

An straightforward entry to new pyrazolo-fused dibenzo[1,4]diazepines†‡

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A series of novel pyrazolodibenzo[1,4]diazepines has been synthesized with good overall yields. The diarylpyrazole intermediates, with structure similarity to biologically relevant compounds such as currently marketed drugs like rimonabant or celecoxib, were prepared by a tandem sequence amine-exchange/heterocyclization starting from readily available enaminones and arylhydrazines. The key step of this efficient methodology was C_{aryl}-N bond construction, accomplished by a palladium-catalyzed intramolecular *N*-arylation reaction, which was conducted in both homogeneous and polymer-supported versions. Reaction scope of such protocols and recycling of the heterogeneous catalyst were also examined.

Introduction

Among nitrogen heterocycles, the benzodiazepine nucleus is considered a significant pharmacophore in a wide range of biological activities. In fact, several members of this group have demonstrated a broad variety of pharmacological actions mainly based on their special affinity for serotonin (5-HT₂) and acetylcholine receptors.¹ Actually, some derivatives of this family of heterocyclic compounds have been used as anti-inflammatory,² anti-HIV,³ antitumor agents, anxiolytics,⁴ or antibiotics.^{5,6} For instance, clozapine and dibenzepine (Fig. 1) are two dibenzo-1,4-diazepine derivatives with unique effectiveness in treating schizophrenia.⁷

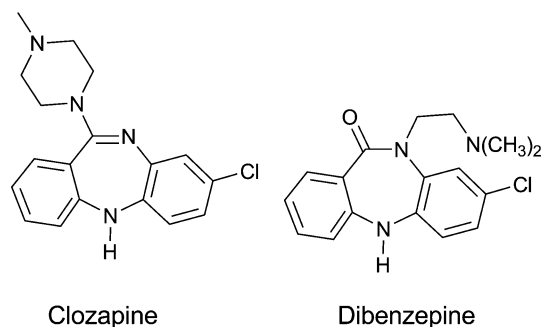


Fig. 1 Biologically relevant dibenzo-1,4-diazepines.

Similarly, pyrazole derivatives constitute another family of heterocyclic compounds with interesting applications in phar-

maceutical, and agrochemical industries.⁸ 1,5-Diarylsubstituted derivatives are particularly active, as demonstrated by rimonabant, a CB1 receptor blocker formerly used to treat obesity disorders and currently assayed in the therapy of Parkinson's disease.^{9,10} Other significant members of this type of compounds are known (e.g. celecoxib, marketed as Celebrex) for their special anti-inflammatory, analgesic and antipyretic activities due to their efficacy as selective inhibitors of cyclo-oxygenase-2 (COX-2) (Fig. 2).^{11,12}

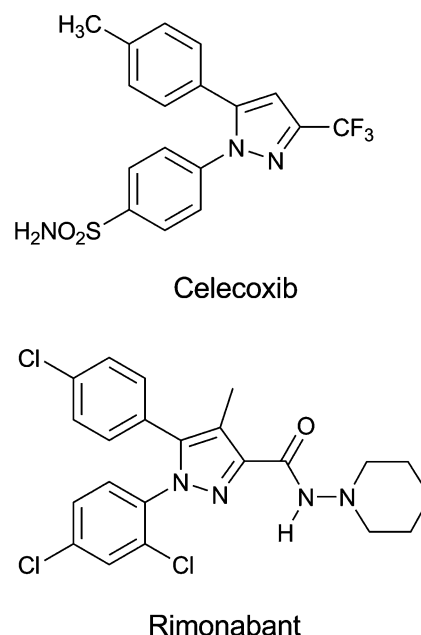


Fig. 2 Two currently marketed drugs containing the 1,5-diarylpyrazole core.

