Cumine, Florimond and Zhou, Shengze and Tuttle, Tell and Murphy, John A. (2017) A study of diketopiperazines as electron-donor initiators in transition metal-free haloarene-arene coupling. Organic and Biomolecular Chemistry, 15. 3324 - 3336. ISSN 1477-0520 , http://dx.doi.org/10.1039/C7OB00036G

Organic & Biomolecular Chemistry

COMMUNICATION

A study of diketopiperazines as electron-donor initiators in transition metal-free haloarene-arene coupling

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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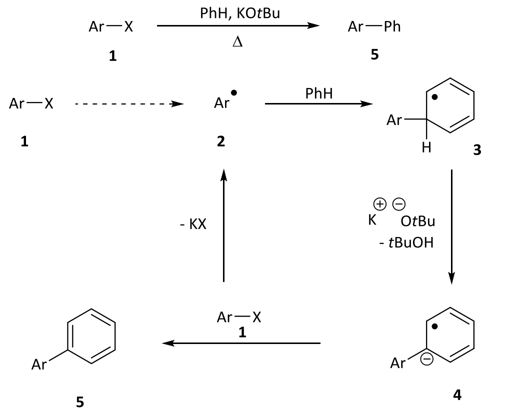
Several diketopiperazines have been shown to promote carbon-carbon coupling between benzene and aryl halides in the presence of potassium *tert*-butoxide and without the assistance of a transition metal catalyst. The structure of the diketopiperazine has an influence on its reductive potential and can help to promote the coupling of the more challenging aryl bromides with benzene.

Introduction

Over the past ten years, transition metal-free cross coupling reactions of aryl halides with benzenes have become a major interest since they were first observed by Itami.[1,2] These reactions require a base (typically potassium *tert*-butoxide) and an additive.[3-16] Whilst organic additives are not always used,[10,11,15] they significantly enhance reaction efficiency in terms of yield and time. The widely-accepted mechanism involved in these coupling reactions is base-promoted homolytic aromatic substitution (BHAS).[17] A molecule of halobenzene **1** receives an electron and forms an aryl radical **2** which adds to benzene to yield an intermediate cyclohexadienyl radical **3**. Deprotonation by the base yields radical anion **4**, which gives an electron to another halobenzene **1**, propagating the chain, and simultaneously releasing biaryl product **5** (Scheme 1).

The initiation process, in other words, the formation of aryl radical **2** from aryl halide **1** to start the chain, has been a main field of research for our group.[18-20] Understanding the nature of this process is the key to extrapolating this transition metal-free cross-coupling reaction to aryl bromides and chlorides which remain more challenging substrates than aryl iodides. We recently reported a study on organic additives and mechanistic studies on their ability to initiate cross-coupling reactions under basic conditions.[19] We have been particularly interested in amino acids as additives since the report of proline and sarcosine as initiators under basic conditions.[11] Amino acids can undergo condensation to form peptides[21] and also cyclic dipeptides under microwave conditions.[22] These cyclic dipeptides, usually called diketopiperazines (DKP), once deprotonated, could act as electron donors. A *N,N'*-dipropyl diketopiperazine **6** has already been reported by our group and was used as an electron donor under basic conditions.[19] This DKP was found to be a good initiator of coupling reactions with iodobenzenes. Herein, we report diketopiperazines **7**-**10**, with different substituents on the nitrogens, all including a phenyl ring in order to improve the DKP solubility in benzene. These DKPs were found to be good initiators for the coupling of iodobenzenes and, for some of them, good initiators for the coupling of bromobenzenes with benzene (Figure 1).

Scheme 1



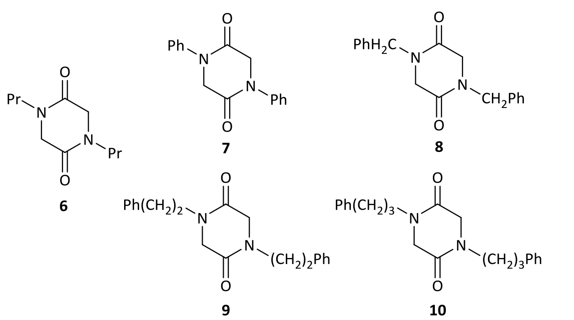


Fig. 1 Diketopiperazines used as precursors to electron donors for coupling reaction of iodo and bromobenzenes with benzene.

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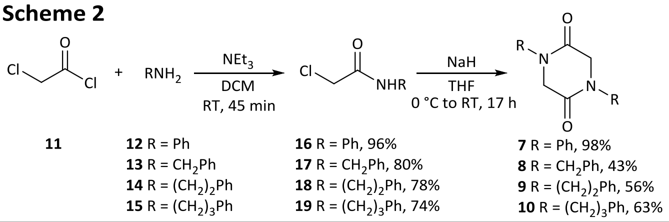
† Electronic Supplementary Information (ESI) available: Experimental procedures, and key spectra are provided. See DOI: 10.1039/x0xx00000x

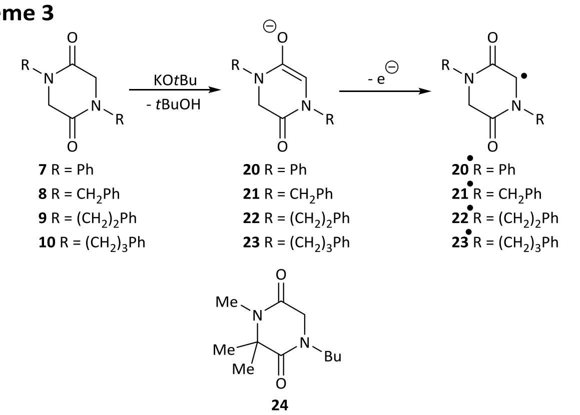
Results and discussion

The diketopiperazines **7**-**10** were each made following the same strategy: amide formation by reaction of an amine with an acyl chloride followed by alkylation reaction under basic conditions (Scheme 2).[19] This easy process afforded the expected diketopiperazines in good to excellent yields. The coupling reactions of several halobenzenes with benzene were made using a substoichiometric amount of DKP, with an excess of potassium *tert*-butoxide used to deprotonate the DKP, forming an enolate that can act as an electron donor (Scheme 3).

