Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 2251

www.rsc.org/obc

PAPER

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

Susana Hernández, Isabel Moreno, Raul SanMartin,* María Teresa Herrero and Esther Domínguez*

Received 1st October 2010, Accepted 22nd December 2010
DOI: 10.1039/c0ob00812e

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-HT_2) 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]

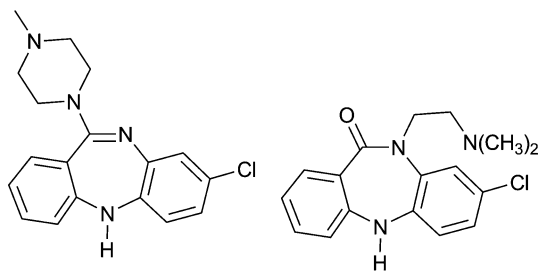


Fig. 1 Biologically relevant dibenzo-1,4-diazepines.

Similarly, pyrazole derivatives constitute another family of heterocyclic compounds with interesting applications in pharmaceutical, 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 or 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]

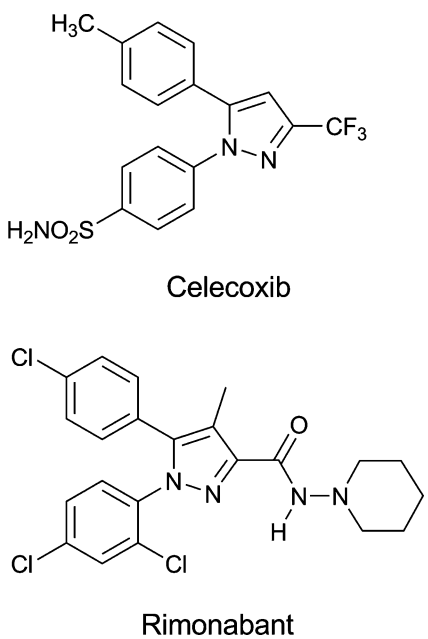


Fig. 2 Two currently marketed drugs containing the 1,5-diarylpyrazole core.

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

Kimika Organikoa II Saila, Zientzia eta Teknologia Fakultatea, Euskal Herriko Unibertsitatea, PO Box 644, 48080, Bilbao, Spain. E-mail: raul.sanmartin@ehu.es; Fax: +34 946012748; Tel: +34 946015435

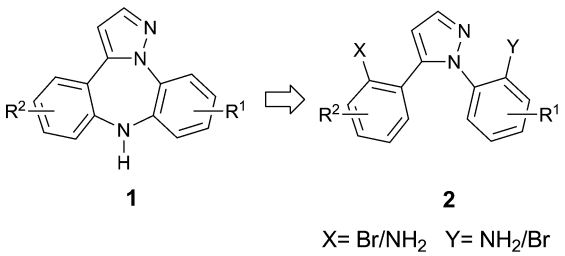
† Electronic supplementary information (ESI) available: Full experimental details about the synthesis and characterization of enaminone, hydrazine and diarylpyrazole intermediates, along with copies of ^{1}H and ^{13}C NMR spectra of diarylpyrazoles and coupling products. See DOI: 10.1039/c0ob00812e

‡ Dedicated to Professor Rafael Suau (recently deceased)

thiophene,[14] pyrrole (PBDs),[15] indole,[16] pyridine[17] 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 Buchwald[19] 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.

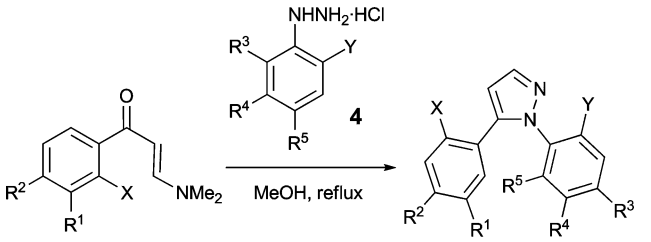


Scheme 1

Results and discussion

As shown in Table 1, an amine exchange/heterocyclation 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 enaminones **3a–c**, prepared by aminomethylenation 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 not detected, presumably due to the strong electron-withdrawing effect of the nitro substituent that would markedly decrease nucleophilicity in hydrazine **4e**.

