Mild Conditions for Copper-Catalysed *N*-Arylation of Pyrazoles

Henri-Jean Cristau,*[a] Pascal P. Cellier,[a] Jean-Francis Spindler,[b] and Marc Taillefer*[a]

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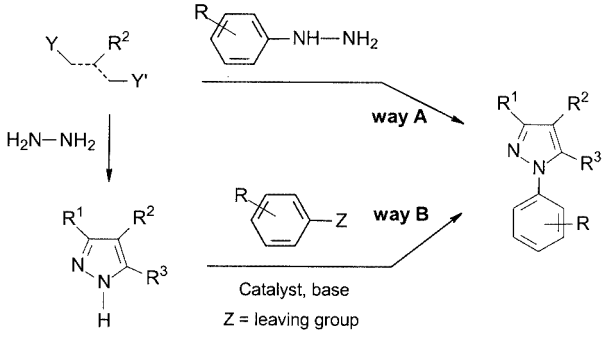
Copper-catalysed *N*-arylation of pyrazoles with aryl or heteroaryl bromides or iodides, which can include functional substituents, was performed under the mildest conditions yet described, with excellent yields and selectivity, by the use as catalyst of a combination of cuprous oxide with a set of inexpensive, chelating oxime-type ligands not previously known to promote such reactions. Other original bi-, tri- or tetradentate ligands providing nitrogen and/or oxygen as chelating atoms were also successfully tested in this type of arylation.

Introduction

N-Arylpyrazoles are particularly interesting synthetic targets as a consequence of their prevalence in numerous agrochemicals and pharmaceuticals.[1] As an example, Celecoxib, a potent and selective COX-2 inhibitor, is a very successful non-steroidal antiinflammatory drug.[2] The *N*-arylpyrazole group is also a structural element present in several leading agrochemicals such as the insecticides Pyraclofos and Fipronil.[3]

The *N*-arylpyrazole structural unit can be obtained by a variety of synthetic methods. Among these, cyclocondensation of *N*-arylhydrazines with various 1,3-difunctionalized compounds is the most commonly used strategy (Scheme 1, pathway A). However, only a limited number of arylhydrazines are commercially available and their preparation from aromatic primary amines as starting materials implies a diazotization−reduction sequence. Although this route has a long industrial background, it is not entirely satisfactory because of its poor volumic productivity and of the thermally instability of aryl diazonium chlorides, which can sometimes be explosive.



Scheme 1. Main synthetic routes to *N*-arylpyrazoles

An alternative method for the preparation of *N*-arylpyrazoles involves the transition metal-catalysed *N*-arylation of 1*H*-pyrazoles (Scheme 1, pathway B). A cobalt-catalysed arylation has thus been reported, but the method employs the poorly available diaryliodonium tetrafluoroborates.[4] Attempts to extend the palladium-catalysed cross-coupling methodology to pyrazoles also failed.[5]

During the past ten years, several reports describing copper-catalysed methods involving various arylating agents − such as arylboronic acids and its anhydride and ester derivatives,[6] aryllead triacetates,[7] aryltrimethylstannanes,[8] triarylbismuth diacetates[9] or diaryliodonium salts[10] − have appeared in the literature. Some of these reagents, synthesized from the corresponding aryl halides, allowed operation under mild conditions but their use is hampered by their poor commercial availability, while their preparation often requires time-consuming multi-step syntheses. Furthermore, these copper-mediated methods often suffer from limitations such as high cost, toxicity, lack of generality, moderate yields and requirement for stoichiometric or greater amounts of copper catalyst, and so none of these new arylation methods has succeeded in supplanting the traditional Ullmann condensation, which uses readily available and cheaper aryl halides in basic medium. This method suffers from drastic reaction conditions, however:[11] condensations have to be conducted at high temperatures (up to 210 °C), sometimes in the presence of stoichiometric amounts of copper reagents. Milder methods involving heteroatom nucleophiles and the use of copper ligands have

[a] UMR 5076 du CNRS, Ecole Nationale Supérieure de Chimie de Montpellier
8 rue de l'Ecole Normale, 34296, Montpellier Cedex 5, France
Fax: (internat.) +33-4-67144319
E-mail: cristau@cit.enscm.fr and taillefe@cit.enscm.fr
[b] Rhodia, Centre de Recherches de Lyon/ISV,
85 av. des Frères Perret − BP 62, 69192 Saint-Fons Cedex, France
Fax: (internat.) +33-4-72896894
E-mail: Jean-Francis.Spindler@eu.rhodia.com

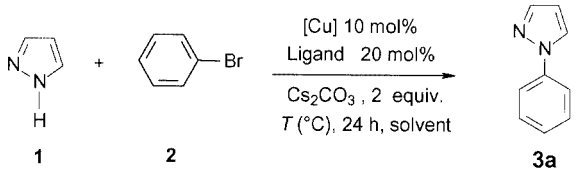
been the focus of several studies.[12−14] As far as pyrazole *N*-arylations are concerned, the mildest method reported to date works at 110 °C with CuI as a precatalyst, racemic *trans*-1,2-diaminocyclohexane as the ligand and an iodoarene (iodo-3,5-dimethylbenzene) as the arylating agent.[15]

Owing to the lack of a mild and general method for the preparation of *N*-arylpyrazoles, there is significant interest in the development of an improved synthesis of these compounds. Here we report our own results in this field, having succeeded in synthesising *N*-arylpyrazoles from readily available, inexpensive aryl bromides or iodides under exceptionally mild conditions (25−82 °C), through the use of air-stable, cheap and commercially available copper-based catalysts. The results, obtained over two years ago,[16] appear in the literature only now due to the time required for patent protection.[17]

Results and Discussion

We have investigated the *N*-arylation of pyrazoles with aryl bromides or iodides in the presence of copper catalysts and a wide range of donor ligands, including members from families known to coordinate copper salts but with no catalytic activity yet reported at this time in the literature, such as Schiff bases, oxazolines, oximes, guanidines, ureas, hydrazides and *N*-heterocyclic carbenes. A series of potential ligands combining diverse electronic and steric properties was carefully selected. This group comprised monodentate or multidentate, hard or soft donor compounds with nitrogen-, oxygen-, phosphorus- or carbon-binding sites, or mixtures thereof.

This search for new suitable ligands for pyrazole arylation was first undertaken for the reaction between bromobenzene **2** and 1.5 equiv. pyrazole **1** in the presence of 10 mol % CuI and 2 equiv. Cs_2CO_3 (Scheme 2, Table 1) in toluene as solvent at 110 °C. Each ligand (20 mol %, based on the limiting reagent) was examined (Scheme 3). We first observed that some ligands (Entries 1−12), never to the best of our knowledge used in Ullmann-type *N*-arylation chemistry, displayed higher activity than 1,10-phenanthroline (Entry 13) and *rac-trans*-1,2-diaminocyclohexane (Entry 14), previously used for the arylation of pyrazole or other nitrogen nucleophiles.[13b,15,18] The most interesting result was the discovery that structurally simple oximes could serve as efficient ligands (the three best compounds tested belong to this family). Thus, owing to their chelating ability, which might contribute to metal stabilization, salicylaldoxime (**4**, salox), dimethylglyoxime (**5**) and 2-pyridinealdoxime (**6**) gave good yields of *N*-phenylpyrazole within 24 h. However, the success achieved with these systems was limited by deactivation of the catalyst, which separated out of the reaction mixture after a few hours, probably due to the poor solubilities of the different metallic complexes involved in the catalytic cycle in toluene. Accordingly, we decided to investigate the effect of solvent on the efficiency of the reaction.



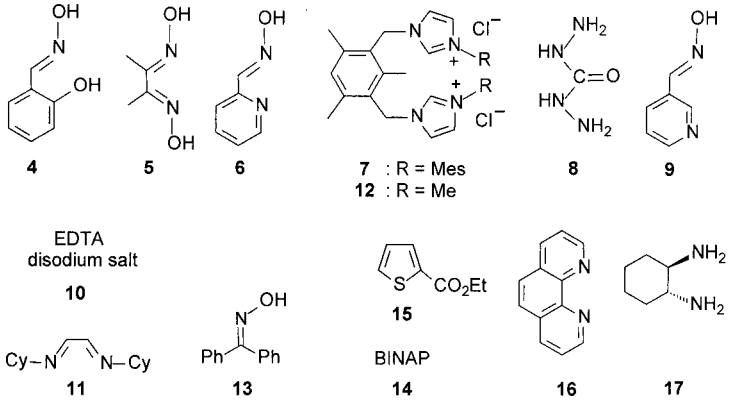
Scheme 2. *N*-Arylation of pyrazole with bromobenzene: influence of ligand, solvent, temperature and nature of the copper precatalyst (Table 1)

The same model reaction was therefore performed in potentially complexing solvents in order to stabilize the copper and to avoid precipitation. Salox (**4**), copper(I) oxide as

Table 1. *N*-Arylation of pyrazole with bromobenzene in toluene at 110 °C: influence of ligands (Entries 1−14);[a] *N*-arylation of pyrazole with bromobenzene in the presence of **4** at 82 °C: influence of solvents (Entries 15−23); influence of the copper precatalysts in acetonitrile (Entries 24−27)[a]

Entry[a]	L	[Cu]	Solvent	*T* (°C)	Yield (%)[b]	Entry	L	[Cu]	Solvent	*T* (°C)	Yield (%)[b]
1	**4**	CuI	toluene	110	60	15	**4**	−	CH_3CN	82	0
2	**5**	CuI	toluene	110	58	16	**4**	Cu_2O	CH_3CN	82	96
3	**6**	CuI	toluene	110	58	17	**4**	Cu_2O	EtCN	82	89
4	**7**	CuI	toluene	110	50	18	**4**	Cu_2O	Pyridine	82	83
5	**8**	CuI	toluene	110	49	19	**4**	Cu_2O	DMF	82	78
6	**9**	CuI	toluene	110	42	20	**4**	Cu_2O	DME	82	77
7	**10**[c]	CuI	toluene	110	40	21	**4**	Cu_2O	BuCN	82	61
8	**11**	CuI	toluene	110	38	22	**4**	Cu_2O	THF[d]	82	52
9	**12**	CuI	toluene	110	38	23	**4**	Cu_2O	toluene	82	13
10	**13**	CuI	toluene	110	33	24	**4**	CuX[e]	CH_3CN	82	96
11	**14**	CuI	toluene	110	31	25	**4**	CuO	CH_3CN	82	89
12	**15**	CuI	toluene	110	22	26	**4**	$CuBr_2$	CH_3CN	82	94
13	**16**	CuI	toluene	110	18	27	**4**	Cu[f]	CH_3CN	82	92
14	**17**	CuI	toluene	110	4						

[a] Reactions were carried out in toluene (300 μL), under N_2, with 0.5 mmol of bromobenzene and 0.75 mmol of pyrazole. Selectivity (*N*-phenylpyrazole yield divided by bromobenzene conversion) was > 96% in all cases. [b] Determined with 1,3-dimethoxybenzene as standard. [c] Dihydrate salt. [d] The same yield was obtained in 2-methylglutaronitrile or adiponitrile as solvent. [e] X = Br or I. [f] Washed with iodine in acetone or precipitated from $CuSO_4$ and Zn.



