

In conclusion, we have developed an efficient method for synthesizing polyheteroarenes, via palladium-catalyzed intramolecular oxidative cross-coupling, which involves dual C(sp^2)–H bond functionalization. Moreover, this reaction accesses the synthesis of the six- and seven-membered rings of pyrazine and diazepine annulated with pyrrole–azole systems.

NMR spectra were recorded in deuterated solvents with the residual protonated solvent signal as internal reference on a Bruker Ava-300 or Bruker Ava-400 spectrometer. Chemical shifts are reported in parts per million using the solvent resonance as internal standard (chloroform, 7.26 and 77.0 ppm; DMSO, 2.50 and 40.0 ppm). Data are reported as follows: chemical shift, multiplicity (standard abbreviations), coupling constant(s), and integration. Electrospray ionization (ESI) high-resolution mass spectrometry was performed on a Bruker microOTOF-Q II mass spectrometer. Solvents for starting material preparation and coupling reactions were dried following the literature procedures before use.

Pyrrolylalkyl-1H-azoles 1; General Procedure for the N-Alkylation of Azoles

To a suspension of NaH (1.0 equiv) in anhydrous DMF at 0 °C was dropwise added a solution of the appropriate 5,6-disubstituted benzimidazole, 4,5-disubstituted imidazole or triazole (1.0 mmol, 1.0 equiv) in anhydrous DMF, and the reaction mixture was allowed to stir at rt for 30 min. Then, a solution of 2-(1H-pyrrol-1-yl)ethyl 4-methylbenzenesulfonate or 3-(1H-pyrrol-1-yl)propyl 4-methylbenzenesulfonate (1.2 equiv) in DMF was added, and the resulting solution was heated at 80 °C for 16 h. Once the reaction was completed (monitored by TLC), the mixture was allowed to cool and saturated brine solution was added. The mixture was extracted with EtOAc (3 ×). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The organic residue was purified by silica gel column chromatography (EtOAc/hexane, 2:3 to 4:1) to provide the desired product **1**.

1-(2-(1H-Pyrrol-1-yl)ethyl)-1H-benzo[d]imidazole (1a)

Brown solid; yield: 184 mg (87%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.82 (d, J = 2.9 Hz, 1 H), 7.31 (d, J = 2.5 Hz, 4 H), 6.37 (d, J = 2.5 Hz, 2 H), 6.13 (d, J = 1.7 Hz, 2 H), 4.43 (br s, 2 H), 4.25 (br s, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 143.4, 142.9, 132.9, 122.8, 122.0, 120.1, 109.1, 108.9, 108.8, 48.4, 46.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{13}$H$_{14}$N$_3$: 212.1182; found: 212.1189.

5,6-Dimethyl-1-(2-(1H-pyrrol-1-yl)ethyl)-1H-benzo[d]imidazole (1b)

White solid; yield: 201 mg (84%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.59 (s, 1 H), 7.29 (dd, J = 2.2, 3.9 Hz, 1 H), 7.04 (s, 1 H), 6.41 (dd, J = 2.1, 4.2 Hz, 2 H), 6.15 (dd, J = 2.1, 4.2 Hz, 2 H), 4.44–4.40 (m, 2 H), 4.29–4.25 (m, 2 H), 2.42 (s, 3 H), 2.41 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 142.2, 141.7, 132.4, 131.5, 131.3, 120.3, 120.1, 109.3, 48.7, 46.5, 20.4, 20.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{18}N_3$: 240.1495; found: 240.1491.

5,6-Dichloro-1-(2-(1*H*-pyrrol-1-yl)ethyl)-1*H*-benzo[*d*]imidazole (1c)

Brown powder; yield: 200 mg (71%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.86 (d, J = 2.3 Hz, 2 H), 7.73 (s, 1 H), 6.55 (s, 2 H), 5.93 (d, J = 1.8 Hz, 2 H), 4.58 (t, J = 5.6 Hz, 2 H), 4.29 (t, J = 5.6 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 146.3, 142.5, 133.2, 124.9, 124.1, 120.6, 120.3, 112.1, 108.1, 48.2, 45.8.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{12}Cl_2N_3$: 280.0402; found: 280.0409.