In recent years, it has been established that the fusion of diazepine core to a heterocyclic system, such as triazole,¹³

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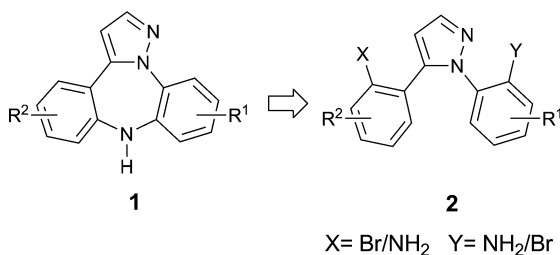
† Electronic supplementary information (ESI) available: Full experimental details about the synthesis and characterization of enaminone, hydrazine and diarylpyrazole intermediates, along with copies of ¹H and ¹³C NMR spectra of diarylpyrazoles and coupling products. See DOI: 10.1039/c0ob00812e

‡ Dedicated to Professor Rafael Suau (recently deceased)

thiophene,¹⁴ pyrrole (PBDs),¹⁵ indole,¹⁶ pyridine¹⁷ or pyrimidine,¹⁸ tends to confer higher activities or novel biological properties. However, despite the inherent interest of the pyrazole ring, no examples of pyrazole fused 1,4-diazepines have been prepared so far.

After the pioneering reports by Buchwald¹⁹ and Hartwig,²⁰ the palladium catalyzed cross-coupling reaction between a nitrogen nucleophile and an aryl halide or pseudohalide has emerged as a crucial tool for the formation of C–N bonds.^{21,22,23} In fact, the intramolecular version of the commonly known Buchwald–Hartwig amination reaction has been employed in the synthesis of several heterocyclic skeletons.²⁴ However, very few examples regarding application of this valuable methodology to the access of 1,4-diazepine derivatives have been reported,^{25,26} probably due to the difficulty derived from the synthesis of a 7-membered ring compared with the access to 5- or 6-member cyclic frameworks.

Following our investigations on the preparation of novel polyheterocyclic derivatives we planned the synthesis of the first series of dibenzo[1,4]diazepines bearing a pyrazole ring fused to the diazepine core. As shown in Scheme 1, we envisaged the access to new dibenzopyrazolodiazepine derivatives **1** through a key step based on an intramolecular amination of conveniently functionalized diarylpyrazole derivatives **2**. That approach would provide a relatively complex tetracyclic system with several potential biological applications due to the fusion of the aforementioned heterocyclic moieties.



Scheme 1

Results and discussion

As shown in Table 1, an amine exchange/heterocyclization sequence was employed for the synthesis of the pyrazole core. In order to circumvent at this initial stage any possible interference with free amino groups, nitro derivatives **5a–i** were elected as suitable precursors, as their reduction would provide haloamines **2** ready for the key intramolecular *N*-arylation step. Thus, treatment of enamines **3a–c**, prepared by aminomethylation of the corresponding *o*-nitroacetophenones with dimethylformamide dimethyl acetal (DMFDMA),²⁷ with a series of *o*-bromoarylhydrazines^{27b} provided diarylpyrazoles **5a–h** with complete regioselectivity (Table 1, entries 1–8). Interestingly, the typical reaction conditions for the aforementioned tandem process (NaOAc/AcOH in refluxing methanol)²⁸ caused decomposition of the starting material without detection of the desired diarylpyrazole. However, the absence of the latter buffering conditions ((NaOAc/AcOH) turned out to be crucial for the reaction outcome. Unfortunately, when enaminoketone **3d** was reacted with nitro-substituted hydrazine **4e** under such optimized conditions, the corresponding pyrazole was

Table 1 Synthesis of nitro-substituted diarylpyrazoles **5**

Entry	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	3	4	5 (%) ^a
1	H	H	H	H	H	NO ₂	Br	3a	4a	5a (94)
2	H	H	F	H	F	NO ₂	Br	3a	4b	5b (95)
3	H	H	H	H	CH ₃	NO ₂	Br	3a	4c	5c (68)
4	H	H	H	CH ₃	H	NO ₂	Br	3a	4d	5d (83)
5	OCH ₃	OCH ₃	H	H	H	NO ₂	Br	3b	4a	5e (97)
6	OCH ₂ O		H	H	H	NO ₂	Br	3c	4a	5f (96)
7	OCH ₂ O		F	H	F	NO ₂	Br	3c	4b	5g (88)
8	OCH ₂ O		H	CH ₃	H	NO ₂	Br	3c	4d	5h (81)
9	H	H	H	H	H	Br	NO ₂	3d	4e	5i (–)