Scheme 3. Ligands tested under the conditions listed in Scheme 2 and Table 1 (the *syn*/*anti* stereochemistry of the oxime groups was not determined)

catalyst and a more challenging temperature (82 °C) were chosen for the study. As shown in Table 1, aprotic solvents (acetonitrile, pyridine, DME) displaying well recognized complexing properties towards cations seem to favour the *N*-arylation reaction. Thus, an almost quantitative yield of 1-phenylpyrazole (**3a**) was obtained within 24 h in acetonitrile at 82 °C (Table 1, Entry 14: this is the lowest temperature ever reported for an Ullmann-type azole *N*-arylation involving an aryl bromide). This excellent result is probably a function of the ability of acetonitrile to avoid dismutation of copper(I) to copper(0) and copper(II),[19] thus stabilizing the copper(I) oxidation state, which is one of the supposed catalytically active species.[20]

Other solvents incorporating an aliphatic cyano group gave good yields with complete selectivity (Entries 17, 21, 22), but their efficiency decreased with the lengths of their alkyl chains, which can be correlated with the lowering of their dielectric constant. It is also important to note that the reaction performed in toluene at 82 °C gave only low yields (Entry 23) and that no reaction took place in the absence of catalyst (Entry 15).

A survey carried out to determine the influence of the nature of the precatalyst (Table 1; Entries 24−27) showed that the model coupling between pyrazole (**1**) and bromobenzene (**2**) could be conducted in acetonitrile with comparable efficiency in the presence of zerovalent, monovalent or divalent copper sources. This suggests that, under the reaction conditions, copper metal and cupric salts are readily transformed into the same cuprous compound, the supposed catalytically active species.[21] Previous work undertaken in this field has shown that certain nucleophiles can reduce copper(II) salts to copper(I) species (the authors have found evidence of such redox processes with phenol[22] and diphenylamine[23]). By virtue of its lower cost and its insensitivity to light and air, copper(I) oxide was chosen as the catalyst precursor for subsequent experiments.[24]

The choice of cesium carbonate as base also plays an important role, potassium carbonate, potassium *tert*-butoxide and tripotassium phosphate all giving poorer results at 82 °C in the presence of ligands such as **4** or **5** (around 30% in standard conditions). Under more drastic conditions (24 h at 110 °C in DMF), however, we were able to carry out the quantitative formation of 1-phenylpyrazole (**3a**) in the presence of K_2CO_3, a more economically interesting base from the industrial point of view. The superiority of cesium carbonate can be explained in terms of a decrease in the extent of ion-pairing on going from K^+ to Cs^+, favouring the nucleophilic reactivity of the associated anion.[25]

Table 2. Influence of the ligand for the *N*-arylation of pyrazole with bromobenzene; conditions as listed in Scheme 2 with Cu_2O (5 mol %) at 82 °C[a]

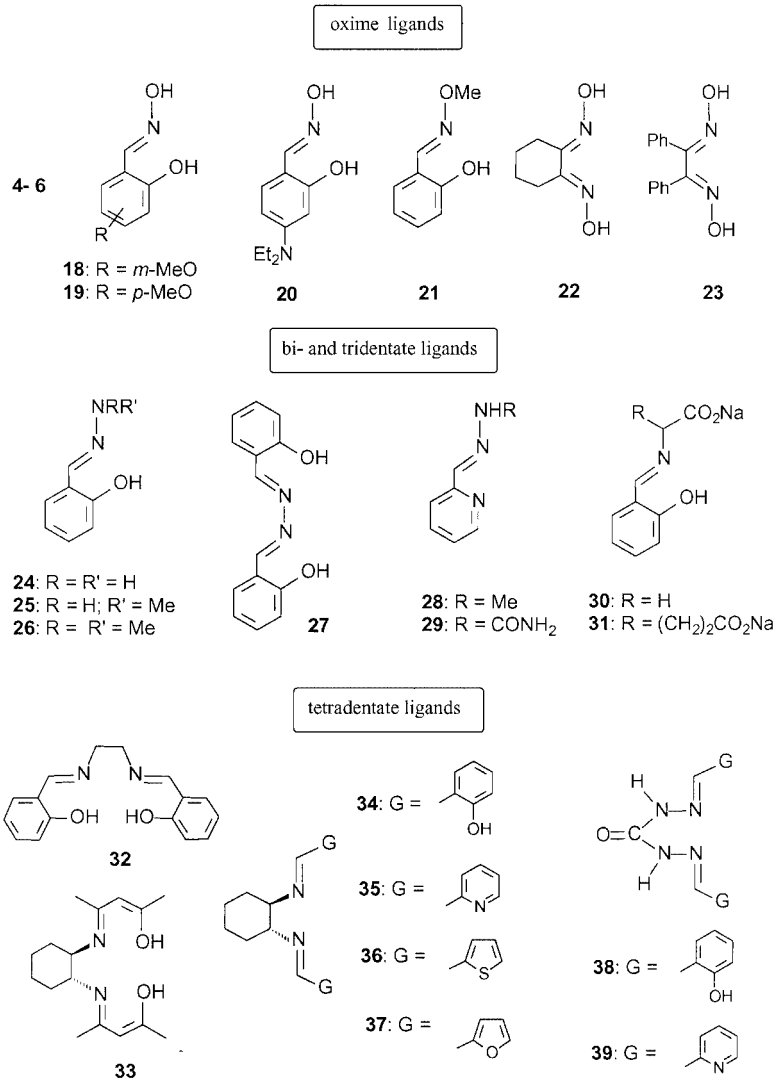
Entry	Oxime ligands	GC yield (%)	Entry	Bi- and tridentate ligands	GC yield (%)	Entry	Tetradentate ligands	GC yield (%)
1	**23**	7	10	**26**	69	18	**37**	17
2	**21**	7	11	**27**	71	19	**33**	41
3	**20**	80	12	**24**	92	20	**32**	47
4	**18**	81	13	**25**	93	21	**36**	80
5	**6**	93	14	**28**	97	22	**34**	92
6	**5**	94	15	**31**	90	23	**35**	93
7	**22**	94	16	**29**	95	24	**8**	54
8	**4**	96	17	**30**	97	25	**39**	73
9	**19**	96				26	**38**	96

[a] Reactions were carried out in acetonitrile (300 μL), under N_2 with 0.5 mmol of bromobenzene and 0.75 mmol of pyrazole; selectivity (*N*-phenylpyrazole yield divided by bromobenzene conversion) was > 97% in all cases.

Moreover, cesium salts are generally more soluble in organic solvents than their potassium counterparts.[26]

The success of salicylaldoxime (**4**) and dimethylglyoxime (**5**) prompted us to examine whether other functionalized oxime or vicinal dioxime ligands could also promote the copper-catalysed *N*-arylation of pyrazole (Table 2; Entries 1−9). Several chelating analogues were synthesized and tested in order to obtain information concerning the key structural features required for binding and for activity. Among the results obtained, it is notable that the pyridine analogue **6** (Entry 5) proved as efficient as the parent compound salox **4**. Moreover, a free oxime hydroxy group and the corresponding in situ formation of an oximate appears necessary, as evidenced by the poor catalytic efficiency displayed by the oxime ether **21** (Entry 2). We also tried to enhance the donating ability of ligands, making them more electron-rich. No effect was observed with a methoxy group located *para* to the hydroxy group (ligand **19**, Entry 9), while electron-donating group substitution *para* to the oxime functionality slightly reduced the catalyst activity (ligands **20** and **18**, Entries 3, 4). As far as vic-dioximes are concerned, the more rigid nioxime® **22** (Entry 7) proved as efficient as dimethylglyoxime (**5**). In contrast, the use of diphenylglyoxime **23** was yield-depressing, probably because of steric and electronic repulsion of the two phenyl rings (Entry 1). Interpretation of the superiority of oxime over previously described ligands is still difficult, since the exact nature of the catalytically active species is not known. However, we can suspect the α-effect[27] related to an oximate group to be one of the key factors responsible for high metal binding affinity and for reaction enhancement.

After study of the oxime family, we focused on a second generation of ligands combining potential nitrogen and/or oxygen chelating atoms. The first category studied involves bidentate ligands **24**−**28** (Scheme 4), analogous to the oximes **4** and **6**, in which the hydroxylamine part has been replaced by a hydrazone group. The very good efficiency observed with these ligands is similar to that seen with the



Scheme 4. Ligands tested under the conditions listed in Scheme 2 and Table 2 (the *syn*/*anti* stereochemistry of the oxime groups was not determined)

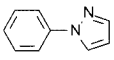
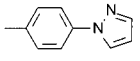
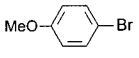
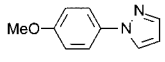
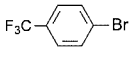
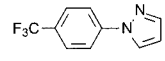
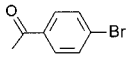
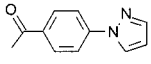
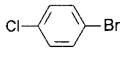
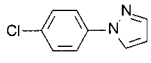
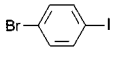
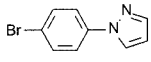
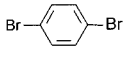
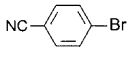
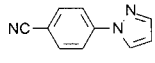
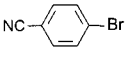
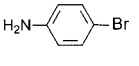
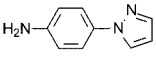
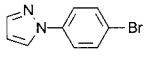
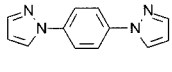
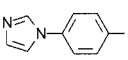
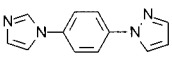
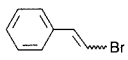
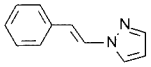
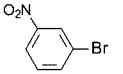
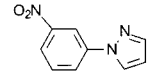
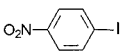
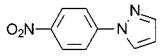
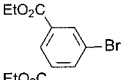
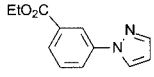
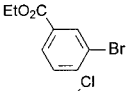
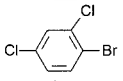
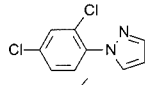
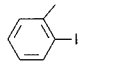
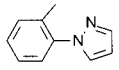
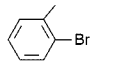
oxime family, particularly when the nitrogen atom of the hydrazone is not doubly substituted (Table 2, Entries 10−14).

The second category tested, the potentially tridentate ligands (Scheme 4), also gave excellent results, the semicarbazone **29**, together with the two ligands **30** and **31** obtained by condensation of α-amino acids with salicylaldehyde and incorporating carboxylate functions, giving very good yields of *N*-phenylpyrazole (Table 3, Entries 15−17).

The third category studied concerns potentially tetradentate ligands (Scheme 4). They can be described as the symmetric combination of two bidentate ligands connected, depending on the case, by ethylene (**32**), cyclohexylidene (**33**−**37**) or carbonyl (**38**, **39**) bridges. One of the best ligands was carbosalzone **38** (Table 2; Entry 26), superior to the pyridine analogue **39** and also to the corresponding potentially bidentate carbohydrazide **8**. In the heterocyclic series **35**−**37**, ligand **35** (Table 3; Entry 23) gave by far the best result, probably because the coordination through the nitrogen site is more efficient than that through the oxygen or the sulfur ones. It is noteworthy that the ligand **34** is much more efficient than the corresponding ligand **32** incorporating an ethylene bridge. This difference in reactivity could correspond to various geometrical requirements around copper, either tetrahedral or square planar.