5,6-Dibromo-1-(2-(1*H*-pyrrol-1-yl)ethyl)-1*H*-benzo[*d*]imidazole (1d)

Brown solid; yield: 283 mg (77%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.05 (s, 1 H), 7.40 (s, 1 H), 7.27 (d, J = 4.8 Hz, 1 H), 6.35 (s, 2 H), 6.13 (s, 2 H), 4.45–4.31 (m, 2 H), 4.26–4.14 (m, 2 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 144.8, 144.0, 133.6, 125.0, 120.4, 118.8, 117.9, 130.8, 110.1, 49.1, 47.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{12}Br_2N_3$: 367.9392; found: 367.9395.

4,5-Dichloro-1-(2-(1*H*-pyrrol-1-yl)ethyl)-1*H*-imidazole (1e)

Brown sticky solid; yield: 170 mg (74%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.71 (s, 1 H), 6.43 (d, J = 1.4 Hz, 2 H), 6.12 (d, J = 1.6 Hz, 2 H), 4.17–4.13 (m, 4 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 134.7, 125.7, 120.1, 112.3, 109.2, 48.4, 47.2.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_9H_{10}Cl_2N_3$: 230.0246; found: 230.0246.

1-(2-(1*H*-Pyrrol-1-yl)ethyl)-1*H*-imidazole-4,5-dicarbonitrile (1f)

Brown sticky solid; yield: 165 mg (78%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.85 (s, 1 H), 6.44 (d, J = 1.1 Hz, 2 H), 6.18 (d, J = 1.0 Hz, 2 H), 4.43 (t, J = 6.0 Hz, 2 H), 4.28–4.23 (t, J = 6.0 Hz, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 141.7, 123.1, 120.2, 111.8, 111.5, 110.7, 107.6, 49.2, 49.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{10}N_5$: 212.0930; found: 212.0938.

4,5-Diphenyl-1-(2-(1*H*-pyrrol-1-yl)ethyl)-1*H*-imidazole (1g)

Brown solid; yield: 295 mg (94%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.51–7.48 (m, 5 H), 7.28–7.17 (m, 6 H), 6.40–6.38 (m, 2 H), 6.16–6.15 (m, 2 H), 4.10 (t, J = 6.0 Hz, 2 H), 3.96 (t, J = 6.0 Hz, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 137.9, 136.8, 134.1, 130.7, 130.1, 129.2, 128.9, 128.0, 126.4, 126.4, 120.3, 109.1, 49.4, 49.2.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{21}H_{20}N_3$: 314.1652; found: 314.1665.

1-(2-(1*H*-Pyrrol-1-yl)ethyl)-1*H*-1,2,4-triazole (1h)

Red oily liquid; yield: 122 mg (75%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.98 (s, 1 H), 7.52 (s, 1 H), 6.39 (dd, J = 4.3, 6.2 Hz, 2 H), 6.11 (dd, J = 4.3, 6.3 Hz, 2 H), 4.45–4.42 (m, 2 H), 4.30 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 152.4, 143.9, 120.3, 109.3, 51.1, 48.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_8H_{11}N_4$: 163.0978; found: 163.0980.

1-(3-(1*H*-Pyrrol-1-yl)propyl)-1*H*-benzo[*d*]imidazole (1i)

Brown solid; yield: 210 mg (93%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.84–7.81 (m, 2 H), 7.31–7.30 (m, 3 H), 6.64 (s, 2 H), 6.22 (s, 2 H), 4.05 (t, J = 6.8 Hz, 2 H), 3.85 (t, J = 6.4 Hz, 2 H), 2.31 (t, J = 6.4 Hz, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 143.6, 142.8, 133.4, 123.0, 122.2, 120.3, 120.2, 109.5, 108.7, 45.9, 41.6, 30.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{16}N_3$: 226.1338; found: 226.1343.