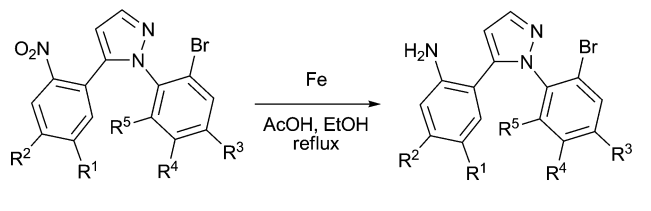
Table 1 Synthesis of nitro-substituted diarylpyrazoles **5**



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_2O		H	H	H	NO_2	Br	**3c**	**4a**	**5f** (96)
7	OCH_2O		F	H	F	NO_2	Br	**3c**	**4b**	**5g** (88)
8	OCH_2O		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**



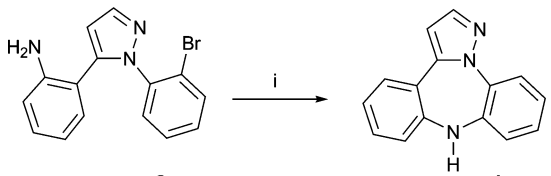
Entry	R^1	R^2	R^3	R^4	R^5	2 (%)[a]
1	H	H	H	H	H	**2a** (98)
2	H	H	F	H	F	**2b** (98)
3	H	H	H	H	CH_3	**2c** (98)
4	H	H	H	CH_3	H	**2d** (98)
5	OCH_3	OCH_3	H	H	H	**2e** (92)
6	OCH_2O		H	H	H	**2f** (93)
7	OCH_2O		F	H	F	**2g** (98)
8	OCH_2O		H	CH_3	H	**2h** (77)

[a] Isolated yields of chromatographically pure compound

The next step in the sequence involved a reduction of the nitro group in derivatives **5**. Standard $SnCl_2$-mediated reduction ($SnCl_2$ 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 (H_2/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

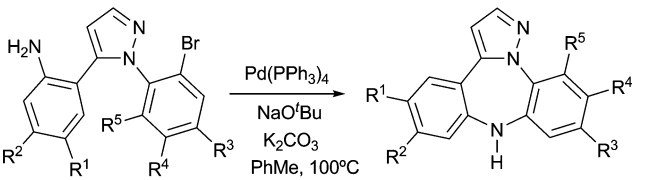


2a **1a**

Entry	i	Product (%)[a]
1	2 mol% $Pd(OAc)_2$, BINAP, NaO^tBu, PhMe, 80 °C, 4d	**2a** (99)
2	5 mol% $Pd(OAc)_2$, BINAP, Cs_2CO_3, PhMe, 80 °C, 4d	**2a** (65) **1a** (14)
3	5 mol% Pd_2 (dba)$_3$, BINAP, NaO^tBu, PhMe, 80 °C, 3d	**2a** (25) **1a** (55)
4	5 mol% Pd_2 (dba)$_3$, BINAP, Cs_2CO_3, PhMe, 80 °C, 3d	**2a** (40) **1a** (44)
5	5 mol% Pd_2 (dba)$_3$, DPPF, NaO^tBu, PhMe, 105 °C, 15h	**2a** (20) **1a** (65)
6	20 mol% $Cu(PPh_3)_3Br$, Cs_2CO_3, PhMe, 110 °C, 2d	**2a** (45)
7	0.5 mol% $(CuOTf)_2PhH$, phen, Cs_2CO_3, *o*–xylene, 130 °C, 2d	**2a** (99)
8	36 mol% CuCl, phen, KOH, PhMe, 130 °C, 1d	**2a** (99)
9	5 mol% CuI, K_3PO_4, $HOCH_2CH_2OH$, ^{i}PrOH, 80 °C, 1d	**2a** (99)
10	10 mol% Cu(neocup)$(PPh_3)_4Br$, KO^tBu, PhMe, 110 °C, 2d	**1a** (<5)[b]
11	5 mol% $Pd(PPh_3)_4$, K_2CO_3, PhMe, 100 °C, 5h	**2a** (85) **1a** (<5)[b]
12	10 mol% $Pd(PPh_3)_4$, NaO^tBu, K_2CO_3, PhMe, 100 °C, 2h	**1a** (94)