We have thus identified several families of ligands, including oximes, hydrazones, carbohydrazones, semicarbazones and Schiff bases, that have proved to be very efficient for the copper-catalysed *N*-arylation of pyrazoles with bromobenzene. The use of these ligands allowed the mildest temperature conditions (82 °C) reported until now for the copper-catalysed *N*-arylation of pyrazole with an aryl bromide. The previous best literature results to date are the copper-catalysed *N*-arylation of pyrazoles performed at 110 °C

Table 3. *N*-Copper-catalysed arylation of pyrazole with functionalized aryl bromides or iodides[a]

Entry	ArX	Product		*T* (°C)	*t* (h)	Yield (%) GC (isolated)
1[b]			**3a**	25	90	80
2[b]		"	**3a**	50	90	70
3[b]		"	**3a**	62	24	84
4[b]			**3b**	82	36	97 (95)
5[b]			**3c**	82	40	96 (93)
6[b]			**3d**	82	36	96 (96)
7[b][d]			**3e**	82	24	100 (91)
8[b][e]			**3f**	82	40	96 (93)
9[c][f]			**3g**	82	30	94
10[c][g]		"	**3g**	82	72	89 (82)
11[b]			**3h**	82	24	82
12[c]		"	**33h**	82	24	96 (91)
13[c][h]			**3i**	82	42	98 (91)
14[c][d]			**3j**	82	48	100 (91)
15[c][d]			**3k**	82	48	100 (92)
16[c][i]			**3l**	82	24	100 (96)
17[b][f]			**3m**	82	24	55 (52)
18[c][d]			**3n**	82	24	100 (90)
19[b]			**3o**	82	24	< 1
20[c][j]		"	**3o**	82	24	53 (50)
21[c][g][k]			**3p**	110	48	65 (60)
22[c][h]			**3q**	82	70	100 (94)
23[b]		"	**3q**	82	96	78
24[b][h][k]		"	**3q**	110	48	100
25[b][l]			**3r**	82	24	97 (93)
26[b][h]			**3s**	82	54	100 (92)
27[b][h]			**3t**	82	24	100 (91)
28[b][h]			**3u**	82	28	100 (96)

[a] Reaction conditions: 3 mmol of pyrazole, 2 mmol of ArX, 4 mmol of Cs_2CO_3, 5 mol % Cu_2O, 20 mol % ligand, MeCN (1.2 mL), under N_2. [b] Ligand salox (**4**). [c] Ligand chxn-py-al (**35**). [d] 2 mmol of pyrazole and 2.4 mmol of ArX. [e] 1.7 equiv. Cs_2CO_3. [f] 2 mmol of pyrazole and 4 mmol of ArX. [g] 2 mmol of pyrazole and 8 mmol of ArX. [h] 2 mmol of pyrazole and 3 mmol of ArX. [i] 10 mmol of pyrazole and 15 mmol of β-bromostyrene. [j] Addition of molecular sieves 3Å, 480 mg. [k] In DMF. [l] 15 mmol of pyrazole and 10 mmol of 3-bromopyridine.

with aryl iodides (ligand: *trans*-1,2-diaminocyclohexane).[15] Our conditions are also the mildest reported for the copper-catalysed *N*-arylation of azoles. Indeed, the previous best literature results to date are copper-catalysed indole *N*-arylation with aryl bromides at 110 °C or with the more reactive aryl iodides at 82 °C (ligand: *trans*-1,2-diaminocyclohexane or *trans*-1,2-bis(methylamino)cyclohexane).[28] For aryl iodides, the lowest temperature reported is 110 °C: i) for the *N*-arylation of various nitrogen heterocycles such as pyrazoles, indazoles, 7-azaindoles, phthalazinone, pyrrole, carbazole (ligand: *trans*-1,2-diaminocyclohexane)[15] or ii) for the *N*-arylation of imidazoles (ligand: 1,10-phenanthroline).[13b]

It is noteworthy that, as in toluene (Scheme 2, Table 1, Entries 13, 14), the use of 1,10-phenanthroline and *trans*-1,2-diaminocyclohexane ligands under our experimental conditions (acetonitrile, 82 °C; Scheme 2, Table 2) give a very weak (5%) or only a poor yield (45%), respectively, of *N*-phenylpyrazole (Figure 1).

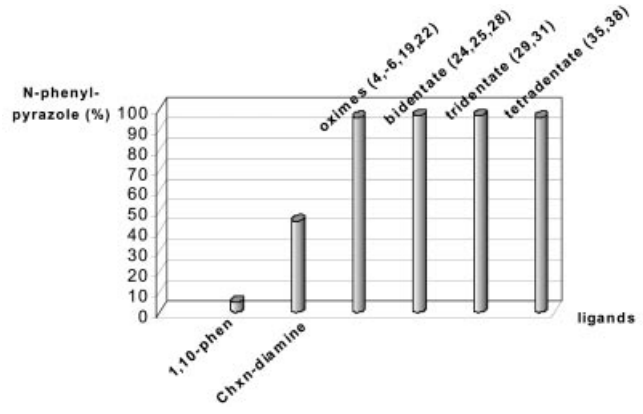


Figure 1. Yields obtained for the best ligands tested in each family and comparison under our experimental conditions (at 82 °C) with 1,10-phenanthroline and *trans*-1,2-diaminocyclohexane (chxn-diamine)

Since temperature is crucial to the reaction outcome, we were also interested in probing this parameter in detail with respect to our system. As can be seen in Figure 2, low conversions of bromobenzene are obtained below 50 °C. A dramatic increase in catalyst efficiency is observed between 50 and 60 °C and the reaction becomes nearly quantitative within 24 h above 70 °C. The other ligands tested, such as **35** or **18**, gave similar results. Kinetic studies revealed that no induction period is involved; 1-phenylpyrazole is beginning to be formed immediately on heating, even at temperatures at which the reaction is sluggish (≈ 50 °C).

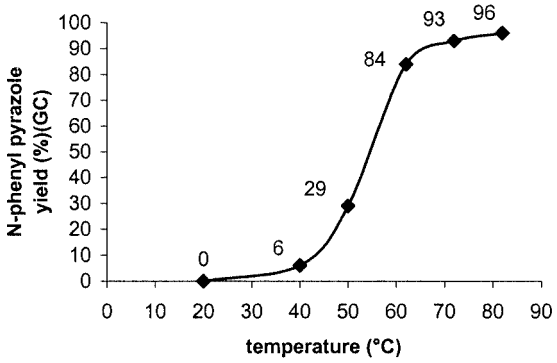
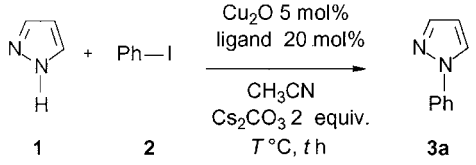


Figure 2. Influence of the temperature on the *N*-arylation of pyrazole with bromobenzene (conditions as listed in Scheme 5. Reaction time 24 h, ligand **4**, PhBr instead of PhI)

The attractiveness of our method was further enhanced by the finding that the coupling between pyrazole and the more reactive iodobenzene is quantitative within 24 h at 50 °C. If reaction time is not an issue, it is even possible to perform this condensation selectively at 25 °C working in the presence of ligand **6**.

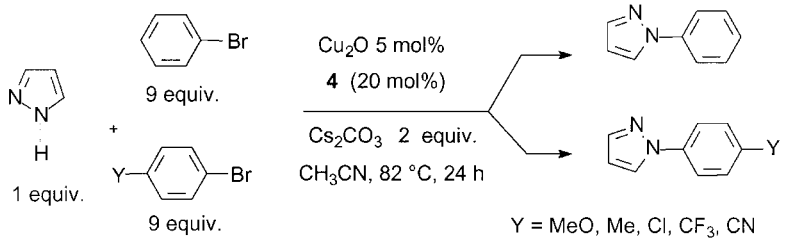
The conclusion arrived at above in the ligand study is reinforced here. Indeed, the results obtained with our system represent not only the mildest conditions yet reported for a copper-catalysed azole *N*-arylation with an aryl bromide (Figure 2) or iodide (Scheme 5), but also the mildest conditions reported whatever the metal catalyst. The best literature result to date is a palladium-catalysed indole *N*-arylation performed at 60 °C (53% yield for the *N*-arylation of the 7-ethylindole from bromo-3,5-dimethylbenzene).[29]

In order to study the influence of the electronic natures of the aromatic substituents, Hammett plots were constructed by measuring the rate of the copper-catalysed *N*-arylation of various *para*-substituted aryl bromides (Scheme 6, Figure 3). Competitive reactions were thus performed under pseudo-first order conditions (an equimolar mixture of the two aryl bromides was used, each in ninefold excess) allowing us to calculate a ρ value of 1.07. This value shows that the nature of substituents has a relatively weak influence on the rate of *N*-arylation. This conclusion is supported further by the excellent yields obtained for the *N*-arylation of various aryl halides whatever the nature of the aromatic substituents, either electron-donating or electron-withdrawing (see Table 3).



T (°C)	L	*t* (h)	Yield (%)
50	**4**	24	100
25	**6**	90	80

Scheme 5. Influence of the temperature on the *N*-arylation of pyrazole with iodobenzene; reaction conditions under N_2: 0.75 mmol of pyrazole, 0.5 mmol of PhI, 0.75 mmol of Cs_2CO_3, 5 mol % Cu_2O, 20 mol % of oxime, MeCN (350 μL); selectivities: 100%



Y	MeO	Me	H	Cl	CF_3	CN
k_Y/k_H	0.51	0.74	1	1.95	3.66	5.74

Scheme 6. Competitive copper-catalysed *N*-arylation of various substituted aryl bromides performed with 4.5 mmol of *p*-Y-C_6H_4Br, 4.5 mmol of PhBr, 0.5 mmol of pyrazole, 1 mmol of Cs_2CO_3, 5 mol % of Cu_2O, 20 mol% of Salox and 300 μL of MeCN, under N_2 (see Figure 3)

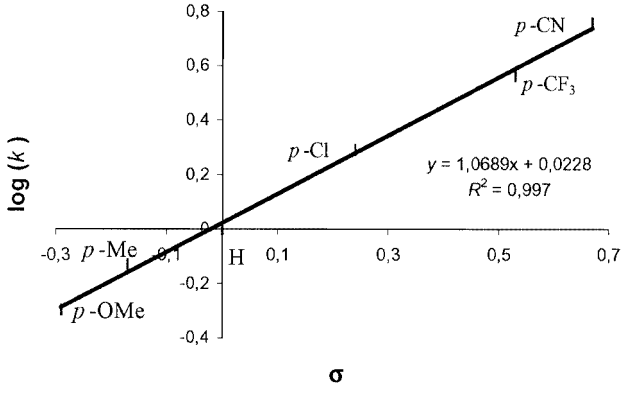
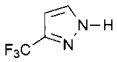
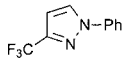
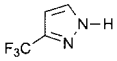
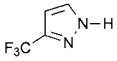
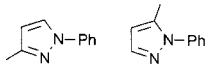
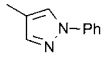


Figure 3. Influence of the electronic nature of aromatic substituents (Scheme 6); Hammett plots were constructed by measuring the *N*-arylation rates of various *para*-substituted aryl bromides (k corresponds to the relative rate k_{ArBr}/k_{PhBr})

The selected reaction conditions were then applied to a variety of substituted aryl halides, mainly bromides (Table 3). Reactions were totally selective with respect to pyrazole and almost totally selective with respect to aryl halides: only 5% of hydrodehalogenated compound was formed in the worst cases, and no by-product arising from biaryl coupling was observed. Condensations were generally complete within 36 h at 82 °C, and reaction products were usually isolated in yields higher than 90%. Coupling involving bromobenzene, efficient at 62 °C (Table 3, Entry 3), was much slower at 50 °C (Table 3, Entry 2) but still occurred with complete selectivity. In contrast to palladium-catalysed arylation, no significant electronic effects were observed in the coupling of aryl halides with pyrazole. Excellent reactivity was obtained both with electron-rich (Entries 4, 5) and with electron-poor (Entries 6−8) aryl bromides. Interestingly, the mild cesium carbonate did not affect the acetyl group (Entry 7). Because of steric hindrance, the *ortho*-substituted 2-bromotoluene required the use either of longer reaction times (Entry 23) or of a higher reaction temperature (110 °C, Entry 24). In the latter case, coupling had to be performed in DMF.