Scheme 2



Scheme 3



Already reported DKP, allowing only formation of mono-enolate, able to initiate coupling reactions with equal efficiency.[19]

In principle, the monoanions **20**-**23** could undergo a second deprotonation leading to a dianion species, as we recently reported the formation of dianions with several additives such as pyridine carbinols.[23] We also reported[19] that the DKP **24**, synthesized so that only one position is available for deprotonation, is able to promote the coupling reaction of iodobenzenes with benzene efficiently. Therefore, we propose that only one deprotonation happens and that this is necessary and sufficient for the reaction to be initiated.

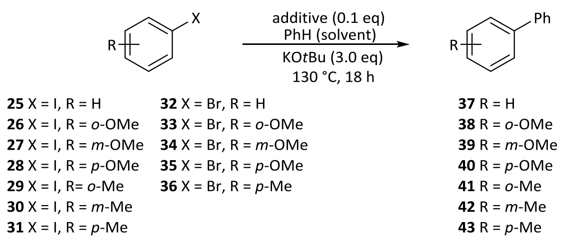


Fig. 2 General reaction and substrate scope.

Once synthesized, each DKP was engaged as an initiator in cross-coupling reactions of unactivated halobenzenes with benzene (Figure 2).

Table 1: Coupling reaction of aryl iodides with benzene initiated by diketopiperazines

Entry	Aryl Halide	DKP	Product	Yield[a] (%)
1	**25** X = I, R = H	**7**	**37** R = H	80
2	**25** X = I, R = H	**8**	**37** R = H	60
3	**25** X = I, R = H	**9**	**37** R = H	74
4	**25** X = I, R = H	**10**	**37** R = H	70
5	**26** X = I, R = *o*-OMe	**7**	**38** R = *o*-OMe	64
6	**26** X = I, R = *o*-OMe	**8**	**38** R = *o*-OMe	51
7	**26** X = I, R = *o*-OMe	**9**	**38** R = *o*-OMe	59
8	**26** X = I, R = *o*-OMe	**10**	**38** R = *o*-OMe	64
9	**27** X = I, R = *m*-OMe	**7**	**39** R = *m*-OMe	61
10	**27** X = I, R = *m*-OMe	**8**	**39** R = *m*-OMe	49
11	**27** X = I, R = *m*-OMe	**9**	**39** R = *m*-OMe	70
12	**27** X = I, R = *m*-OMe	**10**	**39** R = *m*-OMe	69
13	**28** X = I, R = *p*-OMe	**7**	**40** R = *p*-OMe	61
14	**28** X = I, R = *p*-OMe	**8**	**40** R = *p*-OMe	64
15	**28** X = I, R = *p*-OMe	**9**	**40** R = *p*-OMe	80
16	**28** X = I, R = *p*-OMe	**10**	**40** R = *p*-OMe	72
17	**29** X = I, R = *o*-Me	**7**	**41** R = *o*-Me	69
18	**29** X = I, R = *o*-Me	**8**	**41** R = *o*-Me	44
19	**29** X = I, R = *o*-Me	**9**	**41** R = *o*-Me	57
20	**29** X = I, R = *o*-Me	**10**	**41** R = *o*-Me	56
21	**30** X = I, R = *m*-Me	**7**	**42** R = *m*-Me	64
22	**30** X = I, R = *m*-Me	**8**	**42** R = *m*-Me	57
23	**30** X = I, R = *m*-Me	**9**	**42** R = *m*-Me	70
24	**30** X = I, R = *m*-Me	**10**	**42** R = *m*-Me	67
25	**31** X = I, R = *p*-Me	**7**	**43** R = *p*-Me	60
26	**31** X = I, R = *p*-Me	**8**	**43** R = *p*-Me	60
27	**31** X = I, R = *p*-Me	**9**	**43** R = *p*-Me	78
28	**31** X = I, R = *p*-Me	**10**	**43** R = *p*-Me	68

[a] Isolated yield

Additive **7** was particularly efficient to promote the coupling of iodobenzenes to benzene however, its efficiency for the coupling of bromobenzenes to benzene was not satisfactory (Table 1 and Table 2). We were pleased to find that additive **8** was efficient with both iodobenzenes and bromobenzenes (except for the particular case of 3-bromoanisole **34**). This made us consider the effect of the N-substituent on the reductive ability of the electron donors **20**-**23**. The phenyl substituent of **20** decreases the reductive capacity due to its withdrawing inductive effect.[24] Computational optimization[25-26] of the structure of **20** shows there is no co-planarity of the two arene rings with the centre ring, and thus little or no electron delocalisation by resonance (Figure 3). We also checked the spin density of **20**• and found that it is localised only on its central ring and not on the phenyl substituents. DKPs **9** and **10** also promoted the coupling reaction of aryl bromides with benzene but not as efficiently as DKP **8**. Their efficiency with aryl bromides shows a stronger reductive effect than **20** since the inductive effect of the N-substituents of **21**-

23 is donating.[24] We also computationally optimized the electron transfer reaction[27] involving these initiators and found lower barriers for **21**-**23**, derived from **8**-**10**, than **20**, derived from **7** which is in accordance with our experimental results (Table 3). However, none of these DKP donors was able to promote the coupling reaction of chlorobenzenes or fluorobenzenes to benzene.

Table 2: Coupling reaction of aryl bromides with benzene initiated by diketopiperazines

Entry	Aryl Halide	DKP	Product	Yield[a] (%)
1	**32** X = Br, R = H	**7**	**37** R = H	14
2	**32** X = Br, R = H	**8**	**37** R = H	68
3	**32** X = Br, R = H	**9**	**37** R = H	32
4	**32** X = Br, R = H	**10**	**37** R = H	32
5	**33** X = Br, R = *o*-OMe	**7**	**38** R = *o*-OMe	36
6	**33** X = Br, R = *o*-OMe	**8**	**38** R = *o*-OMe	50
7	**33** X = Br, R = *o*-OMe	**9**	**38** R = *o*-OMe	48
8	**33** X = Br, R = *o*-OMe	**10**	**38** R = *o*-OMe	59
9	**34** X = Br, R = *m*-OMe	**7**	**39** R = *m*-OMe	2
10	**34** X = Br, R = *m*-OMe	**8**	**39** R = *m*-OMe	2
11	**34** X = Br, R = *m*-OMe	**9**	**39** R = *m*-OMe	2
12	**34** X = Br, R = *m*-OMe	**10**	**39** R = *m*-OMe	2
13	**35** X = Br, R = *p*-OMe	**7**	**40** R = *p*-OMe	13
14	**35** X = Br, R = *p*-OMe	**8**	**40** R = *p*-OMe	56
15	**35** X = Br, R = *p*-OMe	**9**	**40** R = *p*-OMe	21
16	**35** X = Br, R = *p*-OMe	**10**	**40** R = *p*-OMe	29
17	**36** X = Br, R = *p*-Me	**7**	**43** R = *p*-Me	12
18	**36** X = Br, R = *p*-Me	**8**	**43** R = *p*-Me	47
19	**36** X = Br, R = *p*-Me	**9**	**43** R = *p*-Me	29
20	**36** X = Br, R = *p*-Me	**10**	**43** R = *p*-Me	37