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

Table 4 Synthesis of dibenzopyrazolodiazepine derivatives



2a-h **1a-h**

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_2O		H	H	H	**1f** (93)
7	OCH_2O		F	H	F	**1g** (84)
8	OCH_2O		H	CH_3	H	**1h** (75)

[a] Isolated yields of chromatographically pure compound. [b] Only starting material was recovered. [c] 5 mol% Pd_2 (dba)$_3$, DPPF, NaO^tBu, PhMe, 105 °C, 15h.

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 $Pd(PPh_3)_4$ 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 (K_2CO_3 and NaO^tBu) in a $Pd(PPh_3)_4$-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.

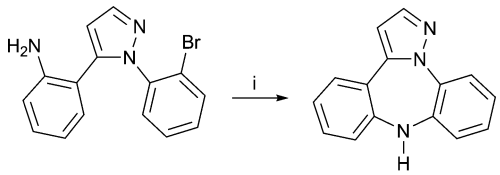
Next, in order to examine the scope of the methodology, we applied the optimized conditions to the rest of pyrazoles **2**. As depicted in Table 4, the cyclization was effectively accomplished with substrates bearing no substituent (entries 1 and 6), electron-withdrawing (entries 2 and 7) or electron-donating groups (entries 3, 4 and 8) in the bromoarene moiety. Regarding the *o*-aminoaryl 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% Pd_2 (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 dibenzo-1,4-diazepine 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



2a **1a**

Entry	i[a]	**1a** (%)[b]
1	Pd/C, NaO^{t}Bu, PhMe, 135 °C, 1d	—[c]
2	Pd/C, NaO^{t}Bu, K_2CO_3, PhMe, 135 °C, 1d	—[c]
3	FC 1001, NaO^{t}Bu, K_2CO_3, PhMe, 100 °C, 1d	<5[d]
4	FC 1000-D7, NaO^{t}Bu, K_2CO_3, PhMe, 100 °C, 1d	<5[d]
5	FC 1026, K_2CO_3, NaO^{t}Bu, PhMe, 100 °C, 1d	<5[d]
6	FC 1001, K_2CO_3, DMF, 120 °C, 1d	—[e]
7	FC 1001, Cs_2CO_3, PhMe, 125 °C, 7d	15
8	FC 1000-D7, Cs_2CO_3, PhMe, 125 °C, 4d	20
9	FC 1026, Cs_2CO_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 ^{1}H NMR. [e] A complex mixture was only detected.

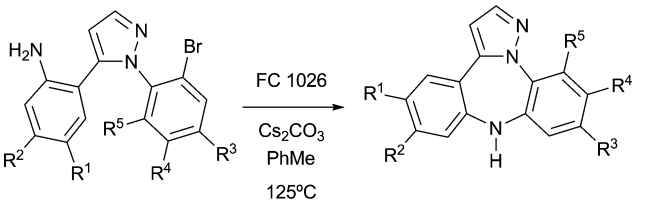
exhibited by these commercially available heterogeneous catalysts in other type of coupling reactions.[36,37]

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 FibreCat™ 1001, FibreCat™ 1000-D7 or FibreCat™ 1026 catalysts were combined with the base system NaO^{t}Bu/K_2CO_3, optimal in the homogeneous version (entries 3–5). To our delight, the change to a weaker, more soluble base (Cs_2CO_3) 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 treatment[38] 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 probably due to a partial leaching caused by the relatively high temperatures and long reaction times required to carry out the coupling.[39]

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



2 **1**

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_2O		H	H	H	**1f** (85) *93*

[a] Isolated yields from 10 mol% FC 1026, Cs_2CO_3, toluene, 125 °C, shown in parentheses. [b] The isolated yields from the homogeneous procedure (10% $Pd(PPh_3)_4$, NaO^{t}Bu, K_2CO_3, toluene, 100 °C) are displayed in italics.. [c] 5% $Pd_2(dba)_3$, DPPF, toluene, 105 °C.