Reactivity differences exhibited by aryl halides toward oxidative addition to copper(I) could also be taken advantage of in order to obtain monosubstitution products from couplings involving *p*-dihalobenzenes. The condensation between pyrazole and bromo-4-chlorobenzene took place on the bromine position with a regioselectivity higher than

Table 4. *N*-Copper-catalysed arylation of substituted pyrazoles by phenyl bromide or iodide[a]

Entry	Pyrazole	ArX	Compound		t (h)	Yield (%) GC (isolated)
1		PhI		**3a**	24	100
2		PhBr	"	**3a**	24	96
3		PhI		**3v**	24	100 (94)
4		PhBr	"	**3v**	24	42
5		PhBr	"	**3v**	96	81
6		PhI	 **3x** **3x'**		24	100[d] (**3x**: 71) (**3x'**: 19)
7		PhBr	"		24	29[e]
8		PhBr	"		96	68[f]
9		PhI		**3y**	24	100 (98)
10		PhBr	"	**3y**	24	48
11		PhBr	"	**3y**	96	100
12		PhI		**3z**	24	12
13[b]		PhI	"	**3z**	24	47
14[b][c]		PhI	"	**3z**	24	75
15[b][c]		PhI	"	**3z**	54	100 (94)

[a] Reaction conditions: 2 mmol of pyrazole, 3 mmol of ArX (Scheme 9). [b] Reaction at 110 °C in DMF. [c] Ligand chxn-py-al (**35**). [d] **3x/3x′** = 4:1.[e] **3x/3x′** = 3.7:1. [f] **3x/3x′** = 3.2:1.

99% (Entry 8), while iodine substitution was observed with 94% regioselectivity when bromo-4-iodobenzene was used as arylating agent (Entry 9). We also studied the regioselectivity of the arylation of pyrazole with bromo-2,4-dichlorobenzene, the 2,4-dichlorophenyl group being of interest in numerous agrochemicals. The best results were obtained when starting from an excess of aryl halide (4 equiv.) but even in this case the formation of the double substitution product (30%), probably in the *para*-position to the first pyrazole, could not be avoided (Entry 21).

Heteroaryl halides, including 3-bromopyridine, bromothiophenes and 4-iodo-1-methylpyrazole, were also transformed into the desired products **3r**−**u** with high yields and full selectivity (Entries 25−28).

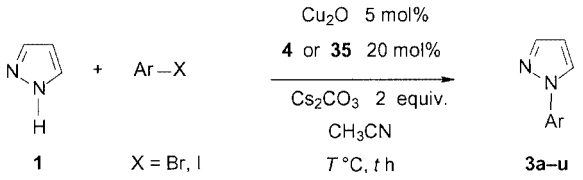
The quantitative *N*-arylation of pyrazole with *p*-bromoaniline is notable. Indeed, the amino substituent is not involved in the reaction, whereas it is incompatible with palladium catalysis (Entry 13). The nitro substituent is also compatible with our catalytic system (Entries 17, 18): the reaction took place easily when starting from the *p*-iodonitrobenzene but more slowly when starting from the *m*-bromonitrobenzene. In this latter case, a double substitution compound (12%) together with a small amount of *cine*-substitution by-product, 1-(*p*-nitrophenyl)pyrazole, were also observed.

In the presence of the ligand **4**, however, our method sometimes encounters limitations. 1-(4-Cyanophenyl)pyrazole (**3h**) was obtained in 82% yield from 4-bromobenzonitrile, but the nitrile group was partially hydrolysed into amides under the coupling conditions (7%) (Table 3, Entry 11). Moreover, attempted coupling between ethyl 3-bromobenzoate and pyrazole was unsuccessful (Entry 19). Instead, almost complete conversion of this aryl halide into 3-bromobenzoic acid took place. In both cases, cesium hydroxide arising from thermal decomposition of cesium hydrogencarbonate generated in situ[30] might be responsible for the observed hydrolysis. However, the use of an aprotic ligand (**35**) could remove or alleviate these limitations. Arylation of pyrazole with 4-bromobenzonitrile proceeds quantitatively (Entry 12) with this ligand, and the product resulting from the arylation with ethyl 3-bromobenzoate is now formed (20% yield and 21% selectivity). In this last case, the addition of a drying agent to the reaction mixture allowed yield (53%) and selectivity to be improved although the saponification of the ester function was not fully abolished (Entry 20).

Finally, our catalytic system also allows the *N*-vinylation of pyrazole with vinylic halides such as β-bromostyrene, and the reaction is quantitative and stereoselective (Entry 16, *E*/*Z* = 99:1).

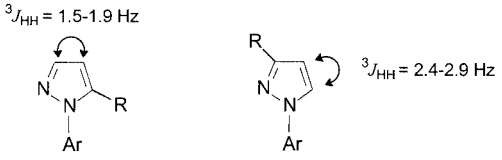
With substituted pyrazoles, we then studied the influence of substitution on arylation with iodo- or bromobenzene.

In the case of unsymmetrical pyrazoles, the *N*-arylation reaction can theoretically give rise to two regioisomeric compounds. We were able to easily assign structures, thanks to physical properties and $^{1}H/^{13}C$ NMR spectroscopic data reported in the literature.[31,32] Notably, regioisomers can be distinguished through the measured coupling constants of



Scheme 7. *N*-Copper-catalysed arylation of pyrazole with functionalized aryl bromides or iodides (Table 3)

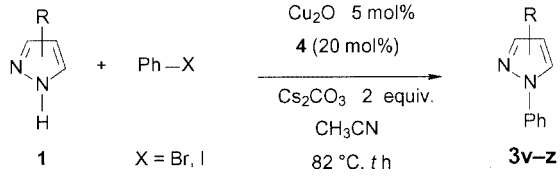
the hydrogen atoms present in the pyrazole ring: 1-aryl-3-substituted pyrazoles exhibit $^{3}J_{H,H}$ = 2.4−2.9 Hz, while 1-aryl-5-substituted pyrazoles exhibit $^{3}J_{H,H}$ = 1.5−1.9 Hz (Scheme 8).[32]



Scheme 8. NMR $^{3}J_{H,H}$ coupling constants in ring-substituted 1-arylpyrazoles

For a trifluoromethyl substituent in position 3, a quantitative and regioselective arylation took place with iodobenzene (Table 4, Entry 3). The reaction was slower with bromobenzene, but remained regioselective, probably thanks to the steric hindrance of the substituent. The inductive effect (−I) of the trifluoromethyl group, deactivating the α-nitrogen more than the β-one, probably favours the observed regioselectivity. For a methyl substituent in the same position the reaction give a mixture of regioisomers (**3x** and **3x′**) resulting from the substitution of the two possible pyrazole tautomers on the NH position (Entries 6−8). The inductive effect of the methyl (+I), which favours arylation on the α-nitrogen, is not sufficient to counterbalance its steric effect, and the major product **3x** results from a β-nitrogen substitution. The arylation of the 4-methylpyrazole was also performed easily with iodobenzene, and with bromobenzene the reaction was quicker than the arylation of 3-methylpyrazole, probably because of comparatively weaker steric hindrance by the substituent. The reaction is slower than that starting from pyrazole, however, maybe owing to the more difficult deprotonation of the 4-methylpyrazole by the cesium carbonate.

The use of 3,5-dimethylpyrazole as substrate strongly slowed down the reaction. The steric and electronic effects are not favourable, but at 110 °C the formation of the coupling product could be carried out quantitatively.



Scheme 9. *N*-Copper-catalysed arylation of substituted pyrazoles by phenyl bromide and iodide (Table 4)

Conclusion

In conclusion, we have developed a general and efficient improved method for *N*-arylation of pyrazoles with aryl bromides and iodides under very mild conditions, through the use of the mild cesium carbonate as base, acetonitrile as solvent and inexpensive copper-based catalytic systems. The last of these comprise a set of various copper salts or copper metal, and commercially available ligands of the oxime type. Moreover, original bi-, tri- and tetradentate compounds combining potential nitrogen and/or oxygen chelating atoms have also been successfully tested as ligands with this copper-based catalytic systems. The condensations exhibit high tolerance toward functional groups and afford the arylated products with uniformly high yields and selectivities in a temperature range 40 to 60 °C lower than required until now. Mildness, low cost and experimental ease make our method particularly suitable for large-scale industrial applications.[16]

These new experimental conditions represent a real breakthrough in the field of metal-catalysed arylation of nitrogen heterocycles, also being applicable to azoles such as imidazoles, triazoles, pyrroles and indoles, which will be the subject of a future publication. Moreover, the new ligands presented here also significantly accelerate copper-catalysed reactions of aryl halides with diverse nucleophilic compounds such as oxygen nucleophiles (phenols, aliphatic alcohols) and other nitrogen nucleophiles (amides, carbamates, pyridazinones), allowing milder conditions than traditional methods. All these results, already published and protected in patent form,[16,17] will also be presented shortly.

Experimental Section

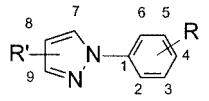
General Remarks: All reactions were carried out in Schlenk tubes under pure and dry nitrogen. All solvents (except for adiponitrile, 2-methylglutaronitrile) were distilled and stored under nitrogen. Acetonitrile and propionitrile were distilled from P_4O_{10} and stored over 3 Å activated molecular sieves. DMF was distilled under vacuum from $MgSO_4$ and stored protected from light over 4 Å molecular sieves. THF and toluene were distilled from sodium benzophenone ketyl and stored over sodium wire. DME was distilled from sodium benzophenone ketyl and stored protected from light over 4 Å molecular sieves. Adiponitrile and 2-methylglutaronitrile were only degassed by nitrogen bubbling prior to use. All solid materials (except for KO*t*Bu) were stored in the presence of P_4O_{10} in a bench-top desiccator under vacuum at room temperature and weighed in air. Pyrazole (Aldrich) was recrystallized from chloroform/petroleum ether prior to use. K_3PO_4 (Fluka), K_2CO_3 (Aldrich) and Cs_2CO_3 (Aldrich) were ground to a fine powder. KO*t*Bu was purified by sublimation and stored under an atmosphere of nitrogen. Copper(I) iodide and copper(I) bromide were purified by literature procedures.[33] The former was stored protected from light. Copper metal was activated either by treatment with iodine[34] to remove superficial oxide or by precipitation from zinc-reduced copper sulfate.[35] Copper(I) oxide, copper(II) oxide and copper(II) bromide were used without further purification. Ligands **4**−**10**, **14**−**17**, **24** and **32** were purchased from commercial sources. The following ligands were synthesized according to or by adaptation of literature procedures: **11**,[36] **13**,[37] **18**,[38] **19**,[38a,39] **20**,[38a] **21**,[38a,40] **22**,[38a,41] **23**,[38a,42] **25**,[43] **26**,[43a,44] **27**,[45] **28**,[46] **29**,[47] **30**,[48] **31**,[48] **33**,[49] **34**,[43a,50] **35**,[43a,51] **36**,[43a] **37**,[43a] **38**[52] and **39**.[43a] The synthesis of the new ligand **12** is described below.

All aryl halides and the vinyl bromide were purchased from commercial sources (Aldrich, Acros, Avocado, Fluka, Lancaster). If solids, they were recrystallized from appropriate solvents. If liquids, they were distilled (except for 3-bromothiophene) under vacuum and stored under nitrogen. Special care was taken with liquid aryl iodides: the samples were regularly distilled from over copper powder to remove iodine and stored protected from light. Molecular sieves were activated and stored under vacuum at 100 °C in the presence of P_4O_{10}.