[a] Isolated yield

In the particular case of 3-bromoanisole **34**, very low yields of the coupling product with benzene were found, no matter which DKP was used. Instead, we found a selective formation of 1-(*tert*-butoxy)-3-methoxybenzene **44** resulting from a selective benzyne formation, by action of potassium *tert*-butoxide on 3-bromoanisole **34**, followed by a selective nucleophilic addition of *tert*-butoxide to the benzyne **45** (Scheme 4). This particular selectivity in both the formation of the benzyne and the addition of *tert*-butoxide is known[27] and can be explained as follows: of the two protons leading to the formation of benzyne by their elimination, the more acidic one is *ortho* to the methoxy group due to the attractive inductive effect of this substituent. Also, the potassium can coordinate with the methoxy group and direct the selective deprotonation on its *ortho* position. The addition of *tert*-butoxide to benzyne **45** is *meta* to the methoxy group as this leads to the formation of the more stable carbanion due to the inductive attractive effects of both the methoxy and *tert*-butoxy groups. The selectivity of the addition is also in accordance with computational results published by Houk and Garg[29] who showed that the nucleophilic addition will happen on the aryne terminus with the larger internal angle which, in the case of a mono-substituted benzyne such as **45**, is at the *meta*-position of the substituent. Our optimized structure of **45** showed the same result with an internal angle of 136˚ at the *meta* position and 118˚ at the *ortho* position. An interesting fact is, while the benzyne formation/nucleophilic addition was favored over the actual coupling reaction with 3-bromoanisole **34**, the opposite happened with 3-iodoanisole **27** where the coupling with benzene was not affected by any other reaction. This shows again that iodobenzenes are more reactive substrates toward electron transfer than bromobenzenes due to the high reactivity of the C-I bond.

Anion **20**

Radical **20˙**

Anion **21**

Radical **21˙**

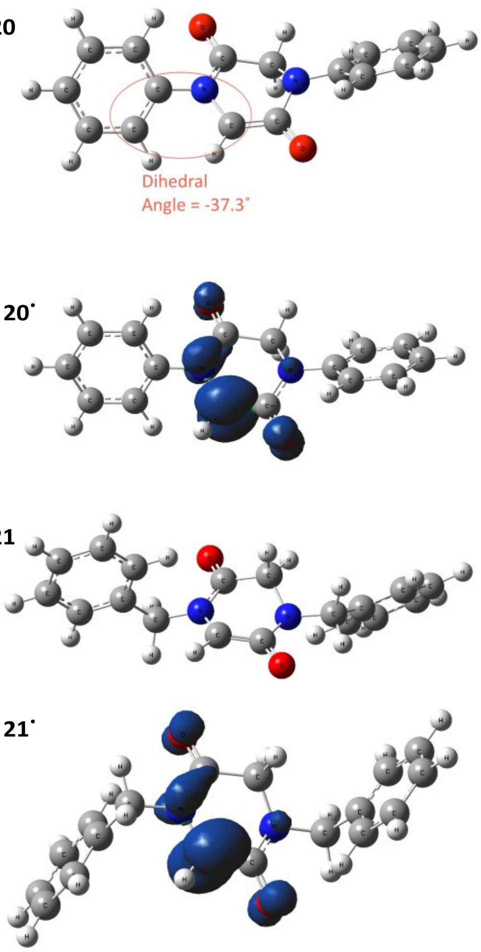


Fig. 3 Optimized structures of anions **20** and **21** and radicals **20˙** and **21˙** (spin density shown in blue).

The ability of aryl halides to generate benzynes[30] should not be underestimated and it is not a process only seen with *meta*-haloanisoles. In fact, it is a process that occurs during all the reactions we report. The key to make the benzyne formation a side-reaction is the use of an additive such as the several DKPs we report here (except for the particular case of 3-bromoanisole **34**). When we reacted 4-bromoanisole **35** with DKP **8** under our general conditions, we found not only the coupling product **40** but also two regioisomers **44** and **46** resulting from the nucleophilic addition of *tert*-butoxide on a benzyne ring (Scheme 5).

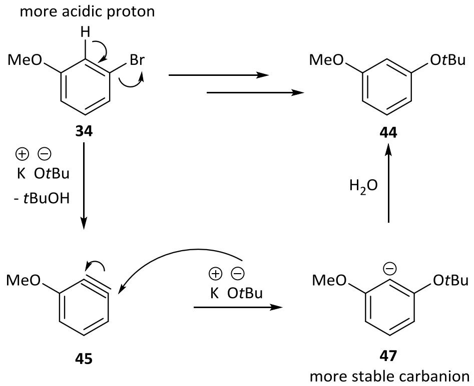
The addition of *tert*-butoxide was also observed when bromobenzene **32** was used under the same conditions and formed *tert*-butoxybenzene **48**.