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 enaminones 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 FibreCat™ 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 Me_4Si and refer as internal standard to the residual solvent $CDCl_3$: (δ = 7.26 for ^{1}H and 77.0 for ^{13}C). Coupling constants, *J*, are reported in hertz (Hz). Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2, and the spots were located with UV light. Flash chromatography was carried out on SiO_2. Drying of organic extracts during work-up of reactions was performed over anhydrous Na_2SO_4. 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), K_2CO_3 (0.8 mmol), NaO^tBu (0.8 mmol), and diarylpyrazole **2** (0.5 mmol) under argon. The suspension was heated to 100 °C for 2h. After cooling, the crude was diluted with CH_2Cl_2 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). ^{1}H NMR (250 MHz, $CDCl_3$): 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). ^{13}C NMR (63 MHz, $CDCl_3$): 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 $C_{15}H_{11}N_3$ 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.). ^{1}H 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). ^{13}C 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 $C_{15}H_9F_2N_3$ 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). ^{1}H NMR (250 MHz, $CDCl_3$): 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). ^{13}C NMR (63 MHz, $CDCl_3$): 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 $C_{16}H_{13}N_3$ 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). ^{1}H NMR (250 MHz, $CDCl_3$): 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). ^{13}C NMR (63 MHz, $CDCl_3$): 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 $C_{16}H_{13}N_3$ 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). ^{1}H NMR (250 MHz, $CDCl_3$): 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). ^{13}C NMR (63 MHz, $CDCl_3$): 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 $C_{16}H_{11}N_3O_2$ 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.). ^{1}H 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). ^{13}C 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 $C_{16}H_9F_2N_3O_2$ 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). ^{1}H NMR (250 MHz, $CDCl_3$): 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). ^{13}C NMR (63 MHz, $CDCl_3$): 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 $C_{17}H_{13}N_3O_2$ 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 $Pd_2(dba)_3$ (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 CH_2Cl_2 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 (Et_2O).^{1}H NMR (250 MHz, $CDCl_3$): 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). ^{13}C NMR (63 MHz, $CDCl_3$): 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 $C_{17}H_{15}N_3O_2$ 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), Cs_2CO_3 (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 CH_2Cl_2 (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.

Acknowledgements

This research was supported by the University of the Basque Country/Basque Government (Project GIU06/87/IT-349-07 and S-PC08UN04) and the Spanish Ministry of Education and Science (MEC CTQ2010-20703). S.H. thanks the University of the Basque Country (UPV/EHU) for a predoctoral scholarship. The authors also thank Petronor, S.A. for generous donation of hexane. Finally, technical and human support provided by SGIker (UPV/EHU, MICINN, GV/EJ, ESF) is gratefully acknowledged.

Notes and references

1 (*a*) J. A. Vida, in *Medicinal Chemistry Part III*M. V. Wolf and A. Burger, ed.; Wiley: New York, 1981; (*b*) J. K. Landquist, in

*Comprehensive Heterocyclic Chemistry*A. R. Katrizky and C. W. Rees, Eds; Pergamon: Oxford, 1984; Vol 1., Ch. 1/06; (*c*) J. T. Sharp, in *Comprehensive Heterocyclic Chemistry*A. R. Katrizky and C. W. Rees, Eds; Pergamon: Oxford, 1984; Vol 7., Ch. 5/18; (*d*) R. Baldessarini, in *The Pharmacologic Basis of Therapeutics*A. G. Gilman, L. S. Goodman, T. W. Ralland and F. Murand, ed.; MacMillan: New York, 1985; Vol 1, pp 391–413; (*e*) R. Ramajayan, R. Girdhar and M. R. Yadav, *Mini-Rev. Med. Chem.*, 2007, **7**, 793–812.

2 Y. Shimada, N. Taniguchi, A. Matsuhisa, K. Sakamoto, T. Yatsu and A. Tanaka, *Chem Pharm. Bull*, 2000, **48**, 1644–1651.