^a Isolated yields of chromatographically pure compound

Table 2 Synthesis of pyrazoles **2** by reduction of nitro derivatives **5**

Entry	R ¹	R ²	R ³	R ⁴	R ⁵	2 (%) ^a
1	H	H	H	H	H	2a (98)
2	H	H	F	H	F	2b (98)
3	H	H	H	H	CH ₃	2c (98)
4	H	H	H	CH ₃	H	2d (98)
5	OCH ₃	OCH ₃	H	H	H	2e (92)
6	OCH ₂ O		H	H	H	2f (93)
7	OCH ₂ O		F	H	F	2g (98)
8	OCH ₂ O		H	CH ₃	H	2h (77)

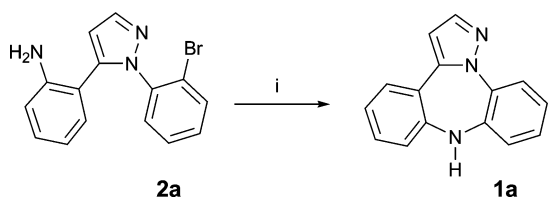
^a Isolated yields of chromatographically pure compound

not detected, presumably due to the strong electron-withdrawing effect of the nitro substituent that would markedly decrease nucleophilicity in hydrazine **4e**.

The next step in the sequence involved a reduction of the nitro group in derivatives **5**. Standard SnCl₂-mediated reduction (SnCl₂ in refluxing methanol) provided an 88% of **2a** from nitroderivative **5a**. However, when the same conditions were applied to **5f**, the corresponding amine **2f** was obtained in a poor 16% yield. Other reducing systems (H₂/Pd–C, NaBH₄, etc.) were also assayed and failed, affording target amines **2** in low to negligible yields. However, as shown in Table 2, Fe powder in acidic media (Fe, AcOH, EtOH)²⁹ turned out to be a far better reducing agent, and amino intermediates **2** were obtained by this method in good to excellent yields.

Pyrazole **2a** was selected as model substrate to perform the initial assays and optimization of the reaction conditions for the

Table 3 Selected intramolecular *N*-arylation assays

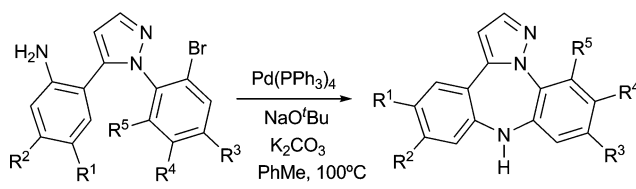
		
Entry	i	Product (%) ^a
1	2 mol% Pd(OAc) ₂ , BINAP, NaO ^t Bu, PhMe, 80 °C, 4d	2a (99)
2	5 mol% Pd(OAc) ₂ , BINAP, Cs ₂ CO ₃ , PhMe, 80 °C, 4d	2a (65) 1a (14)
3	5 mol% Pd ₂ (dba) ₃ , BINAP, NaO ^t Bu, PhMe, 80 °C, 3d	2a (25) 1a (55)
4	5 mol% Pd ₂ (dba) ₃ , BINAP, Cs ₂ CO ₃ , PhMe, 80 °C, 3d	2a (40) 1a (44)
5	5 mol% Pd ₂ (dba) ₃ , DPPF, NaO ^t Bu, PhMe, 105 °C, 15h	2a (20) 1a (65)
6	20 mol% Cu(PPh ₃) ₃ Br, Cs ₂ CO ₃ , PhMe, 110 °C, 2d	2a (45)
7	0.5 mol% (CuOTf) ₂ PhH, phen, Cs ₂ CO ₃ , <i>o</i> -xylene, 130 °C, 2d	2a (99)
8	36 mol% CuCl, phen, KOH, PhMe, 130 °C, 1d	2a (99)
9	5 mol% CuI, K ₃ PO ₄ , HOCH ₂ CH ₂ OH, ^t PrOH, 80 °C, 1d	2a (99)
10	10 mol% Cu(neocup)(PPh ₃) ₄ Br, KO ^t Bu, PhMe, 110 °C, 2d	1a (<5) ^b
11	5 mol% Pd(PPh ₃) ₄ , K ₂ CO ₃ , PhMe, 100 °C, 5h	2a (85) 1a (<5) ^b
12	10 mol% Pd(PPh ₃) ₄ , NaO ^t Bu, K ₂ CO ₃ , PhMe, 100 °C, 2h	1a (94)