Table 3: Energies of electron transfer reactions[a]

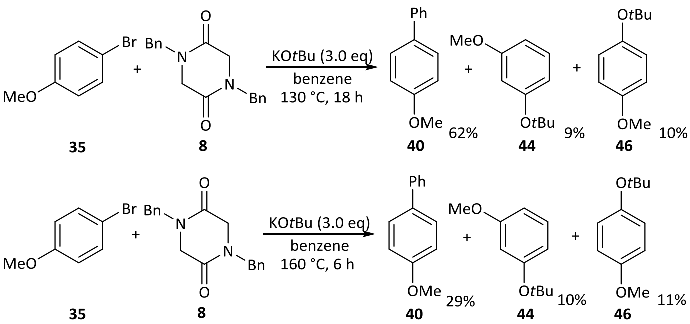
Entry	Substrate	Initiator	ΔG*	ΔG_{rel}
1	**25** X = I, R = H	**20**	31.3	22.9
2	**25** X = I, R = H	**21**	28.6	18.5
3	**25** X = I, R = H	**22**	27.7	17.0
4	**25** X = I, R = H	**23**	27.0	15.1
5	**28** X = I, R = *p*-OMe	**20**	35.7	27.7
6	**28** X = I, R = *p*-OMe	**21**	32.9	23.4
7	**28** X = I, R = *p*-OMe	**22**	31.9	21.8
8	**28** X = I, R = *p*-OMe	**23**	31.2	20.0
9	**32** X = Br, R = H	**20**	31.1	22.8
10	**32** X = Br, R = H	**21**	28.4	18.5
11	**32** X = Br, R = H	**22**	27.4	16.9
12	**32** X = Br, R = H	**23**	26.8	15.0
13	**35** X = Br, R = *p*-OMe	**20**	34.3	24.9
14	**35** X = Br, R = *p*-OMe	**21**	31.7	20.5
15	**35** X = Br, R = *p*-OMe	**22**	30.7	19.0
16	**35** X = Br, R = *p*-OMe	**23**	30.0	17.1

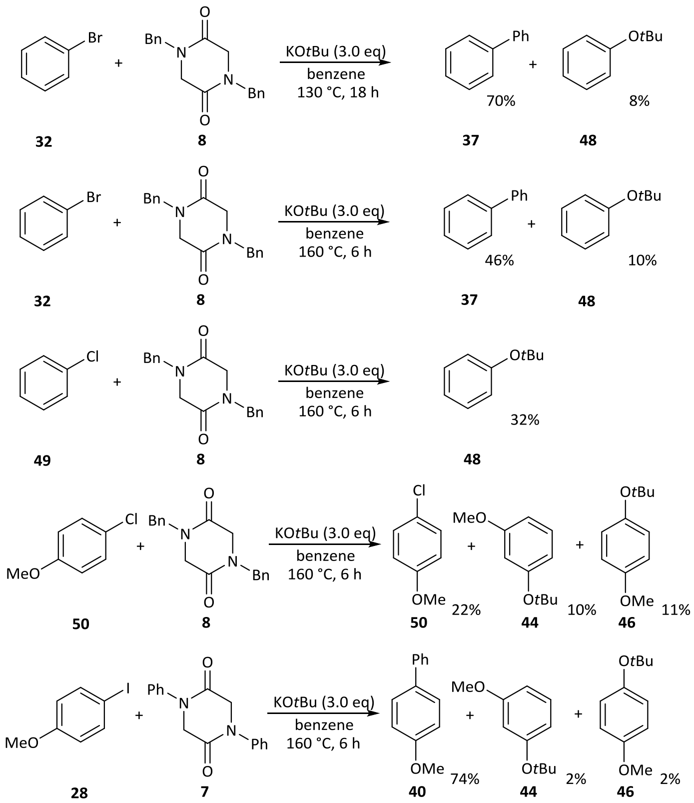
[a] Energies reported in kcal/mol

Scheme 4



When increasing the temperature of the reaction to see if this could improve the coupling reaction with bromobenzenes and eventually chlorobenzenes (chlorobenzene **49** and 4-chloroanisole **50** were tested), noted that an increased temperature actually disfavoured the coupling reaction and did not alter the benzyne formation.

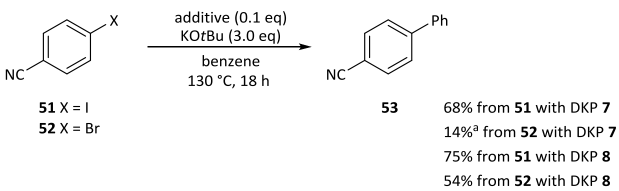




Scheme 5 Evidence of benzyne formation.[a]

[a] Yields calculated from ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Chlorobenzenes as substrates along with a DKP donor initiator never afforded the desired coupling product. These less reactive substrates toward metal-free cross-coupling reactions remain a challenge that will require even more powerful organic electron donors to be overcome. The benzyne formation from aryl halides under basic conditions can also alter the cross-coupling reaction of electron-poor aryl halides with benzene. On one hand, 4-iodobenzonitrile **51** and 4-bromobenzonitrile **52** afforded the expected coupling product **53** with benzene when DKPs **7** and **8** were used (Scheme 6), with a moderate amount of benzyne adducts observed only when DKP **7** was used with 4-bromobenzonitrile **52** alongside with a small amount of **53**.



Scheme 6 Coupling reaction of 4-halobenzonitriles with benzene.

[a] For this reaction, **53** was recovered in an inseparable mixture with the benzyne adducts (see experimental details for more information).

On the other hand, 4-iodobenzotrifluoride **54** and 4-bromobenzotrifluoride **55** did not afford the coupling product with benzene but only the two benzyne adducts **56** and **57**

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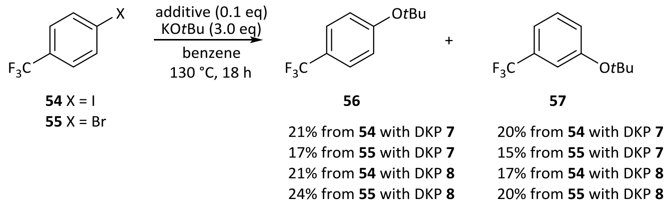
(Scheme 7). The strong attractive inductive effect of the trifluoromethyl group[24] must result in an increased acidity of the protons *ortho* to the halide thus in an easier benzyne formation.



Scheme 7 4-halobenzotrifluorides as non-reactive substrates toward metal-free cross-coupling reaction with benzene promoted by DKPs.

These last results show that some electron poor aryl halides might favour the benzyne mechanism over the cross-coupling reaction thus not being suitable substrates for metal-free cross-coupling reactions involving electron transfer under basic conditions.

Conclusions

Effective additives for initiating the cross-coupling reaction of iodo and bromoarenes with benzene in the presence of potassium *tert*-butoxide were found. These additives are *N*,*N*'-disubstituted diketopiperazine derivatives and may arise from secondary amino acids, such as proline, under the conditions of the cross coupling reactions. Some of these novel additives mediate the transition metal-free cross coupling reactions not only of unactivated aryl iodides but also aryl bromides with benzene, and this depends on the substituents attached to the nitrogens of the diketopiperazines. Achieving the same reaction with aryl chlorides remains a challenging process and likely requires even more powerful electron donors. Under current protocols, chlorobenzenes undergo preferential formation of benzyne rather than the cross-coupling reaction.