5,6-Dimethyl-1-(3-(1*H*-pyrrol-1-yl)propyl)-1*H*-benzo[*d*]imidazole (1j)

White solid; yield: 218 mg (86%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.69 (s, 1 H), 7.61 (s, 1 H), 7.07 (s, 1 H), 6.65 (s, 2 H), 6.24 (s, 2 H), 4.00 (t, J = 6.8 Hz, 2 H), 3.84 (t, J = 6.4 Hz, 2 H), 2.41 (s, 3 H), 2.41 (s, 3 H), 2.32–2.28 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 142.3, 142.0, 132.0, 131.9, 130.9, 120.2, 120.1, 109.6, 108.5, 45.8, 41.4, 30.7, 20.3, 20.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{20}N_3$: 254.1652; found: 254.1651.

5,6-Dichloro-1-(3-(1*H*-pyrrol-1-yl)propyl)-1*H*-benzo[*d*]imidazole (1k)

Brown sticky solid; yield: 256 mg (87%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.68 (s, 1 H), 7.62 (s, 1 H), 7.16 (s, 1 H), 6.49 (s, 2 H), 6.07 (d, J = 1.3 Hz, 2 H), 3.85 (t, J = 6.8 Hz, 2 H), 3.73 (t, J = 6.3 Hz, 2 H), 2.20–2.14 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 144.5, 142.8, 132.5, 126.7, 126.0, 121.2, 120.2, 110.8, 108.8, 45.7, 41.8, 30.5.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{14}Cl_2N_3$: 294.0559; found: 294.0556.

5,6-Dibromo-1-(3-(1*H*-pyrrol-1-yl)propyl)-1*H*-benzo[*d*]imidazole (1l)

Brown solid; yield: 305 mg (80%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.01 (s, 1 H), 7.70 (s, 1 H), 7.48 (s, 1 H), 6.61 (s, 2 H), 6.20 (s, 2 H), 3.97 (t, J = 6.3 Hz, 2 H), 3.86 (d, J = 5.6 Hz, 2 H), 2.31–2.29 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 144.4, 144.0, 139.0, 133.5, 124.6, 120.2, 118.2, 117.4, 114.0, 113.9, 108.9, 45.8, 41.9, 30.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{14}Br_2N_3$: 381.9548; found: 381.9552.

4,5-Dichloro-1-(3-(1*H*-pyrrol-1-yl)propyl)-1*H*-imidazole (1m)

Brown sticky solid; yield: 212 mg (87%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.27 (d, J = 9.0 Hz 1 H), 6.64 (d, J = 3.0 Hz 1 H), 6.20 (s, 1 H), 3.92 (t, J = 6.0 Hz, 2 H), 3.84 (t, J = 6.0 Hz, 2 H), 2.31–2.24 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 134.5, 126.7, 120.4, 113.2, 109.1, 45.9, 43.4, 31.2.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{10}$H$_{12}$Cl$_2$N$_3$: 244.0402; found: 244.0405.

1-(3-(1*H*-Pyrrol-1-yl)propyl)-1*H*-imidazole-4,5-dicarbonitrile (1n)

Brown sticky solid; yield: 171 mg (76%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.49 (s, 1 H), 6.62 (d, J = 1.8 Hz, 2 H), 6.20–6.18 (m, 2 H), 4.07–3.97 (m, 4 H), 2.44–2.37 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 141.4, 123.5, 120.3, 112.0, 111.5, 109.6, 107.8, 45.8, 45.2, 31.4.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{12}$H$_{12}$N$_5$: 226.1087; found: 226.1091.