^a Isolated yields of chromatographically pure compound. ^b ¹H-NMR yield. Diethylene glycol dimethyl ether was used as internal standard.

cyclization step. Accordingly, an array of different palladium- and copper-based catalytic systems were assayed on the latter substrate to promote the *N*-arylation reaction. The successful use of chelating *bis*(phosphine) ligands in palladium catalyzed amination of aryl halides had been reported.³⁰ However, in our case, poor conversions were obtained when BINAP [2,2'-*bis*(diphenylphosphino)-1,1'-binaphthalene] or DPPF [1,1'-*bis*(phenylphosphino)ferrocene] were used (Table 3, entries 1–5). When the coupling was alternatively attempted by means of several copper sources and ligands,³¹ unreacted starting material was recovered in most cases (entries 6–10). We then turned back to palladium catalysts, this time in the absence of bidentate ligands. Although the use of Pd(PPh₃)₄ did not improve the results (entry 5), we took notice of the beneficial effect of NaO^tBu in the Pd(OAc)₂/DPPF assay (entry 5), so it was decided to try a combination of both bases (K₂CO₃ and NaO^tBu) in a Pd(PPh₃)₄-catalyzed experiment. To our delight, dibenzopyrazolodiazepine **1a** was obtained with an excellent 94% yield under such conditions. Unfortunately, attempts to further reduce the catalyst loading (10 mol%) failed.

Next, in order to examine the scope of the methodology, we applied the optimized conditions to the rest of pyrazoles **2**. As depicted in Table 4, the cyclization was effectively accomplished with substrates bearing no substituent (entries 1 and 6), electron-withdrawing (entries 2 and 7) or electron-donating groups (entries 3, 4 and 8) in the bromoarene moiety. Regarding the *o*-aminoaryl

Table 4 Synthesis of dibenzopyrazolodiazepine derivatives

						
Entry	R ¹	R ²	R ³	R ⁴	R ⁵	1 (%) ^a
1	H	H	H	H	H	1a (94)
2	H	H	F	H	F	1b (75)
3	H	H	H	H	CH ₃	1c (78)
4	H	H	H	CH ₃	H	1d (78)
5	OCH ₃	OCH ₃	H	H	H	1e (0) ^b (88) ^c
6	OCH ₂ O		H	H	H	1f (93)
7	OCH ₂ O		F	H	F	1g (84)
8	OCH ₂ O		H	CH ₃	H	1h (75)

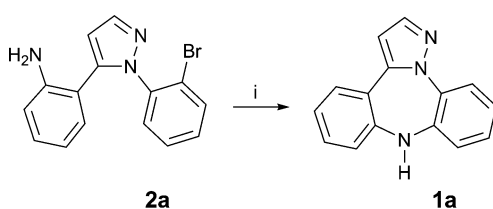
^a Isolated yields of chromatographically pure compound. ^b Only starting material was recovered. ^c 5 mol% Pd₂(dba)₃, DPPF, NaO^tBu, PhMe, 105 °C, 15h.

ring, the intramolecular *N*-arylation reaction was also successfully carried out by using both neutral (entries 1–4) and electron-donating substituents (entries 6–8).

Surprisingly, in spite of its electronic similarity to derivative **2f**, when diarylpyrazole **2e** was submitted to the latter conditions, unreacted starting material was recovered. In this particular case, the use of the conditions assayed in Table 3, entry 5 (5 mol% Pd₂(dba)₃, DPPF, NaO^tBu, toluene) on this rather inert molecule provided the corresponding tetracycle **1e** with good yield, even considering the lower amount of catalyst employed (Table 4, entry 5).

We can conclude that the presented palladium catalyzed intramolecular *N*-arylation is a convenient method for the access to the target tetracyclic skeletons starting from the *o*,*o'*-haloaminodiarylpyrazoles. In fact, the application of this protocol has allowed the effective synthesis of the first series of dibenzodiazepine derivatives bearing a fused pyrazole ring.