Experimental Section

General experimental information

All the reactions were performed in oven-dried apparatus and preparation of the diketopiperazines was carried out under argon atmosphere using dry solvents. Tetrahydrofuran, dichloromethane and hexane were dried with a Pure-Solv 400 solvent purification system by Innovative Technology Inc., U.S.A. A glove box (Innovative Technology Inc., U.S.A.) was used to introduce all the reactants into a pressure tube. All the reagents were bought from commercial suppliers and used without further purification, unless stated otherwise. A Büchi rotary evaporator was used to concentrate the reaction mixtures. Thin layer chromatography (TLC) was performed using aluminium-backed sheets of silica gel and visualized under a UV lamp (254 nm). Column chromatography was performed to purify compounds by using silica gel 60 (200-400 mesh).

Proton NMR (^{1}H) spectra was recorded at 400 MHz on a Bruker DPX 400 spectrometer. Carbon NMR (^{13}C) spectra were recorded at 100 MHz. The chemical shifts are quoted in parts per million (ppm) by taking tetramethylsilane as a reference (δ = 0) but calibrated on the residual non-deuterated solvent signal. Signal multiplicities are abbreviated as: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; m, multiplet; bs, broad singlet; coupling constants are given in Hertz (Hz).

Infra-Red spectra were recorded using a Shimadzu FT-IR Spectrophotometer (Model IRAffinity-1) with a MIRacle Single Reflection Horizontal ATR Accessory. Melting points were determined on a Gallenkamp Melting point apparatus. High resolution mass spectra were recorded at EPSRC National Mass Spectrometry Service Centre, Swansea. The spectra were recorded using electron ionization (EI), chemical ionization (CI), fast atom bombardment (FAB) or electrospray ionization (ESI) techniques as stated for each compound.

Synthesis of Diketopiperazines 7-10

Preparation of 1,4-diphenylpiperazine-2,5-dione 7 [R = Ph]

To a solution of freshly distilled aniline **12** (1.0 equiv, 6.0 g, 64.43 mmol) and triethylamine (1.1 equiv, 9.87 ml, 70.87 mmol) in DCM (100 mL) was slowly added chloroacetyl chloride **11** (1.1 equiv, 5.64 ml, 70.87 mmol).

After addition, the mixture was stirred at RT for 45 min and quenched with water (70 mL) and extracted with DCM (3 x 40 mL).

The combined organic phases were washed with hydrochloric acid (2M, 100 mL) and with a saturated solution of $NaHCO_3$ (100 mL).

The organic phase was dried over Na_2SO_4, filtered and concentrated to afford 2-chloro-*N*-phenylacetamide **16** as a brown/yellow solid (10.52 g, 62.02 mmol, 96.25%). M.Pt: 118-120 °C (lit. 122-125 °C).[31] δ_H (400 MHz, $CDCl_3$): 4.19 (2H, s, C*H*$_2$), 7.17 (1H, m, Ar*H*), 7.36 (2H, m, Ar*H*), 7.55 (2H, m, Ar*H*), 8.23 (1H, bs, N*H*). δ_C (101MHz, $CDCl_3$): 43.0, 120.3, 125.4, 129.3, 136.8, 163.9. IR (NEAT) ν = 688, 748, 856, 1249, 1342, 1442, 1496, 1556, 1600, 1668, 3097, 3143, 3207, 3265 cm^{-1}. *m/z* (APCI) calcd for C_8H_9ClNO $[M+H]^+$: 170.0367, found: 170.0366.

Sodium hydride (60% in oil, 1.0 equiv, 2.47 g, 62.02 mmol) was washed with dry hexane (2 x 20 mL) and the hexane was removed via cannula. Dry THF (50 mL) was added to the sodium hydride and the mixture was cooled to 0 °C. A solution of **16** (1.0 equiv, 10.52 g, 62.02 mmol) in dry THF (150 mL) was slowly added. The resulting mixture was stirred from 0 °C to RT for 17 h.

Water (200 mL) was added and the resulting mixture was filtered on a funnel to isolate the product as a solid, which was washed with DCM. The filtrate was extracted three times with DCM. The organic phase and the isolated solid were combined and concentrated to afford the product 1,4-diphenylpiperazine-2,5-dione **7** as a pale brown solid (8.09 g, 30.38 mmol, 97.9%). M.Pt: 262-264 °C (lit. 266-267 °C).[32] δ_H (400 MHz, $CDCl_3$): 4.55 (4H, s, C*H*$_2$), 7.32-7.38 (6H, m, Ar*H*), 7.44-7.49 (4H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 53.6, 125.1, 127.7, 129.6, 139.7, 164.1. IR (NEAT) ν = 690, 754, 1141, 1251, 1334, 1431, 1450, 1469, 1496, 1591, 1651, 2947, 3059 cm^{-1}. *m/z* (APCI) calcd for $C_{16}H_{15}N_2O_2$ $[M+H]^+$: 267.1128, found: 267.1130.

Preparation of 1,4-dibenzylpiperazine-2,5-dione 8 [R=CH_2Ph]

To a solution of benzylamine **13** (1.0 equiv, 1.0 g, 9.33 mmol) and triethylamine (1.1 eq, 1.43 mL, 10.27 mmol) in DCM (30 mL) was slowly added chloroacetyl chloride (1.1 equiv, 0.82 mL, 10.27 mmol).

After addition, the mixture was stirred at RT for 45 min and quenched with water (20 mL) and extracted with DCM (3 x 20 mL).

The combined organic phases were washed with hydrochloric acid (2M, 20 mL) and with a saturated solution of $NaHCO_3$ (20 mL).

The organic phase was dried over Na_2SO_4, filtered and concentrated to afford the product *N*-benzyl-2-chloroacetamide **17** as a yellow solid (1.380 g, 7.52 mmol, 80.5%). M.Pt: 87-90 °C (lit. 91-92 °C).[33] δ_H (400 MHz, $CDCl_3$): 4.12 (2H, s, C*H*$_2$), 4.50 (2H, d, *J* = 5.6 Hz, C*H*$_2$), 6.87 (1H, bs, N*H*), 7.38-7.29 (5H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 42.7, 44.0, 127.9, 127.9, 129, 137.3, 165.9. IR (NEAT) ν = 723, 744, 783, 1060, 1234, 1550, 1645, 3275. *m/z* (APCI) calcd for $C_9H_{11}ClNO$ $[M+H]^+$: 184.0524, found: 184.0524.