4,5-Diphenyl-1-(3-(1*H*-pyrrol-1-yl)propyl)-1*H*-imidazole (1o)

Brown sticky solid; yield: 275 mg (84%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.60 (s, 1 H), 7.54–7.48 (m, 5 H), 7.39–7.32 (m, 2 H), 7.26–7.15 (m, 3 H), 6.51 (d, J = 1.7 Hz, 2 H), 6.15 (d, J = 1.5 Hz, 2 H), 3.79–3.75 (m, 4 H), 1.99–1.95 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 138.4, 136.9, 134.2, 130.7, 130.5, 129.3, 128.9, 128.2, 126.7, 126.5, 120.2, 108.6, 46.1, 42.4, 32.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{22}$H$_{22}$N$_3$: 328.1808; found: 328.1810.

Intramolecular Dehydrogenative Cross-Coupling of Pyrrolylalkyl-1*H*-azoles 1; General Procedure

A tube was loaded with *N*-alkylated azole **1** (0.2 mmol, 1 equiv), Pd(OAc)$_2$ (0.1 equiv), AgOAc (2 equiv) and AcOH (5 equiv) in DMF (1 mL), then sealed with a screw cap. The reaction mixture was stirred in a preheated silicone oil bath at 120 °C for 12 h. Once the reaction was completed, the mixture was allowed to cool and saturated brine solution was added. The mixture was extracted with EtOAc (3 ×). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 3:7 to 3:2) to provide the desired product **2**.

5,6-Dihydrobenzo[4,5]imidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazine (2a)

Brown solid; yield: 35 mg (83%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.74 (d, J = 8.7 Hz, 1 H), 7.26–7.22 (m, 3 H), 7.03–7.02 (m, 1 H), 6.79 (s, 1 H), 6.31–6.30 (m, 1 H), 4.32 (br s, 4 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 144.9, 143.9, 133.7, 123.1, 122.5, 122.3, 119.3, 119.2, 110.4, 109.7, 108.4, 43.7, 40.8.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{13}$H$_{12}$N$_3$: 210.1026; found: 210.1028.

9,10-Dimethyl-5,6-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrrolo-[2,1-*c*]pyrazine (2b)

White solid; yield: 36 mg (76%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.50 (s, 1 H), 7.07 (s, 1 H), 7.01 (d, J = 1.9 Hz, 1 H), 6.82 (s, 1 H), 6.32 (s, 1 H), 4.37 (br s, 4 H), 2.38 (s, 3 H), 2.37 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 144.1, 132.3, 131.5, 131.4, 122.8, 122.4, 119.6, 110.4, 109.4, 108.9, 43.9, 40.9, 20.6, 20.4.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{15}$H$_{16}$N$_3$: 238.1339; found: 238.1339.

9,10-Dichloro-5,6-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazine (2c)

Brown solid; yield: 43 mg (77%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.92 (s, 1 H), 7.79 (s, 1 H), 7.15 (s, 1 H), 6.83–6.82 (m, 1 H), 6.29–6.27 (m, 1 H), 4.49–4.48 (m, 4 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 146.8, 143.3, 133.7, 124.5, 124.0, 123.7, 120.8, 119.1, 111.3, 109.6, 109.4, 42.9, 40.9.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{13}$H$_{10}$Cl$_2$N$_3$: 278.0246; found: 278.0258.

9,10-Dibromo-5,6-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazine (2d)

Brown solid; yield: 52 mg (72%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.97 (s, 1 H), 7.57 (s, 1 H), 7.04 (s, 1 H), 6.86 (s, 1 H), 6.35 (s, 1 H), 4.42–4.35 (m, 4 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 146.7, 144.7, 134.2, 123.9, 123.7, 121.5, 117.7, 117.2, 113.1, 111.0, 111.0, 46.7, 41.2.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{13}$H$_{10}$Br$_2$N$_3$: 365.9236; found: 365.9217.