Flash column chromatography was performed with SDS 60 A C.C silica gel (35−70 μm or 70−200 μm). Thin layer chromatography was carried out on Merck silica gel 60 F_{254} plates. All products were characterized by ^1H NMR, ^{13}C NMR and GC/MS. New compounds and previously partially characterized compounds were further characterized by IR and HRMS. IR spectra were recorded with a Nicolet 210 FT-IR instrument (neat, thin film for liquid products and KBr pellet or in dichloromethane solution for solid products). ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were recorded at room temperature with a Bruker AC 200 MHz or a Bruker Avance 250 MHz instrument with chemical shifts reported in ppm relative to the residual deuterated solvent peak. $^{19}F\{^1H\}$ NMR spectra were recorded at room temperature with a Bruker Avance 250 MHz instrument with chemical shifts reported in ppm relative to $CFCl_3$. The signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quadruplet; dd, doublet of doublets; m, multiplet. Gas chromatographic analyses were performed with a Delsi Nermag DI-200 instrument with a FID detector, a Delsi Nermag Enica 31 integrator and a SGE BPX5 25 m × 0.53 mm semi-capillary apolar column (stationary phase: 5% phenylpolysil-phenylenesiloxane film, 1 μ). Gas chromatography − mass spectra (GC/MS) were recorded with a Argilent Technologies 6890 N instrument with an Agilent 5973 N mass detector (EI) and a HP5-MS 30 m × 0.25 mm capillary apolar column (stationary phase: 5% diphenyldimethylpolysiloxane film, 0.25 μm). FAB $^+$ mass spectra were recorded with a JEOL JMS-DX300 spectrometer (3 Kev, xenon) in a *m*-nitrobenzyl alcohol (NBA) matrix. High resolution mass spectra (HRMS) were recorded with a JEOL JMS-SX102 spectrometer (10 Kev, xenon, FAB ionization mode) in the same matrix. Melting points were determined with a Büchi B-540 apparatus and are uncorrected.

General Procedure for the *N*-Arylation of Pyrazoles: After standard evacuation and back-fill cycles with dry and pure nitrogen, an oven-dried Schlenk tube fitted with a magnetic stirrer bar was charged with Cu_2O, the ligand, the pyrazole, $CsCO_3$ and, if a solid, the aryl halide. The tube was evacuated, back-filled with nitrogen and capped with a rubber septum. If a liquid, the aryl halide was then added under a stream of nitrogen by syringe at room temperature, followed by anhydrous and degassed acetonitrile (1.2 mL). The septum was removed, and the tube was sealed under a positive pressure of nitrogen and stirred in an oil bath (preheated to 82 °C) for the required time period. The reaction mixture was cooled to room temperature, diluted with dichloromethane and filtered through a plug of celite, the filter cake being further washed with dichloromethane (≈ 20 mL). The filtrate was concentrated in vacuo to yield a residue that was dissolved in dichloromethane (50 mL). The resulting organic layer was washed with water (2 × 20 mL) and saturated saline solution (2 × 20 mL), and was then dried over $MgSO_4$. The solvent was removed in vacuo to yield the crude product, which was purified by flash column chromatography on silica

gel. In a few cases (pointed out below), the extraction sequence was skipped and the crude residue was directly adsorbed onto silica gel.



1-Phenyl-1*H*-pyrazole (3a): As described in the General Procedure (82 °C, 36 h), pyrazole (204 mg, 3 mmol) was coupled with bromobenzene (211 μL, 2 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), salicylaldoxime (**4**; 55 mg, 0.4 mmol) and acetonitrile (1.2 mL). The crude product was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2 90:10 to 70:30) to provide 282 mg (98% yield) of the desired product as a colourless oil: b.p. 58 °C under 0.2 Torr (ref.[53] 58−60 °C under 0.2 Torr). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.92 (dd, ^3J = 2.4, ^4J = 0.5 Hz, 1 H, 7-H), 7.70 (m, 3 H, 2,6,9-H,), 7.45 (m, 2 H, 3,5-H), 7.29 (m, 1 H, 4-H) 6.46 (dd, ^3J = 2.4, ^3J = 1.8, 1 H, 8-H) ppm. ^{13}C NMR {^{1}H} (50 MHz, $CDCl_3$): δ[31b] = 141.08 (C9), 140.23 (C1), 129.43 (C3,5), 126.75 (C7) 126.44 (C4) 119.21 (C-2,6), 107.61 (C8) ppm. GC/MS: room temp.: 13.15 min, *m*/*z* = 144. IR (KBr): $\tilde{\nu}$ = 3142, 3121, 3150, 1601, 1521, 1501, 1464, 1393, 1332, 1253, 1198, 1120, 1074, 1046, 1036, 936, 915, 905, 756 cm^{-1}. R_f: 0.40 (eluent: CH_2Cl_2/petroleum ether, 60:40).

1-(4-Tolyl)-1*H*-pyrazole (3b): As described in the General Procedure (82 °C, 36 h), pyrazole (204 mg, 3 mmol) was coupled with 4-bromotoluene (342 mg, 2 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), salicylaldoxime (**4**, 55 mg, 0.4 mmol) and acetonitrile (1.2 mL). The crude product was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 90:10 to 70:30) to provide 301 mg (95% yield) of the desired product as a colourless solid. M.p. 31 °C (ref.[7b] 30−31 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.88 (dd, ^3J = 2.4, ^4J = 0.5 Hz, 1 H, 7-H), 7.71 (dd, ^3J = 1.9, ^4J = 0.5 Hz, 1 H, 9-H), 7.57 (m, 2 H, 2,6-H), 7.24 (m, 2 H, 3,5-H), 6.61 (dd, ^3J = 1.9, ^3J = 2.4 Hz, 1 H, 8-H), 2.38 (s, 3 H, *C*H$_3$) ppm. ^{13}C NMR {^{1}H} (50 MHz, $CDCl_3$): δ = 140.77 (C9), 138.03 (C4), 136.19 (C1), 126.65 (C7), 129.94 (C3,5), 119.15 (C2,6), 107.34 (C8), 20.90 (C*Me*) ppm. GC/MS: room temp.: 14.73 min, *m*/*z* = 158. R_f: 0.41 (eluent: CH_2Cl_2/petroleum ether, 60:40).

1-(4-Methoxyphenyl)-1*H*-pyrazole (3c): As described in the General Procedure (82 °C, 40 h), pyrazole (204 mg, 3 mmol) was coupled with 4-bromoanisole (250 μL, 2 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), salicylaldoxime (**4**, 55 mg, 0.4 mmol) and acetonitrile (1.2 mL). The crude product was purified by flash chromatography on silica gel (eluent CH_2Cl_2/hexane, 50:50) to provide 324 mg (93% yield) of the desired product as a light yellow solid. M.p. 45.5 °C (ref.[54] 45 °C). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.35 (dd, ^3J = 2.5, ^4J = 0.6 Hz, 1 H, 7-H), 7.72−7.79 (m, 2 H, 2,6-H), 7.70 (dd, ^3J = 1.8, ^4J = 0.6 Hz, 1 H, 9-H), 7.04 (m, 2 H, 3,5-H), 6.49 (dd, ^3J = 1.8, ^3J = 2.5 Hz, 1 H, 8-H), 3.78 (s, 3 H, *C*H$_3$) ppm. ^{13}C NMR {^{1}H} (50 MHz, [D$_6$]DMSO): δ = 157.51 (C4), 140.23 (C9), 133.44 (C1), 127.30 (C7), 119.90 (C2,6), 114.46 (C3,5), 107.22 (C8), 55.28 (C*Me*) ppm. GC/MS: room temp.: 16.40 min, *m*/*z* = 174. R_f: 0.33 (eluent: CH_2Cl_2/petroleum ether, 60:40).

1-(4-Trifluoromethylphenyl)-1*H*-pyrazole (3d): As described in the General Procedure (82 °C, 36 h), pyrazole (204 mg, 3 mmol) was coupled with 1-bromo-4-trifluoromethylbenzene (280 μL, 2 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), salicylaldoxime (**4**, 55 mg, 0.4 mmol) and acetonitrile (1.2 mL). The crude product was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 90:10 to 60:40) to provide 407 mg (96% yield) of the desired product as a colourless solid. M.p. 94−95 °C. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.66 (dd, ^3J = 2.6, ^4J = 0.4 Hz, 1 H, 7-H), 8.08 (m, 2 H, 2,6-H), 7.85 (m, 3 H, 3,5,9-H), 6.61 (dd, ^3J = 2.6, ^3J = 1.7 Hz, 1 H, 8-H) ppm. ^{13}C NMR {^{1}H} (50 MHz, [D$_6$]DMSO): δ = 142.34 (C1), 141.88 (C9), 128.24 (C7), 126.70 (q, $^3J_{C,F}$ = 3.8 Hz, C3,5), 126.14 (q, $^2J_{C,F}$ = 32.3 Hz, C4), 124.04 (q, $^1J_{C,F}$ = 271.7 Hz, CF_3), 118.44 (C2,6), 108.59 (C8) ppm. ^{19}F NMR{^{1}H}(235 MHz, [D$_6$]DMSO): δ = −61.14 (s) ppm. GC/MS: room temp.: 13.27 min, *m*/*z* = 212. R_f: 0.51 (eluent: CH_2Cl_2/petroleum ether, 50:50).

1-(4-Acetylphenyl)-1*H*-pyrazole (3e): As described in the General Procedure (82 °C, 24 h), pyrazole (136 mg, 2 mmol) was coupled with 4-bromoacetophenone (478 mg, 2.4 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), salicylaldoxime (**4**, 55 mg, 0.4 mmol) and acetonitrile (1.2 mL). The crude orange solid was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 50:50) to provide 339 mg (91% yield) of the desired product as a colourless solid. Alternatively, the crude orange solid can be purified by recrystallisation in ethanol instead of flash column chromatography, to provide 313 mg (84% yield) of the desired product as an off-white solid. M.p. 110 °C (EtOH) (ref.[55] 109−110 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.03−8.07 (m, 2 H, 3,5-H), 8.01 (dd, ^3J = 2.5, ^4J = 0.6 Hz, 1 H, 7-H), 7.78−7.82 (m, 2 H, 2,6-H), 7.77 (dd, ^3J = 1.8, ^4J = 0.6 Hz, 1 H, 9-H), 6.50 (dd, ^3J = 1.8, ^3J = 2.5 Hz, 1 H, 8-H), 2.61 (s, 3 H, *C*H$_3$) ppm. ^{13}C NMR {^{1}H} (50 MHz, $CDCl_3$): δ = 196.76 (C=*O*), 143.30 (C1), 142.02 (C9), 134.79 (C4), 129.97 (C3,5), 126.86 (C7), 118.36 (C2,6), 108.55 (C8), 26.54 (C*Me*) ppm. GC/MS: room temp.: 18.58 min, *m*/*z* = 186. R_f: 0.24 (eluent: CH_2Cl_2).