Sodium hydride (60% in oil, 1.1 equiv, 0.33 g, 8.25 mmol) was washed with dry hexane (2 x 10 mL) and the hexane was removed. Dry THF (15 mL) was added to the sodium hydride and cooled down to 0 °C and a solution of **17** (1.0 equiv, 1.380 g, 7.52 mmol) in dry THF (25 mL) was slowly added.

The resulting mixture was stirred from 0 °C to RT for 17 h. The mixture was quenched with water (50 ml). The non-soluble solid in water was filtered and the filtrate was extracted with DCM (2 x 30 ml). The combined organic phases and solid previously filtered were concentrated at Büchi. The crude product was dissolved into DCM and purified by column chromatography on silica gel using DCM/MeOH (97%/3%).

1,4-Dibenzylpiperazine-2,5-dione **8** was obtained as an off-white solid (0.476 g, 1.62 mmol, 43%). M.Pt: 94-95 °C (lit. 95-97 °C).[34] δ_H (400 MHz, $CDCl_3$): 3.96 (4H, s, C*H*$_2$), 4.58 (4H, s, C*H*$_2$), 7.28-7.26 (4H, m, Ar*H*), 7.37-7.31 (6H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 49.3, 49.4, 128.3, 128.7, 129.1, 135.1, 163.4. IR (NEAT) ν = 717, 933, 1065, 1160, 1275, 1328, 1483, 1643. *m/z* (APCI) calcd for $C_{19}H_{19}N_2O_2$ $[M+H]^+$: 295.1441, found: 295.1442.

Preparation of 1,4-diphenethylpiperazine-2,5-dione 9 [R = $(CH_2)_2$Ph]

To a solution of 2-phenylethan-1-amine **14** (1.0 equiv, 1.0 g, 8.25 mmol) and triethylamine (1.1 equiv, 1.4 mL, 9.08 mmol) in DCM (30 mL) was slowly added chloroacetyl chloride (1.1 equiv, 0.73 mL, 9.08 mmol).

After addition, the mixture was stirred at RT for 45 min and quenched with water (20 mL) and extracted with DCM (3 x 20 mL).

The combined organic phases were washed with hydrochloric acid (2M, 20 mL) and with a saturated solution of $NaHCO_3$ (20 mL).

The organic phase was dried over Na_2SO_4, filtered and concentrated to afford the product 2-chloro-N-phenylacetamide **18** as a brown solid (1.275 g, 6.45 mmol, 78.2%). M.Pt: 60-61 °C (lit. 66-67 °C).[35] δ_H (400 MHz, $CDCl_3$): 2.85 (2H, t, *J* = 6.8 Hz, C*H*$_2$), 3.57 (2H, q, *J* = 6.8 Hz, C*H*$_2$), 4.02 (2H, s, C*H*$_2$), 6.60 (1H, bs, N*H*), 7.21 (2H, m, Ar*H*), 7.25 (1H, m, Ar*H*), 7.33 (2H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 35.6, 41.1, 42.8, 126.9, 128.9, 138.5, 165.86. IR (NEAT) ν = 696, 750, 1040, 1188, 1260, 1541, 1643, 3335. *m/z* (APCI) calcd for $C_{10}H_{13}ClNO$ $[M+H]^+$: 198.0680, found: 198.0680.

Sodium hydride (60% in oil, 1.0 equiv, 258 mg, 6.45 mmol) was washed with dry hexane (2 x 10 mL) and the hexane was removed. Dry THF (20 mL) was added to the sodium hydride and cooled down to 0 °C and a solution of **18** (1.0 equiv, 1.275 g, 6.45 mmol) in dry THF (30 mL) was slowly added.

The resulting mixture was stirred from 0 °C to RT for 17 h. The mixture was quenched with water (30 ml) and extracted with DCM (4 x 30 ml). The combined organic phases were concentrated at Büchi. The crude product was dissolved into DCM and purified by column chromatography on silica gel using DCM/MeOH (98%/2%). 1,4-diphenethylpiperazine-2,5-dione **9** was obtained as a beige solid (588 mg, 1.82 mmol, 56.4%). M.Pt.: 205-207 °C (lit. 210 °C).[36] δ_H (400 MHz, $CDCl_3$): 2.88 (4H, t, *J* = 7.6 Hz, C*H*$_2$), 3.60 (4H, t, *J* = 7.6 Hz, C*H*$_2$), 3.78 (4H, s, C*H*$_2$), 7.19 (4H, m, Ar*H*), 7.24 (2H, m, Ar*H*), 7.31 (4H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 33.3, 48.1, 50.9, 127.0, 128.8, 128.9, 138.1, 163.5. IR (NEAT) ν = 696, 739, 1169, 1244, 1298, 1339, 1429, 1485, 1643, 2938. *m/z* (APCI) calcd for $C_{20}H_{23}N_2O_2$ $[M+H]^+$: 323.1754, found: 323.1758.

Preparation of 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 10 [R = $(CH_2)_3$Ph]

To a solution of 3-phenylpropan-1-amine **15** (1.0 equiv, 1.0 g, 7.40 mmol) and triethylamine (1.1 equiv, 1.14 mL, 8.12 mmol) in DCM (30 mL) was slowly added chloroacetyl chloride (1.1 equiv, 0.65 mL, 8.12 mmol). After addition, the mixture was stirred at RT for 30 min and quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic phases were washed with a 2M solution of HCl in water (20 mL) and with a saturated solution of $NaHCO_3$ (20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to afford the product 2-chloro-N-(3-phenylpropyl)acetamide **19** as an orange oil (1.167 g, 5.51 mmol, 74.5%). δ_H (400 MHz, $CDCl_3$): 1.90 (2H, qu, *J* = 7.6 Hz, C*H*$_2$), 2.68 (2H, t, *J* = 7.6 Hz, C*H*$_2$), 3.50 (2H, q, *J* = 6.0 Hz, C*H*$_2$), 4.02 (2H, s, C*H*$_2$), 6.56 (1H, bs, N*H*), 7.20 (3H, m, Ar*H*), 7.30 (2H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 30.9, 33.3, 39.6, 42.8, 126.3, 128.5, 128.7, 141.2, 166.0. IR (NEAT) ν = 698, 745, 1260, 1537, 1653, 2938, 3292. *m/z* (APCI) calcd for $C_{11}H_{15}ClNO$ $[M+H]^+$: 212.0837, found: 212.0835.