3 A. L. Sabb, R. L. Vogel, G. S. Welmaker, J. E. Sabalski, J. Coupet, J. Dunlop, S. Rosenzweig-Lipson and B. Harrison, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2603–2607.

4 See for example: B. Petit-Demouliere, F. Masse, N. Cogrel, M. Hascoet and M. Bourin, *Behav. Brain Res.*, 2009, **204**, 200–205.

5 D. E. Thurston, in *Molecular Aspects of Anticancer Drug-DNA Interactions*S. Needle and M. J. Waring, ed.; The Macmillan Press Ltd.: London, UK, 1993; Vol. 1, pp 54–88.

6 A. Kamal, N. Shankaraiah, S. Prabhakar, C. R. Reddy, N. Markandeya, K. Laxma and X. Devaiah, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2434–2439.

7 (*a*) J. Ip, J. X. Wilson and J. P. Uetrecht, *Chem. Res. Toxicol.*, 2008, **21**, 869–873; (*b*) A. Bali, S. Malhotra, H. Dhir, A. Kumar and A. Sharma, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3041–3044.

8 (*a*) C. Lamberth, *Heterocycles*, 2007, **71**, 1467–1502; (*b*) W. Zheng, S. R. Yates and S. K. Papiernik, *J. Agric. Food Chem.*, 2008, **56**, 7367–7372.

9 Diaryl heterocycles in general are a selective class of COX-2 inhibitors. See: P. Chavatte, S. Yous, C. Marot, N. Baurin and D. Lesieur, *J. Med. Chem.*, 2001, **44**, 3223–3230.

10 (*a*) J. Kelsey, O. Harris and J. Cassin, *Behav. Brain Res.*, 2009, **203**, 304–307; (*b*) V. K. Kotagiri, S. Suthrapu, J. M. Reddy, C. P. Rao, V. Bollugoddu, A. Bhattacharya and R. Bandichhor, *Org. Process Res. Dev.*, 2007, **11**, 910–912.

11 (*a*) Other applications of Celecoxib include treatment of preterm labour, osteoarthritis and rheumatoid arthritis, inflammatory bowel disease and duodenal polyposis in familial adenomatous polyposis. See C. S. Stika, G. A. Gross, G. Leguizamon, S. Gerber, R. Levy, A. Mathur, L. M. Bernhard, D. M. Nelson and Y. Sadovsky, *Am. J. Obstet. Gynecol.*, 2002, **187**, 653–660; (*b*) K. Dilger, C. Herrlinger, J. Peters, H. W. Seyberth, H. Scheweer and U. Klotz, *J. Clin. Pharmacol.*, 2002, **42**, 985–994; (*c*) K. M. Woessner, R. A. Simon and D. D. Stevenson, *Arthritis Rheum.*, 2002, **46**, 2201–2206.

12 This type of compounds comprises a class of non-steroidal anti-inflammatory drugs (NSAID). See for example: (*a*) J. P. O'Connor and T. Lysz, *Drugs of Today*, 2008, **44**, 693–709; (*b*) U. Taeuber, *Drugs Exp. Clin. Res.*, 1990, **16**, 7–15; (*c*) A. G. Habeeb, P. N. Praveen and E. E. Knaus, *J. Med. Chem.*, 2001, **44**, 3039–3042; (*d*) H. Liu, X. Huang, J. M. Shen, X. Luo, M. Li, B. Xiong, G. Chen, J. Shen, Y. Yang, H. Jiang and K. Chen, *J. Med. Chem.*, 2002, **45**, 4816–4827; (*e*) S. K. Singh, S. Vobbalareddy, S. Shivaramakrishna, A. Krishnamraju, S. A. Rajjak, S. R. Casturi, V. Akhila and Y. K. Rao, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1683–1688; (*f*) A. Weber, A. Casini, A. Heine, D. Kuhn, C. T. Sapuran, A. Scozzafava and G. Klebe, *J. Med. Chem.*, 2004, **47**, 550–557.