1-(4-Chlorophenyl)-1*H*-pyrazole (3f): As described in the General Procedure (82 °C, 40 h), pyrazole (204 mg, 3 mmol) was coupled with 4-bromochlorobenzene (382.9 mg, 2 mmol) by treatment with cesium carbonate (1.108 g, 3.4 mmol), Cu_2O (14.4 mg, 0.1 mmol), salicylaldoxime (**4**, 55 mg, 0.4 mmol) and acetonitrile (1.2 mL). The crude product was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 80:20) to provide 357 mg (93% yield) of the desired product as a colourless solid. M.p. 52 °C (MeOH) (ref.[56] 51 °C, MeOH). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.88 (dd, ^3J = 2.5, ^4J = 0.5 Hz, 1 H, 7-H), 7.72 (dd, ^3J = 1.6, ^4J = 0.5 Hz, 1 H, 9-H), 7.60−7.68 (m, 2 H, 2,6-H), 7.37−7.45 (m, 2 H, 3,5-H), 6.47 (dd, ^3J = 1.6, ^3J = 2.5 Hz, 1 H, 8-H) ppm.^{13}C NMR {^{1}H} (50 MHz, $CDCl_3$): δ = 141.36 (C9), 138.75 (C1), 131.88 (C4), 129.51 (C3,5), 126.69 (C7), 120.30 (C2,6), 107.98 (C8) ppm. GC/MS: room temp.: 15.65 min, *m*/*z* = 178 and 180. R_f: 0.56 (eluent: petroleum ether/CH_2Cl_2, 50:50).

1-(4-Bromophenyl)-1*H*-pyrazole (3g): As described in the General Procedure (82 °C, 72 h), pyrazole (136 mg, 2 mmol) was coupled with 1,4-dibromobenzene (1.887 g, 8 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), Chxn-Py-Al (**35**, 117 mg, 0.4 mmol) and acetonitrile (1.6 mL). The crude residue was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 50:50) to provide 366 mg (82% yield) of the desired product as a colourless solid. M.p. 71 °C (MeOH) (ref.[57] 70 °C MeOH). ^{1}H NMR (250 MHz, $CDCl_3$): δ[58] = 7.88 (dd, ^3J = 2.5, ^4J = 0.5 Hz, 1 H, 7-H), 7.72 (dd, ^3J = 1.7, ^4J = 0.5 Hz, 1 H, 9-H), 7.52−7.62 (m, 4 H, 2,3,5,6-H), 6.46 (dd, ^3J = 1.7, ^3J = 2.5 Hz, 1 H, 8-H) ppm. ^{13}C NMR {^{1}H} (50 MHz, $CDCl_3$): δ = 141.41 (C9), 139.21 (C1), 132.46 (C2,6), 126.64 (C7), 120.59 (C3,5), 119.62 (C4), 108.03 (C8) ppm. GC/MS:

room temp.: 16.9 min, *m*/*z* = 222 and 224. R_f: 0.21 (eluent: hexane/CH_2Cl_2, 50:50).

1-(4-Cyanophenyl)-1*H*-pyrazole (3h): As described in the General Procedure (82 °C, 24 h), pyrazole (204 mg, 3 mmol) was coupled with 4-bromobenzonitrile (364 mg, 2 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), Chxn-Py-Al (**35**, 117 mg, 0.4 mmol) and acetonitrile (1.2 mL). The residue was purified by flash chromatography on silica gel (eluent: gradient CH_2Cl_2/hexane, 50:50 to 100:0) to provide 308 mg (91% yield) of the desired product as a colourless solid. M.p. 87.5 °C (ref.[55]89−91 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.98 (dd, ^3J = 2.6, ^4J = 0.6 Hz, 1 H, 7-H), 7.82 (m, 2 H, 3,5-H), 7.76 (dd, ^3J = 1.8, ^4J = 0.6 Hz, 1 H, 9-H), 7.73 (m, 2 H, 2,6-H), 6.51 (dd, ^3J = 1.8, ^3J = 2.6 Hz, 1 H, 8-H) ppm. ^{13}C NMR {^{1}H} (50 MHz, $CDCl_3$): δ = 142.96 (C1), 142.42 (C9), 133.64 (C3,5), 126.84 (C7), 118.93 (C2,6), 118.39 (C*N*), 109.55 (C4), 109.04 (C8) ppm. GC/MS: room temp.: 17.52 min, *m*/*z* = 169. R_f: 0.41 (eluent: CH_2Cl_2).

1-(4-Aminophenyl)-1*H*-pyrazole (3i): As described in the General Procedure (82 °C, 42 h), pyrazole (136 mg, 2 mmol) was coupled with 4-bromoaniline (516 mg, 3 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), Chxn-Py-Al (**35**, 117 mg, 0.4 mmol) and acetonitrile (1.2 mL). The oil obtained after the filtration step was directly purified by flash chromatography on alumina gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 50:50) to provide 290 mg (91% yield) of the desired product as an orange solid. M.p. 42−43 °C (ref.[57] 45 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.75 (dd, ^3J = 2.4, ^4J = 0.5 Hz, 1 H, 7-H), 7.66 (dd, ^3J = 1.8, ^4J = 0.5 Hz, 1 H, 9-H), 7.40 (m, 2 H, 2,6-H), 6.66 (m, 2 H, 3,5-H), 6.38 (dd, ^3J = 1.8, ^3J = 2.4 Hz, 1 H, 8-H), 3.79 (s, 2 H, *N*H$_2$) ppm. ^{13}C NMR {^{1}H} (50 MHz, $CDCl_3$): δ = 145.47 (C4), 140.22 (C9), 132.31 (C1), 126.80 (C7), 121.10 (C2,6), 115.43 (C3,5), 106.83 (C8) ppm. GC/MS: room temp.: 17.77 min, *m*/*z* = 159. R_f: 0.17 (eluent: CH_2Cl_2/CH_3CO_2Et, 95:5; silica).

1*H*,1′*H*-1,1′-*p*-Phenylenebis(pyrazole) (3j): As described in the General Procedure (82 °C, 48 h), pyrazole (136 mg, 2 mmol) was coupled with 1-(4′-bromophenyl)-1*H*-pyrazole (535 mg, 2.4 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), Chxn-Py-Al (**35**, 117 mg, 0.4 mmol) and acetonitrile (1.2 mL). The residue obtained after the filtration step was directly purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2/CH_3CO_2Et, 40:60:0 to 0:100:0 to 0:90:10) to provide 383 mg (91% yield) of the desired product as a yellow solid. M.p. 180 °C ($CHCl_3$, white solid) (ref.[59] 182 °C, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.94 (dd, ^3J = 2.5, ^4J = 0.6 Hz, 2 H, 7,7′-H), 7.78 (s, 4 H, 2,3,5,6-H), 7.74 (dd, ^3J = 1.8, ^4J = 0.6 Hz, 1 H, 9,9′-H), 6.48 (dd, ^3J = 1.8, ^3J = 2.5 Hz, 1 H, 8,8′-H) ppm. ^{13}C NMR{^{1}H}(50 MHz, $CDCl_3$): δ = 141.30 (C9,9′), 138.40 (C1,4), 126.71 (C7,7′), 120.01 (C2,3,5,6), 107.89 (C8,8′) ppm. GC/MS: room temp.: 21.28 min, *m*/*z* = 210. IR (KBr): $\tilde{\nu}$ = 3119, 1533, 1507, 1395, 1053, 938, 837, 760 cm^{-1}. R_f: 0.38 (eluent: CH_2Cl_2/CH_3CO_2Et, 90:10).

1-(4-Imidazol-1-ylphenyl)-1*H*-pyrazole (3k): As described in the General Procedure (82 °C, 48 h), pyrazole (136 mg, 2 mmol) was coupled with 1-(4′-bromophenyl)-1*H*-imidazole (535 mg, 2.4 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), Chxn-Py-Al (**35**, 117 mg, 0.4 mmol) and acetonitrile (1.2 mL). The residue obtained was purified by flash chromatography on silica gel (eluent: gradient CH_2Cl_2/MeOH, 100:0 to 98:2) to provide 387 mg (92% yield) of the desired product as a colourless solid. M.p. 174−176 °C. ^{1}H NMR (250 MHz, [D$_6$]acetone): δ = 8.40 (dd, ^3J = 2.5, ^4J = 0.6 Hz, 1 H, 7-H), 8.15 (s large, 1 H, H *N*−C*H*=*N*), 7.98−8.04 (m, 2 H, 3,5-H), 7.73−7.79 (m, 2 H, 2,6-H), 7.73 (dd, ^3J = 1.7, ^4J = 0.6 Hz, 1 H, 9-H), 7.66 (s broad, 1 H, H *C*4−*N*−C*H*=*C*), 7.16 (s broad, 1 H, H *C*=C*H*−*N*=*C*), 6.54 (dd, ^3J = 1.7, ^3J = 2.5 Hz, 1 H, 8-H) ppm. ^{13}C NMR {^{1}H} (50 MHz, [D$_6$]DMSO): δ = 141.28 (C9), 138.57 (C1), 135.27 (C *N*−C*H*=*N*), 134.12 (C4), 127.92 (C7) 127.54 (C *C*=C*H*−*N*=*C*), 121.75 (C2,6), 119.36 (C3,5), 118.68 (C *C4*-*N*−C*H*=*C*), 108.12 (C8) ppm. GC/MS: room temp.: 22.49 min, *m*/*z* = 210. IR (KBr): $\tilde{\nu}$ = 3114, 1533, 1507, 1490, 1395, 1339, 1308, 1110, 1059, 937, 830, 760, 744 cm^{-1}. R_f: 0.22 (eluent: Et_2O/MeOH, 90:10).

(*E*)-1-Styryl-1*H*-pyrazole (3l): As described in the General Procedure (82 °C, 24 h), pyrazole (680 mg, 10 mmol) was coupled with β-bromostyrene (1.935 mL, 15 mmol, *E*/*Z* = 91:9) by treatment with cesium carbonate (6.52 g, 20 mmol), Cu_2O (72 mg, 0.5 mmol), Chxn-Py-Al (**35**, 584 mg, 2 mmol) and acetonitrile (6 mL). The residue obtained was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 50:50) to provide 1.64 g (96% yield) of the desired product (*E*/*Z* = 100:0) as a light yellow solid. M.p. 53 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.66−7.67 (m, 2 H, 7,9-H), 7.52 (d, ^3J = 14.5 Hz, 1 H, H *N*−C*H*=), 7.22−7.48 (m, 5 H, H Ph), 7.06 (d, ^3J = 14.5 Hz, 1 H, H *C*=*C*H−*C*), 6.40 (m, 1 H, 8-H) ppm. ^{13}C NMR {^{1}H} (50 MHz, $CDCl_3$): δ = 141.13 (C9), 135.09 (C *ipso*-Ph), 128.89 (2C, C *m*-Ph), 128.14 (C *N*−C*H*=), 127.60 (C *p*-Ph), 126.48 (C7), 126.26 (2 C, C *o*-Ph), 116.88 (C *C*=C*H*−*C*), 107.34 (C8) ppm. GC/MS: room temp.: 17.05 min, *m*/*z* = 170. R_f: 0.22 (eluent: hexane/CH_2Cl_2, 50:50).

1-(3-Nitrophenyl)-1*H*-pyrazole (3m): As described in the General Procedure (82 °C, 24 h), pyrazole (136 mg, 2 mmol) was coupled with 3-bromonitrobenzene (808 mg, 4 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), salicylaldoxime (**4**, 55 mg, 0.4 mmol) and acetonitrile (1.2 mL). The residue obtained after the filtration step was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 50:50) to provide 197 mg (52% yield) of the desired product as a light yellow solid. M.p. 94 °C (EtOH, ref.[57] 94−95 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.55 (t, ^4J = 2.1 Hz, ^4J = 2.1 Hz, 1 H, 6-H), 8.05−8.15 (m, 2 H, 2,4-H), 8.02 (dd, ^3J = 2.5, ^4J = 0.6 Hz, 1 H, 7-H), 7.77 (dd, ^3J = 1.6, ^4J = 0.6 Hz, 1 H, 9-H), 7.63 (t, ^3J = 8.2 Hz, ^3J = 8.2 Hz, 1 H, 3-H), 6.54 (dd, ^3J = 1.6, ^3J = 2.5 Hz, 1 H, 8-H) ppm. ^{13}C NMR{^{1}H}(50 MHz, $CDCl_3$): δ = 148.94 (C5), 142.12 (C9), 140.90 (C1), 130.40 (C3), 126.83 (C7), 124.32 (C2), 120.66 (C4), 113.65 (C6), 108.83 (C8) ppm. GC/MS: room temp.: 18.35 min, *m*/*z* = 189. R_f: 0.39 (eluent: hexane/CH_2Cl_2, 50:50).