Sodium hydride (60% in oil, 1.0 equiv, 220.5 mg, 5.51 mmol) was washed with dry hexane (2 x 10 mL) and the hexane was removed. Dry THF (20 mL) was added to the sodium hydride and cooled down to 0 °C and a solution of **19** (1.0 equiv, 1.167 g, 5.51 mmol) in dry THF (30 mL) was slowly added. The resulting mixture was stirred from 0 °C to RT for 22 h. The mixture was quenched with water (30 ml) and extracted with DCM (4 x 30 ml). The combined organic phases were concentrated at rotavap. The crude product was dissolved into DCM and purified by column chromatography on silica gel using DCM/MeOH (98%/2%). 1,4-bis(3-phenepropyl)piperazine-2,5-dione **10** was obtained as a pale yellow solid (604 mg, 1.72 mmol, 62.6%). M.Pt.: 115-118 °C (no lit. value). δ_H (400 MHz, $CDCl_3$): 1.90 (4H, qt, *J* = 7.2 Hz, C*H*$_2$), 2.64 (4H, t, *J* = 7.6 Hz, C*H*$_2$), 3.42 (4H, t, *J* = 7.6 Hz, C*H*$_2$), 3.85 (4H, s, C*H*$_2$), 7.19 (6H, m, Ar*H*), 7.29 (4H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 28.1, 33.2, 45.9, 50.1, 126.3, 128.4, 128.6, 141.0, 163.5. IR (NEAT) ν = 608, 694, 723, 754, 1024, 1487, 1647, 2932, 3292. *m/z* (APCI) calcd for $C_{22}H_{27}N_2O_2$ $[M+H]^+$: 351.2067, found: 351.2064.

Coupling Reactions of Aryl Iodides and Bromides with Benzene (Table 1 and Table 2)

General Reaction Conditions

All reactions were performed on a 1.0 mmol scale of the aryl halide. The mixture of the aryl halide (1.0 mmol), additive (0.1 mmol) and potassium *tert*-butoxide (337 mg, 3.0 mmol) in 10 mL of benzene was sealed in a 15 mL pressure tube in glovebox. The tube was removed from the glovebox and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the reaction was quenched by water (30 mL). The mixture was extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography eluting with hexane when R = H, Me and with Et_2O (2%) in hexane when R = OMe.

Substrate: iodobenzene 25, Additive: 1,4-diphenylpiperazine-2,5-dione 7 (Table 1, Entry 1)

Iodobenzene **25** (0.204 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.026 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **37** as a white solid (123.4 mg, 0.800 mmol, 80.0%). M.Pt: 69-71 °C (lit. 70-71 °C).[37] δ_H (400 MHz, $CDCl_3$): 7.35 (2H, m, Ar*H*), 7.44 (4H, m, Ar*H*), 7.60 (4H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 127.3, 127.4, 128.9, 141.4. IR (NEAT) ν = 694, 725, 902, 1004, 1429, 1475, 2924, 3034, 3061. *m/z* (APCI) calcd for $C_{12}H_{11}$ $[M+H]^+$: 155.0855, found: 155.0851.

Substrate: iodobenzene 25, Additive: 1,4-dibenzylpiperazine-2,5-dione 8 (Table 1, Entry 2)

Iodobenzene **25** (0.204 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **37** as a white solid (92.5 mg, 0.600 mmol, 60.0%). NMR spectra details as above.

Substrate: iodobenzene 25, Additive: 1,4-diphenethylpiperazine-2,5-dione 9 (Table 1, Entry 3)

Iodobenzene **25** (0.204 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **9** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **37** as a white solid (114.1 mg, 0.740 mmol, 74.0%). NMR spectra details as above.

Substrate: iodobenzene 25, Additive: 1,4-bis(3-phenylpropyl)-piperazine-2,5-dione 10 (Table 1, Entry 4)

Iodobenzene **25** (0.204 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **10** (0.035 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **37** as a white solid (107.9 mg, 0.700 mmol, 70.0%). NMR spectra details as above.

Substrate: 2-iodoanisole 26, Additive: 1,4-diphenylpiperazine-2,5-dione 7 (Table 1, Entry 5)

2-iodoanisole **26** (0.234 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.026 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1′-biphenyl **38** as a colourless oil (118.1 mg, 0.640 mmol, 64.0%). δ_H (400 MHz, $CDCl_3$): 3.87 (3H, s, CH_3), 7.06 (1H, m, Ar*H*), 7.11 (1H, m, Ar*H*), 7.37-7.42 (3H, m, Ar*H*), 7.48 (2H, m, Ar*H*), 7.62 (2H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 55.6, 111.4, 120.9, 127.0, 128.0, 128.7, 129.6, 130.8, 131.0, 138.6, 156.6. IR (NEAT) ν = 696, 731, 752, 1026, 1122, 1234, 1257, 1429, 1481, 2833, 3059. *m/z* (APCI) calcd for $C_{13}H_{12}O$ $[M]^+$: 184.0883, found: 184.0878.

Substrate: 2-iodoanisole 26, Additive: 1,4-dibenzylpiperazine-2,5-dione 8 (Table 1,Entry 6)

2-Iodoanisole **26** (0.234 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1′-biphenyl **38** as a colourless oil (94.0 mg, 0.510 mmol, 51.0%). NMR spectra details as above.

Substrate: 2-iodoanisole 26, Additive: 1,4-diphenethylpiperazine-2,5-dione 9 (Table 1, Entry 7)

2-Iodoanisole **26** (0.234 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **9** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1′-biphenyl **38** as a colourless oil (108.7 mg, 0.590 mmol, 59.0%). NMR spectra details as above.

Substrate: 2-iodoanisole 26, Additive: 1,4-bis(3-phenylpropyl)-piperazine-2,5-dione 10 (Table 1, Entry 8)

2-iodoanisole **26** (0.234 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **10** (0.035 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1′-biphenyl **38** as a colourless oil (117.9 mg, 0.640 mmol, 64.0%). NMR spectra details as above.