13 Narayama *et al.* reported the synthesis and anticonvulsant activity of a series of triazolo-fused benzodiapepine derivatives. See: (*a*) B. Narayana, K. K. V. Raj, B. V. Ashalatha and N. S. Kumari, *Eur. J. Med. Chem.*, 2006, **41**, 417–422; (*b*) Later, the same authors described the antianxiety properties and the anticancer activity of some of these derivatives: K. K. V. Raj, B. Narayana, N. S. Kumari, B. V. Ashalatha and B. K. Sarojini, *Journal of Pharmacology and Toxicology*, 2006, **1**, 471–477.

14 It is well known the pharmacological activity of some thieno-fused diazepines such as *clotiazepam*, *brotizolam* and *etizolam*. See for example: V. Lisowsky, F. Fabis, A. Pierre, D. H. Caignard, P. Renard and S. Rault, *J. Enzyme Inhib. Med. Chem.*, 2002, **17**, 403–407.

15 Some pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) such us DC-81, tomamycin and anthramycin are naturally occurring anticancer antibiotics produced by some species of *Streptomyces* bacteria. See: (*a*) A. Kamal, D. Rajender, D. R. Reddy, M. K. Reddy, G. Balakishan, T. B. Shaik, M. Chourasia and G. N. Sastry, *Bioorg. Med. Chem.*, 2009, **17**, 1557–1572; (*b*) W. P. Hu, J. J. Liang, Ch. L. Kao, Y. Ch. Chen, Ch. Y. Chung, F. Y. Tsai, M. J. Wu, L. S. Chang, Y. L. Chen and J. J. Wang, *Bioorg. Med. Chem.*, 2009, **17**, 1172–1182.

16 See for example: Y. Ohta, H. Chiba, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2008, **10**, 3535–3538 and references cited therein.

17 Pirenzepine is a pyridobenzodiazepine with multiple biological activities. See for example: B. Ilien, N. Glasser, J.-P. Clamme, P. Didier, E. Piemont, R. Chinnappan, S. B. Daval, J.-L. Galzi and Y. Mely, *J. Biol. Chem.*, 2009, **284**, 19533–19543.

18 (*a*) B. Insuasty, F. Orozco, J. Quiroga, R. Abonia, M. Nogueras and J. Cobo, *Eur. J. Med. Chem.*, 2008, **43**, 1955–1962; (*b*) B. Insuasty, F. Orozco, C. Lizarazu, J. Quiroga, R. Abonia, M. Hursthouse, M. Nogueras and J. Cobo, *Bioorg. Med. Chem.*, 2008, **16**, 8492–8500.

19 A. Guram, R. A. Rennels and S. L. Buchwald, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1348–1350.

20 J. Louis and J. F. Hartwig, *Tetrahedron Lett.*, 1995, **36**, 3609–3612.

21 For a revision on the Buchwald–Hartwig reaction see: (*a*) D. Prim, J.-M. Campagne, D. Joseph and B. Andrioletti, *Tetrahedron* 2002, 58, 2041–2075; (*b*) A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, **219**, 131–209.

22 The Buchwald–Hartwig amination from an industrial point of view is described in: B. Schlummer and U. Scholz, *Adv. Synth. Catal.*, 2004, **346**, 1599–1626.

23 The Buchwald–Hartwig cross-coupling reaction has been used in pharmaceutical synthesis, natural product synthesis, and material science. A very good revision of these applications in: D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 6338–6361.