1-(4-Nitrophenyl)-1*H*-pyrazole (3n): As described in the General Procedure (82 °C, 24 h), pyrazole (136 mg, 2 mmol) was coupled with 4-iodonitrobenzene (598 mg, 2.4 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), Chxn-Py-Al (**35**, 117 mg, 0.4 mmol) and acetonitrile (1.2 mL). The residue obtained after the filtration step was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2 100:0 to 50:50) to provide 341 mg (90% yield) of the desired product as a dark yellow solid. M.p. 169−170 °C (EtOH) (ref.[57]:170 °C). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 8.71 (dd, ^3J = 2.6, ^4J = 0.6 Hz, 1 H, 7-H), 8.36 (m, 2 H, 3,5-H), 8.11 (m, 2 H, 2,6-H), 7.88 (dd, ^3J = 1.7, ^4J = 0.6 Hz, 1 H, 9-H), 6.65 (dd, ^3J = 1.7, ^3J = 2.6 Hz, 1 H, 8-H) ppm. ^{13}C NMR{^{1}H}(50 MHz, [D$_6$]DMSO): δ = 144.71 (C4), 144.02 (C1), 142.73 (C9), 128.78 (C7), 125.32 (C3,5), 118.41 (C2,6), 109.29 (C8) ppm. GC/MS: room temp.: 18.90 min, *m*/*z* = 189. R_f: 0.29 (eluent: hexane/CH_2Cl_2, 40:60).

Ethyl 3-(1*H*-Pyrazol-1-yl)benzoate (3o): As described in the General Procedure (82 °C, 24 h), pyrazole (204 mg, 3 mmol) was coupled with ethyl 3-bromobenzoate (320 μL, 2 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), Chxn-Py-Al (**35**, 117 mg, 0.4 mmol), pulverized molecular sieves (3 Å, 480 mg) and acetonitrile (1.2 mL). The residue obtained was purified by flash chromatography on silica gel (eluent: CH_2Cl_2) to provide 216 mg (50% yield) of the desired product as a yellowish oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.32 (t, ^4J = 1.9 Hz, ^4J = 2.0 Hz, 1 H, 6-H), 7.98 (dd, ^3J = 2.5, ^4J = 0.5 Hz, 1 H, 7-H), 7.91−7.96 (m, 2 H, 2,4-H), 7.75 (dd, ^3J = 1.8, ^4J = 0.5 Hz, 1 H, 9-H), 7.52 (t, ^3J = 8.1 Hz, ^3J = 8.0 Hz, 1 H, 3-H), 6.49 (dd, ^3J = 2.5, ^3J = 1.8 Hz, 1 H, 8-H), 4.41 (q, ^3J = 7.1 Hz, 2 H, H OCH_2), 1.41 (t, ^3J = 7.1 Hz, 3 H, H Me) ppm. ^{13}C NMR{^{1}H}(50 MHz, $CDCl_3$): δ = 165.70 (C C=*O*), 141.35 (C9), 140.21 (C1), 131.80 (C5), 129.45 (C3), 127.20 (C2), 126.81 (C7), 123.20 (C4), 119.62 (C6), 107.97 (C8), 61.26 (C OCH_2), 14.26 (C Me) ppm. GC/MS: room temp.: 18.98 min, *m*/*z* = 216. FAB$^+$ (NBA): *m*/*z* (%) = 217 (100) [M + H$^+$], 73 (22), [$^+CO_2Et$], 189 (19) [M − Et + 2H$^+$], 171 (19) [M$^+$ − EtO], 147 (10), 143 (9), 433 (1) [2M + 1]. HRMS: $C_{12}H_{13}N_2O_2$ (M$^+$ + H) calcd. 217.0977. found: 217.1008. IR (CH_2Cl_2): ṽ = 1729 (C=O), 1250 (C=O) cm^{-1}. R_f: 0.19 (eluent: CH_2Cl_2).

1-(2,4-Dichlorophenyl)-1*H*-pyrazole (3p): As described in the General Procedure (110 °C, 48 h), pyrazole (136 mg, 2 mmol) was coupled with bromo2,4-dichlorobenzene (1052 μL, 8 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), Chxn-Py-Al (**35**, 117 mg, 0.4 mmol) and DMF (1.2 mL). The residue obtained after the filtration step was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 80:20) to provide 256 mg (60% yield) of the desired product as a light yellow solid. M.p. 47−48 °C (EtOH) (ref.[60] 56 °C, EtOH). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.87 (dd, ^3J = 2.4, ^4J = 0.6 Hz, 1 H, 7-H), 7.74 (dd, ^3J = 1.4, ^4J = 0.6 Hz, 1 H, 9-H), 7.54 (d, ^3J = 8.6 Hz, 1 H, 2-H), 7.53 (d, ^4J = 2.4 Hz, 1 H, 5-H), 7.35 (dd, ^3J = 8.6, ^4J = 2.4 Hz, 1 H, 3-H), 6.47 (dd, ^3J = 1.4, ^3J = 2.4 Hz, 1 H, 8-H) ppm. ^{13}C NMR{^{1}H}(50 MHz, $CDCl_3$): δ = 141.18 (C9), 136.90 (C1), 134.01 (C4), 131.21 (C5), 130.35 (C7), 128.76 (C6), 128.46 (C3), 127.96 (C2), 107.01 (C8) ppm. GC/MS: room temp.: 16.63 min, *m*/*z* = 212. 214 and 216. R_f: 0.25 (eluent: hexane/CH_2Cl_2, 50:50).

1-(2-Tolyl)-1*H*-pyrazole (3q): As described in the General Procedure (82 °C, 70 h), pyrazole (136 mg, 2 mmol) was coupled with 2-iodotoluene (383 μL, 3 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), Chxn-Py-Al (**35**, 117 mg, 0.4 mmol) and acetonitrile (1.2 mL). The residue obtained was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 0:100) to provide 297 mg (94% yield) of the desired product as a light yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ[31a] = 7.72 (dd, ^3J = 1.9, ^4J = 0.8 Hz, 1 H, 9-H), 7.60 (dd, ^3J = 2.4, ^4J = 0.8 Hz, 1 H, 7-H), 7.24−7.36 (m, 4 H, 2,3,4,5-H), 6.44 (dd, ^3J = 1.9, ^3J = 2.4 Hz, 1 H, 8-H), 2.24 (s, 3 H, CH_3) ppm. ^{13}C NMR{^{1}H}(50 MHz, $CDCl_3$): δ = 140.25 (C9), 140.02 (C1), 133.74 (C6), 131.28 (C5), 130.51 (C7), 128.37 (C2), 126.55 (C4), 126.16 (C3), 106.18 (C8), 18.06 (C Me) ppm. GC/MS: room temp.: 13.43 min, *m*/*z* = 158. R_f: 0.27 (eluent: hexane/CH_2Cl_2, 70:30).

1-(3-Pyridyl)-1*H*-pyrazole (3r): As described in the General Procedure (82 °C, 24 h), pyrazole (1.02 g, 15 mmol) was coupled with 3-bromopyridine (963 μL, 10 mmol) by treatment with cesium carbonate (5.21 g, 16 mmol), Cu_2O (72 mg, 0.5 mmol), salicylaldoxime (**4**, 274 mg, 2 mmol) and acetonitrile (6 mL). The crude yellow oil was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 50:50) to provide 1.35 g (93% yield) of the desired product as a greenish oil, which could be crystallised in a few hours at 0 °C (off-white crystals). M.p. 29−31 °C (ref.[55] 30−31 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ[61] = 8.97 (dd, ^4J = 2.7, ^5J = 0.7 Hz, 1 H, 2-H), 8.52 (dd, ^3J = 4.8, ^4J = 1.5 Hz, 1 H, 4-H), 8.04 (ddd, ^3J = 8.3, ^4J = 2.7, ^4J = 1.5 Hz, 1 H, 6-H), 7.96 (dd, ^3J = 2.5, ^4J = 0.6 Hz, 1 H, 7-H), 7.76 (dd, ^3J = 1.8, ^4J = 0.6 Hz, 1 H, 9-H), 7.38 (ddd, ^3J = 8.3, ^3J = 4.8, ^5J = 0.7 Hz, 1 H, 5-H), 6.50 (dd, ^3J = 1.8, ^3J = 2.5 Hz, 1 H, 8-H) ppm. ^{13}C NMR{^{1}H}(50 MHz, $CDCl_3$): δ = 147.35 (C4), 141.79 (C9), 140.39 (C2), 136.39 (C1), 126.75 (C6), 126.19 (C7), 123.79 (C5), 108.30 (C8) ppm. GC/MS: room temp.: 13.90 min, *m*/*z* = 145. R_f: 0.39 (eluent: hexane/CH_2Cl_2, 40:60).

1-(3-Thienyl)-1*H*-pyrazole (3s): As described in the General Procedure (82 °C, 54 h), pyrazole (136 mg, 2 mmol) was coupled with 3-bromothiophene (284 μL, 3 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), salicylaldoxime (**4**, 55 mg, 0.4 mmol) and acetonitrile (1.2 mL). The crude product was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 50:50) to provide 276 mg (92% yield) of the desired product as a colourless oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.79 (dd, ^3J = 2.5, ^4J = 0.6 Hz, 1 H, 6-H), 7.67 (dd, ^3J = 1.8, ^4J = 0.6 Hz, 1 H, 8-H), 7.33−7.40 (m, 3 H, 2,4,5-H), 6.40 (dd, ^3J = 1.8, ^3J = 2.5 Hz, 1 H, 7-H) ppm. ^{13}C NMR{^{1}H}(50 MHz, $CDCl_3$): δ = 140.62 (C8), 139.84 (C1), 127.49 (C4), 126.51 (C6), 120.31 (C5), 110.53 (C2), 107.09 (C7) ppm. GC/MS: room temp.: 13.34 min, *m*/*z* = 150. R_f: 0.28 (eluent: hexane/CH_2Cl_2, 50:50).

1-(2-Thienyl)-1*H*-pyrazole (3t): As described in the General Procedure (82 °C, 24 h), pyrazole (136 mg, 2 mmol) was coupled with 2-bromothiophene (291 μL, 3 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), salicylaldoxime (**4**, 55 mg, 0.4 mmol) and acetonitrile (1.2 mL). The crude product was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 50:50) to provide 273 mg (91% yield) of the desired product as an orange oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.80 (dd, ^3J = 2.4, ^4J = 0.6 Hz, 1 H, 6-H), 7.67 (dd, ^3J = 1.5, ^4J = 0.6 Hz, 1 H, 8-H), 7.02−7.06 (m, 2 H, 3,5-H), 6.92−6.97 (m, 1 H, 4-H), 6.43 (dd, ^3J = 1.5, ^3J = 2.4 Hz, 1 H, 7-H) ppm.^{13}C NMR{^{1}H}(50 MHz, $CDCl_3$): δ = 143.77 (C1), 141.09 (C8), 128.04 (C3), 126.06 (C6), 120.10 (C4), 113.93 (C5), 107.72 (C7) ppm. GC/MS: room temp.: 13.05 min, *m*/*z* = 150. R_f: 0.26 (eluent: hexane/CH_2Cl_2, 50:50).