In the last decade the search of more sustainable, eco-friendly synthetic methodologies has emerged as an essential field of chemical research. It is well known that, in spite of their high activity and selectivity, the application of homogeneous catalysts is limited principally due to the difficulties arising from catalyst separation steps. In addition, the ligands required to stabilize the transition metal catalyst, typically phosphines, are moisture and air sensitive and consequently need careful handling. In consequence, much effort has been devoted to the search of new heterogeneous catalyst reproducing the high activity and selectivity of the homogeneous counterparts. In this sense, different protocols have been reported such as the anchoring of the metal complex to a polymeric or mineral support,³² liquid phase catalysis,³³ biphasic catalysis,³⁴ or activated carbon as solid support for the catalyst.³⁵ Taking into account our excellent results in the construction of the dibenzodiazepine framework employing homogeneous palladium catalysts, and in order to develop a more sustainable methodology we decided to explore the use of polymer-supported palladium catalysts in this context. We chose FibreCat™ 1001, FibreCat™ 1000-D7 and FibreCat™ 1026 because of the high activity

Table 5 Selected assays for the heterogeneously catalyzed intramolecular *N*-arylation


Entry	i ^a	1a (%) ^b
1	Pd/C, NaO ^t Bu, PhMe, 135 °C, 1d	— ^c
2	Pd/C, NaO ^t Bu, K ₂ CO ₃ , PhMe, 135 °C, 1d	— ^c
3	FC 1001, NaO ^t Bu, K ₂ CO ₃ , PhMe, 100 °C, 1d	<5 ^d
4	FC 1000-D7, NaO ^t Bu, K ₂ CO ₃ , PhMe, 100 °C, 1d	<5 ^d
5	FC 1026, K ₂ CO ₃ , NaO ^t Bu, PhMe, 100 °C, 1d	<5 ^d
6	FC 1001, K ₂ CO ₃ , DMF, 120 °C, 1d	— ^e
7	FC 1001, Cs ₂ CO ₃ , PhMe, 125 °C, 7d	15
8	FC 1000-D7, Cs ₂ CO ₃ , PhMe, 125 °C, 4d	20
9	FC 1026, Cs ₂ CO ₃ , PhMe, 125 °C, 4d	79

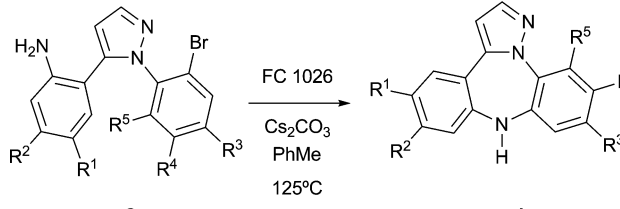
^a A 10 mol% of Pd was employed in all cases. The proportion of FC (%) refers to the relative amount of Pd metal from FC catalyst. ^b Isolated yield of chromatographically pure compound. ^c Starting material was recovered unchanged. ^d Detected by ¹H NMR. ^e A complex mixture was only detected.

exhibited by these commercially available heterogeneous catalysts in other type of coupling reactions.^{36,37}

Again, diaryl derivative **2a** was selected as model substrate to carry out the initial assays. As shown in Table 5, two control experiments were performed with a classic heterogeneous system, Pd on charcoal, and only starting material was recovered (entries 1–2). Slightly better results were achieved when FibreCatTM 1001, FibreCatTM 1000-D7 or FibreCatTM 1026 catalysts were combined with the base system NaO^tBu/K₂CO₃, optimal in the homogeneous version (entries 3–5). To our delight, the change to a weaker, more soluble base (Cs₂CO₃) resulted in a more effective coupling (entries 7–9). From three polymer-supported catalysts FC 1026, which integrates acetonitrile and chloride ligands in its structure,³⁶ showed a highest activity, surpassing significantly that of the other members of the FC 1000 series.

With these promising results in hand, we next attempted the application of the optimized heterogeneous protocol to the synthesis of other dibenzopyrazolodiazepine derivatives. Although a poorer activity for heterogeneous catalysts in comparison with their homogeneous analogues is well documented,^{32–35} in our case, the yields of tetracyclic diazepines **1** obtained by means of polymer-supported FC 1026 were fairly comparable with those from the homogeneous procedure, with the bonus of an easy catalyst recovery by simple filtration. For comparative purposes, isolated yields from both homogeneous and heterogeneous protocols have been displayed in Table 6.