2,3-Dichloro-5,6-dihydroimidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazine (2e)

Brown sticky solid; yield: 31 mg (69%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.70 (d, J = 3.1 Hz, 2 H), 6.24–6.22 (m, 1 H), 4.30–4.26 (m, 2 H), 4.20–4.14 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 138.2, 126.2, 122.0, 121.5, 110.8, 110.2, 107.1, 43.4, 41.9.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_9$H$_8$Cl$_2$N$_3$: 228.0090; found: 228.0092.

5,6-Dihydroimidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazine-2,3-dicarbonitrile (2f)

White powder; yield: 31 mg (73%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.16 (s, 1 H), 6.77 (dd, J = 2.1, 3.4 Hz, 1 H), 6.29–6.27 (m, 1 H), 4.48–4.42 (m, 4 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 143.9, 125.0, 120.6, 119.2, 112.6, 110.7, 109.7, 109.3, 108.9, 43.6, 42.4.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{11}$H$_8$N$_5$: 210.0774; found: 210.0763.

2,3-Diphenyl-5,6-dihydroimidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazine (2g)

Brown sticky solid; yield: 36 mg (58%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.54 (dd, J = 5.3, 3.1 Hz, 2 H), 7.44 (q, J = 4.8 Hz, 3 H), 7.35–7.33 (m, 2 H), 7.26–7.16 (m, 3 H), 6.89 (d, J = 3.6 Hz, 1 H), 6.72 (d, J = 1.4 Hz, 1 H), 6.29–6.27 (m, 1 H), 4.23–4.19 (m, 2 H), 4.08–4.05 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 140.0, 138.4, 134.5, 130.5, 130.3, 129.1, 128.5, 128.2, 127.4, 126.8, 126.6, 122.9, 121.3, 109.8, 106.7, 43.9, 42.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{21}$H$_{18}$N$_3$: 312.1495; found: 312.1505.

5,6-Dihydropyrrolo[1,2-*a*][1,2,4]triazolo[5,1-*c*]pyrazine (2h)

Brown powder; yield: 15 mg (48%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.89 (d, J = 2.6 Hz, 1 H), 6.83 (d, J = 4.7 Hz, 2 H), 6.30 (d, J = 2.7 Hz, 1 H), 4.51–4.49 (m, 2 H), 4.40–4.38 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 151.6, 147.3, 123.3, 120.6, 110.6, 109.3, 45.4, 44.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_8$H$_9$N$_4$: 161.0827; found: 161.0823.

6,7-Dihydro-5*H*-benzo[4,5]imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]diazepine (2i)

Brown solid; yield: 32 mg (71%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.78 (dd, J = 1.7, 6.4 Hz, 1 H), 7.29–7.25 (m, 4 H), 6.80 (d, J = 1.8 Hz, 1 H), 6.28–6.26 (m, 1 H), 4.35–4.29 (m, 4 H), 2.57–2.51 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 147.4, 143.3, 135.7, 125.4, 124.2, 122.6, 122.1, 119.2, 114.9, 109.5, 108.9, 48.6, 44.5, 27.9.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{14}$H$_{14}$N$_3$: 224.1182; found: 224.1188.

10,11-Dimethyl-6,7-dihydro-5*H*-benzo[4,5]imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]diazepine (2j)

White solid; yield: 31 mg (62%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.51 (s, 1 H), 7.14–7.13 (m, 1 H), 7.03 (s, 1 H), 6.73 (s, 1 H), 6.24–6.22 (m, 1 H), 4.25–4.20 (m, 4 H), 2.49–2.41 (m, 2 H), 2.38 (s, 3 H), 2.37 (s, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 146.7, 141.9, 134.2, 131.2, 131.2, 124.9, 124.6, 119.4, 114.2, 109.3, 109.2, 48.5, 44.3, 28.0, 20.6, 20.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{16}$H$_{18}$N$_3$: 252.1495; found: 252.1508.