24 The synthesis of indoles or indolines by the Buchwald–Hartwig aimantion is described in: (*a*) J. A. Brown, *Tetrahedron Lett.*, 2000, **41**, 1623–1626; (*b*) M. Watanabe, T. Yamamoto and M. Nishiyama, *Angew. Chem., Int. Ed.*, 2000, **39**, 2501–2504; (*c*) J. P. Wolfe, R. A. Rennels and S. L. Buchwald, *Tetrahedron*, 1996, **52**, 7525–7546; (*d*) B. H. Yang and S. L. Buchwald, *Org. Lett.*, 1999, **1**, 35–37; (*e*) Preparation of indazoles by this methodology: Y.-M. Zhu, Y. Kiyu and H. Katayama, *Tetrahedron Lett.*, 2002, **43**, 3577–3580; (*f*) J. J. Song and N. K. Yee, *Tetrahedron Lett.*, 2001, **42**, 2937–2940; (*g*) J. J. Song and N. K. Yee, *Org. Lett.*, 2000, **2**, 519–521; (*h*) The access to phenazines by this procedure is described in: T. Emoto, N. Kubosaki, Y. Yamagiwa and T. Kamikawa, *Tetrahedron Lett.*, 2000, **41**, 355–358; (*i*) Synthesis of benzimidazoles: C. T. Brian and S. A. Brunton, *Tetrahedron Lett.*, 2002, **43**, 1893–1895; (*j*) T. Iwaki, A. Yasuhara and T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1505–1510; (*k*) C. Venkatesh, G. S. M. Sundaram, H. Ila and H. Junjappa, *J. Org. Chem.*, 2006, **71**, 1280–1283; (*l*) C. T. Brian and J. T. Steer, *J. Org. Chem.*, 2003, **68**, 6814–6816; (*m*) Synthesis of oxazepines an thiazepines: B. J. Margolis, J. J. Swisorski and B. N. Rogers, *J. Org. Chem.*, 2003, **68**, 644–647; (*n*) Preparation of imidazoles and its benzo- and aza- analogues: K. T. J. Loones, B. U. W. Maes, R. A. Dommisse and G. L. F. Lemiere, *Chem. Commun.*, 2004, 2466–2467; (*o*) Preparation of oxindoles: F. Bonnaterre, M. Bois-Choussy and J. Zhu, *Org. Lett.*, 2006, **8**, 4351–4354.

25 An elegant synthetic route for the access to a series of dibenzodiazepine-11-ones based on an intramolecular amination process was reported in: E. M. Beccalli, G. Broggini, G. Paladino and C. Zoni, *Tetrahedron*, 2005, **61**, 61–68.

26 For the synthesis of 1,4-benzodiazepine-2,5-diones by the combination of an Ugi multicomponent reaction and a palladium catalyzed *N*-arylation, see: (*a*) G. Cuny, M. Bois-Choussy and J. Zhu, *J. Am. Chem. Soc.*, 2004, **126**, 14475–14484; (*b*) C. Kalinsky, M. Umkehrer, G. Ross, J. Kolb, C. Burdack and W. Hiller, *Tetrahedron Lett.*, 2006, **47**, 3423–3426.

27 A recent application of the modified Vilsmeier-Haak reagent DMFDMA is described in: (*a*) F. M. Abdelrazek and N. H. Metwally, *Synth. Commun.*, 2009, **39**, 4088–4099; (*b*) *Ortho*-bromoarylhydrazines 4b–d were prepared by diazotization/reduction of the corresponding anilines. For a related procedure, see: D. Gennet, P. Michel and A. Rassat, *Synthesis*, 2000, 447–451.

28 This tandem has been successfully applied by our group to the synthesis of different heterocycles. See for example: (*a*) E. Domínguez, E. Ibeas, E. Martinez de Marigorta, J. K. Palacios and R. SanMartin, *J. Org. Chem.*, 1996, **61**, 5435–5439; (*b*) R. Olivera, R. SanMartin, F. Churruca and E. Domínguez, *J. Org. Chem.*, 2002, **67**, 7215–7225; (*c*) S. Hernández, R. SanMartin, I. Tellitu and E. Domínguez, *Org. Lett.*, 2003, **5**, 1095–1098.

29 (*a*) V. T. Bandurco, C. F. Schewender, S. C. Bell, D. W. Combs, R. M. Kanojia, S. D. Levine, D. M. Mulvey, M. A. Appollina, M. S. Reed, E. A. Malloy, R. Falotico, J. B. Moore and A. J. Tobia, *J. Med. Chem.*, 1987, **30**, 1421–1426; (*b*) G. Broggini, L. Garanti, G. Molteni, T. Pilati, A. Ponti and G. Zecchi, *Tetrahedron: Asymmetry*, 1999, **10**, 2203–2212.