As commented above, one of the benefits associated to the use of heterogeneous catalysts is the possibility of reusing them. Accordingly, several recycling assays were performed in order to restore the activity of the recovered FC 1026 catalyst. The best results were obtained after a treatment³⁸ to regain the aforementioned acetonitrile and chloride ligands, but even in that case significantly lower conversions (45–51%) were observed on the second run. The loss of efficacy of this recycled catalyst was

Table 6 Synthesis of pyrazolodiazepines **1** by using FC 1026 catalyst


Entry	R ¹	R ²	R ³	R ⁴	R ⁵	1 (%) ^{a,b}
1	H	H	H	H	H	1a (79) 94
2	H	H	H	H	CH ₃	1c (70) 78
3	OCH ₃	OCH ₃	H	H	H	1e (80) 80 ^c
4	OCH ₂ O		H	H	H	1f (85) 93

^a Isolated yields from 10 mol% FC 1026, Cs₂CO₃, toluene, 125 °C, shown in parentheses. ^b The isolated yields from the homogeneous procedure (10% Pd(PPh₃)₄, NaO^tBu, K₂CO₃, toluene, 100 °C) are displayed in italics. ^c 5% Pd₂(dba)₃, DPPF, toluene, 105 °C.

probably due to a partial leaching caused by the relatively high temperatures and long reaction times required to carry out the coupling.³⁹

Conclusions

In this paper we have described an efficient synthesis of a series of dibenzopyrazolo[1,4]diazepine derivatives (*e.g.* tetracycle **1a** has been prepared in 82% overall yield starting from commercially available *o*-nitroacetophenone). The access to these promising polycyclic derivatives involved the preparation of conveniently *o,o'*-substituted 1,5-diarylpyrazoles by an effective tandem amine exchange/heterocyclization process using readily available enamines and arylhydrazines. The last step, a palladium-catalyzed intramolecular amination was regioselectively conducted to provide the target system, which constitutes the first example of a dibenzodiazepine skeleton fused to pyrazole ring. The alternative use of polymer-supported heterogeneous FibreCatTM catalysts to perform the key *N*-arylation reaction resulted in comparable yields to those obtained in the homogeneous version and catalyst separation was carried out by simple filtration. Finally, partial recovery and recycling of the latter heterogeneous catalyst allowed a subsequent coupling, although with significantly lower conversion rates.

Experimental section

General methods

All reagents were purchased and used as received. Chemical shifts (δ) are given in ppm downfield from Me₄Si and refer as internal standard to the residual solvent CDCl₃: (δ = 7.26 for ¹H and 77.0 for ¹³C). Coupling constants, *J*, are reported in hertz (Hz). Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO₂, and the spots were located with UV light. Flash chromatography was carried out on SiO₂. Drying of organic extracts during work-up of reactions was performed over anhydrous Na₂SO₄. Evaporation of solvents was accomplished with a rotary evaporator.

Synthesis of dibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]diazepine derivatives 1 by homogeneous palladium catalysis. General procedure. Dry toluene (6 mL) was added to round-bottom flask charged with Pd(OAc)₂ (0.05 mmol), K₂CO₃ (0.8 mmol), NaO^tBu (0.8 mmol), and diarylpyrazole **2** (0.5 mmol) under argon. The suspension was heated to 100 °C for 2 h. After cooling, the crude was diluted with CH₂Cl₂ and filtrated. The solvents were evaporated under reduced pressure, and the so-obtained residue was purified by flash chromatography on silica gel with EtOAc/Hexanes as eluent.

Dibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]diazepine (1a). 94%, white powder, m.p. 148–151 °C (hexanes). ¹H NMR (250 MHz, CDCl₃): δ 5.34 (1H, bs), 6.52 (1H, d, *J* 2.0), 6.84–6.91 (2H, m), 7.00–7.23 (4H, m), 7.47 (1H, dd, *J* 7.5, *J* 1.6), 7.74 (1H, d, *J* 1.6), 7.80 (1H, dd, *J* 7.5, *J* 2.0). ¹³C NMR (63 MHz, CDCl₃): δ 106.6, 119.6, 120.5, 120.9, 123.3, 123.8, 124.1, 127.7, 129.2, 129.9, 132.9, 140.6, 141.3, 142.7, 146.7. IR: 3295, 1612. HRMS: Calcd for C₁₅H₁₁N₃ 233.0953; found 233.0955.