10,11-Dichloro-6,7-dihydro-5*H*-benzo[4,5]imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]diazepine (2k)

Yellow solid; yield: 37 mg (64%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.73 (s, 1 H), 7.28–7.27 (d, J = 3.4 Hz, 1 H), 7.18–7.16 (m, 1 H), 6.75–6.74 (m, 1 H), 6.23–6.21 (m, 1 H), 4.29–4.18 (m, 4 H), 2.51–2.44 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 149.1, 142.8, 135.1, 126.4, 126.1, 125.6, 123.4, 119.9, 115.8, 110.3, 109.7, 48.9, 45.2, 27.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{14}$H$_{12}$Cl$_2$N$_3$: 292.0403; found: 292.0403.

10,11-Dibromo-6,7-dihydro-5*H*-benzo[4,5]imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]diazepine (2l)

Brown solid; yield: 52 mg (69%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.92 (s, 1 H), 7.49 (s, 1 H), 7.18 (dd, J = 1.6, 3.7 Hz, 1 H), 6.76 (d, J = 1.8 Hz, 1 H), 6.24–6.22 (m, 1 H), 4.29–4.27 (m, 2 H), 4.23–4.20 (m, 2 H), 2.51–2.49 (m, 2 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 149.0, 143.8, 136.0, 126.2, 123.3, 123.1, 117.7, 116.8, 116.0, 113.5, 109.8, 49.02, 45.2, 27.3.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{14}$H$_{12}$Br$_2$N$_3$: 379.9392; found: 379.9364.

2,3-Dichloro-6,7-dihydro-5*H*-imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]diazepine (2m)

Brown solid; yield: 25 mg (52%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.87 (dd, J = 1.7, 3.8 Hz, 1 H), 6.70–6.69 (m, 1 H), 6.19–6.17 (m, 1 H), 4.20 (t, J = 6.0 Hz, 2 H), 4.09 (t, J = 6.0 Hz, 2 H), 2.45–2.37 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 140.1, 126.1, 124.3, 123.8, 112.5, 112.0, 109.2, 47.9, 45.5, 27.9.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{10}$H$_{10}$Cl$_2$N$_3$: 242.0246; found: 242.0254.

6,7-Dihydro-5*H*-imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]diazepine-2,3-dicarbonitrile (2n)

Brown solid; yield: 26 mg (58%).

^{1}H NMR (300 Hz, DMSO-d_6): δ = 7.05 (m, 1 H), 6.96–6.94 (m, 1 H), 6.18–6.16 (m, 1 H), 4.39–4.33 (m, 4 H), 2.38–2.36 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 145.3, 127.3, 121.3, 120.9, 115.4, 112.6, 112.0, 109.3, 109.0, 49.1, 48.9, 25.4.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{12}$H$_{10}$N$_5$: 224.0930; found: 224.0935.

2,3-Diphenyl-6,7-dihydro-5*H*-imidazo[1,2-*a*]pyrrolo[2,1-*c*][1,4]diazepine (2o)

Brown solid; yield: 30 mg (46%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.56–7.52 (m, 2 H), 7.48–7.42 (m, 3 H), 7.38–7.34 (m, 2 H), 7.23–7.14 (m, 3 H), 6.92–6.90 (m, 1 H), 6.75–6.74 (m, 1 H), 6.24–6.22 (m, 1 H), 4.21 (t, J = 6.3 Hz, 2 H), 3.85 (t, J = 6.3 Hz, 2 H), 2.36–2.32 (m, 2 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 142.7, 134.7, 131.0, 130.8, 130.6, 129.3, 129.2, 128.6, 128.3, 128.1, 127.1, 126.4, 123.4, 111.4, 108.7, 46.5, 43.0, 29.9.

HRMS (ESI): m/z [M + H]$^+$ calcd for C$_{22}$H$_{20}$N$_3$: 326.1652; found: 326.1645.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691492.

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(21) CCDC 1918664 (**2a**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.