30 (*a*) J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, 1997, **62**, 1264–1267; (*b*) J. L. Louie, M. S. Driver, B. C. Hamann and J. F. Hartwing, *J. Org. Chem.*, 1997, **62**, 1268–1273; (*c*) J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1144–1157.
31 Copper catalyzed *N*-arylation reactions are reported in: (*a*) H. B. Goodbrand and N.-X. Hu, *J. Org. Chem.*, 1999, **64**, 670–674; (*b*) A. Kiyomori, J.-F. Marcoux and S. L. Buchwald, *Tetrahedron Lett.*, 1999, **40**, 2657–2660; (*c*) R. Gujadhur, D. Venkataraman and J. T. Kintigh, *Tetrahedron Lett.*, 2001, **42**, 4791–4793; (*d*) F. Y. Kwong, A. Klapars and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 581–584; (*e*) The employment of Cu(neocup)(PPh_3)Br and other copper derivatives soluble in organic solvents is described in: R. K. Gujadhur, C. G. Bates and D. Venkataraman, *Org. Lett.*, 2001, **3**, 4315–4317.
32 (*a*) J. Schward, V. P. W. Bohm, M. G. Gardiner, M. Grosche, W. A. Herrmann, W. Hieringer and G. Raudaschl-Sieber, *Chem.–Eur. J.*, 2000, **6**, 1773–1780; (*b*) L. Djakovitch, V. Dufaud and R. Zaide, *Adv. Synth. Catal.*, 2006, **348**, 715–724; (*c*) J. Demel, X. Sujandi, S.-E. Park, J. Cejka and P. Stepnicka, *J. Mol. Catal. A: Chem.*, 2009, **302**, 28–35.
33 (*a*) S. Fugita, Y. Yoshida, B. M. Bhanage, M. Shirai and M. Arai, *J. Mol. Catal. A: Chem.*, 2002, **180**, 277–284; (*b*) B. M. Bhanage, M. Shirai and M. Arai, *J. Mol. Catal. A: Chem.*, 1999, **145**, 69–74.
34 (*a*) R. V. Chaudhari, B. M. Bhanage, R. M. Deshpande and H. Delmas, *Nature*, 1995, **373**, 501–503; (*b*) B. M. Bhanage, Y. Ikushima, M. Shirai and M. Arai, *Tetrahedron Lett.*, 1999, **40**, 6427–6430.
35 P. J. Tambade, Y. P. Patil, M. J. Bhanushali and B. M. Bhanage, *Tetrahedron Lett.*, 2008, **49**, 2221–2224 and references cited therein.
36 The FibreCat 1000 series is commercialized by Johnson Matthey Chemicals. Futher information about FibreCat catalysts, including their application in Suzuki–Miyaura and Mizoroki–Heck coupling reactions, can be found at http://www.chemicals.matthey.com. See also: (*a*) T. J. Colacot, E. S. Gore and A. Kuber, *Organometallics*, 2002, **21**, 3301–3304; (*b*) T. J. Colacot, *Top. Catal.*, 2008, **48**, 91–98; (*c*) T. J. Colacot, W. A. Carole, B. A. Neide and A. Harad, *Organometallics*, 2008, **27**, 5605–4611.
37 Our group has reported the application of FibreCat catalysts in arylation of ketone enolates: (*a*) F. Churruca, R. SanMartin, M. Carril, I. Tellitu and E. Domínguez, *Tetrahedron*, 2004, **60**, 2393–2408; (*b*) F. Churruca, R. SanMartin, I. Tellitu and E. Dominguez, *Eur. J. Org. Chem.*, 2005, 2481–2490; (*c*) In the direct C–H activation reaction: S. Hernández, I. Moreno, R. SanMartin, G. Gómez, M. T. Herrero and E. Domínguez, *J. Org. Chem.*, 2010, **75**, 434–441.
38 After filtration the recovered catalyst was successively washed with aqueous 5% HCl, 10% Na_2CO_3, H_2O, THF and a saturated solution of NaCl in CH_3CN. For, more details see reference 37a.
39 The limit of thermal stability of FibreCat™ series is at around 120 °C. A partial loss of activity on recycling this type of heterogeneous catalyst has been observed in other cross-coupling reactions. See for example references 36–37.