5,7-Difluorodibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]diazepine (1b). 75%, white powder, m.p. 170–175 °C (dec.). ¹H NMR (250 MHz, DMSO-*d*₆): 5.40 (1H, bs), 6.47 (1H, d, *J* 1.6), 6.52–6.57 (1H, m), 6.67–6.76 (1H, m), 6.88–6.91 (1H, m), 7.10–7.16 (1H, m), 7.24–7.31 (1H, m), 7.50 (1H, dd, *J* 1.2, *J* 7.5), 7.80 (1H, d, *J* 2.0). ¹³C NMR (63 MHz, DMSO-*d*₆): 99.9 (dd, *J* 25.1, *J* 25.1), 103.8 (d, *J* 21.5), 106.6 (d, *J* 10.8), 117.7 (dd, *J* 9.0, *J* 3.6), 120.3, 123.7, 129.0, 130.4, 131.8, 141.5, 142.8, 147.3, 156.1 (dd, *J* 298.0, *J* 14.4), 160.1 (dd, *J* 289.0, *J* 14.4). IR: 3342, 1619. HRMS: Calcd for C₁₅H₉F₂N₃ 269.0765; found 269.0765.

7-Methyldibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]diazepine (1c). 78%, yellow powder, m.p. 151–155 °C (pentane). ¹H NMR (250 MHz, CDCl₃): δ 2.30 (1H, s), 5.29 (1H, bs), 6.50 (1H, d, *J* 2.0), 6.70 (1H, s), 6.82–6.85 (1H, m), 6.89–6.92 (1H, m), 6.99–7.06 (1H, m), 7.18–7.24 (1H, m), 7.44–7.48 (1H, m), 7.66–7.69 (1H, m), 7.72 (1H, d, *J* 1.6). ¹³C NMR (63 MHz, CDCl₃): δ 20.7, 106.4, 119.6, 120.9, 121.0, 123.2, 123.9, 124.5, 129.2, 129.9, 130.6, 137.8, 140.4, 141.0, 142.5, 146.8. IR: 3283, 1590. HRMS: Calcd for C₁₆H₁₃N₃ 247.1109; found 247.1109.

6-Methyldibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]diazepine (1d). 78%, yellow powder, m.p. 146–149 °C (pentane). ¹H NMR (250 MHz, CDCl₃): δ 2.32 (1H, s), 5.28 (1H, bs), 6.50 (1H, d, *J* 2.0), 6.75–6.85 (2H, m), 6.95–7.05 (2H, m), 7.18–7.24 (1H, m), 7.44–7.47 (1H, m), 7.63 (1H, s), 7.73 (1H, d, *J* 1.6). ¹³C NMR (63 MHz, CDCl₃): δ 20.5, 106.5, 119.5, 120.3, 120.8, 123.1, 124.4, 128.2, 129.1, 129.8, 132.6, 133.6, 138.1, 141.1, 142.8, 147.1. IR: 3295, 1590. HRMS: Calcd for C₁₆H₁₃N₃ 247.1109; found 247.1108.

11,12-Methylenedioxydibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]diazepine (1f). 93%, yellow powder, m.p. 170–173 °C (MeOH). ¹H NMR (250 MHz, CDCl₃): δ 5.07 (1H, bs), 5.95 (2H, s), 6.42 (1H, d, *J* 2.0), 6.43 (1H, s), 6.86–6.89 (1H, m), 6.89 (1H, s), 7.08–7.21 (2H, m), 7.71 (1H, d, *J* 2.0), 7.77 (1H, dd, *J* 7.5, *J* 1.6). ¹³C NMR (63 MHz, CDCl₃): δ 101.4, 101.6, 105.9, 108.2, 113.8, 120.4, 124.1, 127.6, 133.3, 141.2, 141.8, 142.7, 144.0, 149.2. IR: 3295, 1502. HRMS: Calcd for C₁₆H₁₁N₃O₂ 277.0851; found 277.0852.