1-Methyl-4-(1*H*-pyrazol-1-yl)-1*H*-pyrazole (3u): As described in the General Procedure (82 °C, 28 h), pyrazole (136 mg, 2 mmol) was coupled with 4-iodo-1-methylpyrazole (624 mg, 3 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), salicylaldoxime (**4**, 55 mg, 0.4 mmol) and acetonitrile (1.2 mL). The extraction sequence was skipped and the crude residue was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2/MeOH, 20:80:0 to 0:100:0 to 0:98:2) to provide 284 mg (96% yield) of the desired product as a yellow oil, which could be crystallised in a few hours if left at 0 °C (pale yellow crystals). M.p. 63−64 °C. ^{1}H NMR (250 MHz, [D$_6$]acetone): δ = 8.0 (dd, ^3J = 2.4, ^4J = 0.65 Hz, 1 H5 Hz, 6-H), 8.0 (d, ^4J = 0.75 Hz, 1 H, 5-H), 7.77 (d, ^4J = 0.75 Hz, 1 H, 2-H), 7.60 (dd, ^3J = 1.85, ^4J = 0.65 Hz, 1 H, 8-H), 6.41 (dd, ^3J = 1.85, ^3J = 2.4 Hz, 1 H, 7-H), 3.94 (s, 3 H, CH_3) ppm. ^{13}C NMR{^{1}H}(50 MHz, $CDCl_3$): δ = 140.34 (C8), 130.55 (C6), 127.98 (C2), 126.30 (C1), 121.93 (C5), 106.68 (C7), 39.51 (C Me) ppm. GC/MS: room temp.: 14.13 min, *m*/*z* = 148. IR (KBr): ṽ = 3057,

1530, 1396, 1342, 1308, 1060, 937, 834 cm^{-1}. R_f: 0.28 (eluent: CH_2Cl_2/ MeOH, 98:2). FAB^+ (NBA): *m/z* (%) = 149 (100) [M + H^+], 55 (24), 148 (22), 69 (20) [pyrazole + H^+], 297 (3) [2M + 1]. HRMS: $C_7H_9N_4$ (M^+ + H) calcd. 149.0827. found: 149.0819.

1-Phenyl-3-trifluoromethyl-1*H*-pyrazole (3v): As described in the General Procedure (82 °C, 24 h), 3-trifluoromethyl-1*H*-pyrazole (272 mg, 2 mmol) was coupled with iodobenzene (336 μL, 3 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), salicylaldoxime (**4**, 55 mg, 0.4 mmol) and acetonitrile (1.2 mL). The crude residue was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 90:10) to provide 399 mg (94% yield) of the desired product as a yellow oi. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.93 (dq, ^3J = 2.5, $^5J_{H,F}$ = 1.0 Hz, 1 H, 7-H), 7.68 (m, 2 H, 2,6-H), 7.31−7.51 (m, 3 H, 3,4,5-H), 6.71 (dq, ^3J = 2.5, $^4J_{H,F}$ = 0.55 Hz, 1 H, 8-H) ppm. ^{13}C NMR{^1H}(50 MHz, $CDCl_3$): δ = 143.86 (q, $^2J_{C,F}$ = 38.3 Hz, C9), 139.35 (C1), 129.49 (C3,5), 128.30 (C7), 127.64 (C4), 121.47 (q, $^1J_{C,F}$ = 268.6 Hz, CF_3), 119.61 (C2,6), 105.85 (q, $^3J_{C,F}$ = 2.1 Hz, C8) ppm. ^{19}F NMR{^1H}(235 MHz, [D_6]acetone): δ = −62.91 (dd, $^5J_{H,F}$ = 0.6, $^4J_{H,F}$ = 1.0 Hz) ppm. GC/MS: room temp.: 13.14 min, *m/z* = 212. IR (KBr): $\tilde{\nu}$ = 3157, 3152, 1602, 1500, 1482, 1465, 1392, 1274 (CF_3), 1172, 1142, 1074, 1055, 971, 950, 908, 757, 744 cm^{-1}. R_f: 0.32 (eluent: petroleum ether/CH_2Cl_2, 90:10). HRMS: $C_{10}H_8N_2F_3$ (M^+ + H) calcd. 213.0640. found: 213.0643.

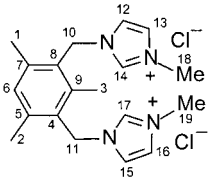
3-Methyl-1-phenyl-1*H*-pyrazole (3x) and 5-Methyl-1-phenyl-1*H*-pyrazole (3x′): As described in the General Procedure (82 °C, 24 h), 3-methyl-1*H*-pyrazole (161 μL, 2 mmol) was coupled with iodobenzene (336 μL, 3 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), salicylaldoxime (**4**, 55 mg, 0.4 mmol) and acetonitrile (1.2 mL). The crude residue was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 15:85) to provide 225 mg (71% yield) of **3x** as a colourless solid and 60 mg (19% yield) of **3x′** as a yellowish oil. **3x:** M.p. 36 °C (ref.[31a] 35−36 °C). ^1H NMR (250 MHz, $CDCl_3$): δ[31a] = 7.80 (d, ^3J = 2.4 Hz, 1 H, 7-H), 7.65 (m, 2 H, 2,6-H), 7.42 (m, 2 H, 3,5-H), 7.23−7.27 (m, 1 H, 4-H), 6.24 (d, ^3J = 2.4 Hz, 1 H, 8-H), 2.39 (s, 3 H, CH_3) ppm. ^{13}C NMR{^1H}(50 MHz, $CDCl_3$): δ[31b] = 150.54 (C9), 140.25 (C1), 129.36 (C3,5), 127.34 (C7), 125.92 (C4), 118.82 (C2,6), 107.52 (C8), 13.76 (C Me) ppm. GC/MS: room temp.: 14.41 min, *m/z* = 158. R_f: 0.55 (eluent CH_2Cl_2). **3x′:** ^1H NMR (250 MHz, $CDCl_3$): δ[31a] = 7.58 (dq, ^3J = 1.6, ^5J = 0.5 Hz, 1 H, 9-H), 7.35−7.49 (m, 5 H, 2,3,4,5,6-H), 6.20 (dq, ^3J = 1.6, ^4J = 0.8 Hz, 1 H, 8-H), 2.34 (dd, ^4J = 0.8, ^5J = 0.5 Hz, 1 H, CH_3) ppm.^{13}C NMR{^1H}(50 MHz, [D_6]DMSO): δ[31b] = 139.56 (C1), 139.46 (C9), 138.40 (C7), 129.05 (C3,5), 127.31 (C4), 124.30 (C2,6), 107.01 (C8), 12.02 (C Me) ppm. GC/MS: room temp.: 14.32 min, *m/z* = 158. R_f: 0.26 (eluent CH_2Cl_2).

4-Methyl-1-phenyl-1*H*-pyrazole (3y): As described in the General Procedure (82 °C, 24 h), 4-methyl-1*H*-pyrazole (165 μL, 2 mmol) was coupled with iodobenzene (336 μL, 3 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), salicylaldoxime (**4**, 55 mg, 0.4 mmol) and acetonitrile (1.2 mL). The oil obtained after the filtration step was directly purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 60:40) to provide 310 mg (98% yield) of a yellow solid. M.p. 41−43 °C (ref.[62] 42−43 °C). ^1H NMR (250 MHz, [D_6]acetone): δ[63] = 8.01 (d, ^4J = 0.7 Hz, 1 H, 7-H), 7.77−7.83 (m, 2 H, 2,6-H), 7.53 (d, ^4J = 0.7 Hz, 1 H, 9-H), 7.40−7.49 (m, 2 H, 3,5-H), 7.24 (m, 1 H, 4-H), 2.12 (s, 1 H, CH_3) ppm. ^{13}C NMR{^1H}(50 MHz, $CDCl_3$): δ[63] = 141.79 (C9), 140.33 (C1), 129.36 (C3,5), 125.95 (C7), 125.34 (C4), 118.70 (C2,6), 118.21 (C8), 8.94 (C Me) ppm. GC/MS: room temp.: 14.89 min, *m/z* = 158. R_f: 0.25 (eluent: CH_2Cl_2/petroleum ether, 20:80).

3,5-Dimethyl-1-phenyl-1*H*-pyrazole (3z): As described in the General Procedure (110 °C, 54 h), 3,5-dimethyl-1*H*-pyrazole (192 mg, 2 mmol) was coupled with iodobenzene (336 μL, 3 mmol) by treatment with cesium carbonate (1.303 g, 4 mmol), Cu_2O (14.4 mg, 0.1 mmol), Chxn-Py-Al (**35**, 117 mg, 0.4 mmol) and DMF (1.2 mL). The crude residue was purified by flash chromatography on silica gel (eluent: gradient hexane/CH_2Cl_2, 100:0 to 10:90) to provide 323 mg (94% yield) of a yellow oil: ^1H NMR (250 MHz, $CDCl_3$): δ = 7.25−7.40 (m, 5 H, 2,3,4,5,6-H), 5.95 (broad singlet, 1 H, 8-H), 2.27 (d, ^4J = 0.8 Hz, 3 H, *C*7-*C*H_3), 2.25 (broad singlet, 3 H, *C*9−*C*H_3) ppm. ^{13}C NMR{^1H}(50 MHz, $CDCl_3$): δ[31b] = 148.86 (C9), 140.0 (C1), 139.28 (C7), 128.93 (C3,5), 127.14 (C4), 124.69 (C2,6), 106.92 (C8), 13.48 (*C*7−CMe), 12.31 (*C*9−CMe) ppm. GC/MS: room temp.: 15.30 min, *m/z* = 172. R_f: 0.17 (eluent: CH_2Cl_2).

Bis(imidazolium) Derivative 12: 2,4-Bis(chloromethyl)mesitylene (500 mg, 2.3 mmol) was added to a solution of *N*-methylimidazole (378 mg, 4.6 mmol) in xylene (20 mL). The mixture was heated at reflux for 48 h. After having cooled, the reaction mixture was filtered and washed with petroleum ether, thus allowing the formation of 702 mg (80%) of bis(imidazolium) salt as a colourless powder. M.p. 270 °C. ^1H NMR (250 MHz, [D_6]DMSO): δ = 9.30 (m, 2 H, 14,17-H), 7.79−7.82 (m, 4 H, 12,13,15,16-H), 7.15 (s, 1 H, 6-H), 5.50 (s, 4 H, 10,11-H), 3.88 (s, 6 H, 18,19-H), 2.33 (s, 3 H, 3-H), 2.29 (s, 6 H, 1,2-H) ppm. ^{13}C NMR{^1H}(50 MHz, [D_6]DMSO): δ = 139.65 (C5,7), 138.98 (C4,8), 136.20 (C9), 131.12 (C6), 128.47 (C14,17), 123.59 (C13,16), 122.33 (C12,15), 47.26 (C10,11), 35.71 (C18,19), 19.43 (C1,2), 15.71 (C3) ppm. IR (KBr): $\tilde{\nu}$ = 1569, 1559, 1457, 1328, 1156, 1110, 765 cm^{-1}. FAB^+ (NBA): *m/z* (%) = 55 (100) [imidazole − N], 95 (72), 69 (71) [imidazole + H^+], 77 (68), 91 (49), 227 (16), 345 (13) [M + Cl^-], 257 (12) [M − MeNCHCH], 309 (11) [M − H^+]. HRMS: $C_{19}H_{26}N_4Cl$ (M^{2+}+Cl^-) calcd. 345.1846. found: 345.1881.

12



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