5,7-Difluoro-11,12-methylenedioxydibenzo[*b,f*]pyrazolo [1,5-*d*][1,4]diazepine (1g). 84%, yellow powder, m.p. 164–170 °C (dec.). ¹H NMR (250 MHz, DMSO-*d*₆): δ 5.13 (1H, bs), 5.97 (2H, s), 6.37 (1H, d, *J* 2.0), 6.45 (1H, s), 6.69 (1H, dd, *J* 8.3, *J*

2.8), 6.93 (1H, s), 7.18 (1H, dd, *J* 7.9, *J* 2.8), 7.77 (1H, d, *J* 1.6). ¹³C NMR (63 MHz, DMSO-*d*₆): δ 100.0 (dd, *J* 25.1, *J* 25.2), 101.8, 103.7 (d, *J* 23.3), 106.1, 107.9, 113.1, 117.9 (dd, *J* 9.0, *J* 3.6), 141.3, 142.4, 142.9, 143.9, 148.9, 156.0 (dd, *J* 303.4, *J* 14.4), 160.0 (dd, *J* 294.4, *J* 14.4). IR: 3307, 1613. HRMS: Calcd for C₁₆H₉F₂N₃O₂ 313.0663; found 313.0667.

6-Methyl-11,12-methylenedioxydibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]diazepine (1h). 75% brownish powder, m.p. 196–199 °C (pentane). ¹H NMR (250 MHz, CDCl₃): δ 2.32, 5.00 (1H, bs), 5.94 (2H, s), 6.40 (1H, d, *J* 1.2), 6.41 (1H, s), 6.75–6.78 (1H, m), 6.88 (1H, s), 6.95–6.98 (1H, m), 7.58–7.69 (2H, m, H-2). ¹³C NMR (63 MHz, CDCl₃): δ 20.6, 101.2, 101.5, 105.9, 108.2, 113.8, 120.3, 124.4, 128.2, 132.9, 133.9, 138.7, 141.0, 142.2, 142.8, 143.9, 149.1. IR: 3283, 1508. HRMS: Calcd for C₁₇H₁₃N₃O₂ 291.1008; found 291.1006.

Synthesis of 11,12-dimethoxydibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]diazepine (1e). Dry toluene (6 mL) was added to round-bottom flask charged with Pd₂(dba)₃ (0.015 mmol), DPPF (0.02 mmol), NaO^tBu (0.4 mmol), and diarylpyrazole **2** (0.25 mmol) under argon. The suspension was heated at 110 °C for 24 h. After cooling, the crude was diluted with CH₂Cl₂ and filtrated. The solvents were evaporated under reduced pressure, and the so-obtained residue was purified by flash chromatography on silicagel with 60% EtOAc/hexanes as eluent to provide diazepine **1e** as a white powder. 88%, m.p. 160–163 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃): δ 3.86 (6H, s), 5.21 (1H, bs), 6.41 (1H, s), 6.43 (1H, d, *J* 2.0), 6.87 (1H, dd, *J* 1.6, *J*), 6.91 (1H, s), 6.91–7.18 (2H, m), 7.71 (1H, d, *J* 2.0), 7.77 (1H, dd, *J* 1.6, *J* 7.5). ¹³C NMR (63 MHz, CDCl₃): δ 55.9, 56.4, 103.7, 105.6, 111.8, 112.5, 120.3, 123.8, 124.1, 127.6, 133.0, 140.6, 141.1, 141.3, 142.8, 145.2, 150.5. IR: 3342, 1601. HRMS: Calcd for C₁₇H₁₅N₃O₂ 293.1164; found 293.1164.

Synthesis of dibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]diazepine derivatives 1 by heterogeneous palladium-catalyzed *N*-arylation. General procedure. Dry toluene (6 mL) was added to round-bottom flask charged with polymer-supported catalyst FC 1026 (0.03 mmol), Cs₂CO₃ (0.64 mmol), and diarylpyrazole **2** (0.32 mmol) under argon. The suspension was heated at 125 °C for 4 days. After cooling, the crude was diluted with CH₂Cl₂ (30 mL) and filtrated. The solvents were evaporated under reduced pressure, and the so-obtained residue was purified by flash chromatography on silicagel with EtOAc/Hexanes as eluent.

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