Substrate: 3-iodoanisole 27, Additive: 1,4-diphenylpiperazine-2,5-dione 7 (Table 1, Entry 9)

3-Iodoanisole **27** (0.234 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.026 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1′-biphenyl **39** as a colourless oil (111.6 mg, 0.610 mmol, 61.0%). δ_H (400 MHz, $CDCl_3$): 3.88 (3H, s, CH_3), 6.92 (1H, m, Ar*H*), 7.15 (1H, m, Ar*H*), 7.20 (1H, m, Ar*H*), 7.35-7.39 (2H, m, Ar*H*), 7.45 (2H, m, Ar*H*), 7.61 (2H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 55.4, 112.8, 113.0, 119.8, 127.3, 127.5, 128.8, 129.8, 141.2, 142.9, 160.1. IR (NEAT) ν = 694, 754, 850, 862, 1018, 1037, 1053, 1211, 1294, 1419, 1477, 1571, 1597, 2833, 3057. *m/z* (APCI) calcd for $C_{13}H_{12}O$ $[M]^+$: 184.0883, found: 184.0878

Substrate: 3-iodoanisole 27, Additive: 1,4-dibenzylpiperazine-2,5-dione 8 (Table 1, Entry 10)

3-Iodoanisole **27** (0.234 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1′-biphenyl **39** as a colourless oil (90.3 mg, 0.490 mmol, 49.0%). NMR spectra details as above.

Substrate: 3-iodoanisole 27, Additive: 1,4-diphenethylpiperazine-2,5-dione 9 (Table 1, Entry 11)

3-Iodoanisole **27** (0.234 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **9** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1′-biphenyl **39** as a colourless oil (129.0 mg, 0.700 mmol, 70.0%). NMR spectra details as above.

Substrate: 3-iodoanisole 27, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 10 (Table 1, Entry 12)
3-Iodoanisole **27** (0.234 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **10** (0.035 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1′-biphenyl **39** as a colourless oil (127.1 mg, 0.690 mmol, 69.0%). NMR spectra details as above.

Substrate: 4-iodoanisole 28, Additive: 1,4-diphenylpiperazine-2,5-dione 7 (Table 1, Entry 13)
4-Iodoanisole **28** (0.234 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.026 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1′-biphenyl **40** as a white solid (112.4 mg, 0.610 mmol, 61.0%). M.Pt: 84-85 °C (lit. 84-85 °C).[38] δ_H (400 MHz, $CDCl_3$): 3.86 (3H, s, CH_3), 6.98 (2H, m, Ar*H*), 7.30 (1H, m, Ar*H*), 7.42 (2H, m, Ar*H*), 7.51-7.57 (4H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 55.5, 114.4, 126.8, 126.9, 128.3, 128.9, 133.9, 141.0, 159.3. IR (NEAT) ν = 686, 758, 833, 1033, 1184, 1199, 1247, 1483, 1604, 2835, 2962, 3003, 3034, 3066. *m/z* (APCI) calcd for $C_{13}H_{12}O$ $[M]^+$: 184.0883, found: 184.0878.

Substrate: 4-iodoanisole 28, Additive: 1,4-dibenzylpiperazine-2,5-dione 8 (Table 1, Entry 14)
4-Iodoanisole **28** (0.234 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1′-biphenyl **39** as a white solid (117.9 mg, 0.640 mmol, 64.0%). NMR spectra details as above.

Substrate: 4-iodoanisole 28, Additive: 1,4-diphenethylpiperazine-2,5-dione 9 (Table 1, Entry 15)
4-Iodoanisole **28** (0.234 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **9** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1′-biphenyl **40** as a white solid (147.4 mg, 0.800 mmol, 80.0%). NMR spectra details as above.

Substrate: 4-iodoanisole 28, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 10 (Table 1, Entry 16)
4-Iodoanisole **28** (0.234 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **10** (0.035 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1′-biphenyl **40** as a white solid (132.6 mg, 0.720 mmol, 72.0%). NMR spectra details as above.

Substrate: 2-iodotoluene 29, Additive: 1,4-diphenylpiperazine-2,5-dione 7 (Table 1, Entry 17)
2-Iodotoluene **29** (0.218 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.026 g, 0.1 mmol), KO*t*Bu (0.337 mg, 3.0 mmol) in benzene (10 mL) and afforded 2-methyl-1,1′-biphenyl **41** as a colourless oil (116.0 mg, 0.690 mmol, 69.0%). δ_H (400 MHz, $CDCl_3$): 2.33 (3H, s, CH_3), 7.30 (3H, m, Ar*H*), 7.37 (3H, m, Ar*H*), 7.44-7.66 (3H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 20.6, 125.9, 126.9, 127.3, 127.4, 128.2, 128.9, 129.3, 129.9, 130.4, 135.5, 142.1, 142.2. IR (NEAT) ν = 700, 725, 746, 773, 1439, 1479. *m/z* (APCI) calcd for $C_{13}H_{12}$ $[M]^+$: 168.0934, found: 168.0930.

Substrate: 2-iodotoluene 29, Additive: 1,4-dibenzylpiperazine-2,5-dione 8 (Table 1, Entry 18)
2-Iodotoluene **29** (0.218 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methyl-1,1′-biphenyl **41** as a colourless oil (74.0 mg, 0.440 mmol, 44.0%). NMR spectra details as above.

Substrate: 2-iodotoluene 29, Additive: 1,4-diphenethylpiperazine-2,5-dione 9 (Table 1, Entry 19)
2-Iodotoluene **29** (0.218 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **9** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methyl-1,1′-biphenyl **41** as a colourless oil (95.9 mg, 0.570 mmol, 57.0%). NMR spectra details as above.

Substrate: 2-iodotoluene 29, Additive: 1,4-bis(3-phenylpropyl)-piperazine-2,5-dione 10 (Table 1, Entry 20)
2-Iodotoluene **29** (0.218 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **10** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methyl-1,1′-biphenyl **41** as a colourless oil (94.2 mg, 0.560 mmol, 56.0%). NMR spectra details as above.

Substrate: 3-iodotoluene 30, Additive: 1,4-diphenylpiperazine-2,5-dione 7 (Table 1, Entry 21)
3-Iodotoluene **30** (0.218 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.026 g, 0.1 mmol), KO*t*Bu (0.337 mg, 3.0 mmol) in benzene (10 mL) and afforded 3-methyl-1,1′-biphenyl **42** as a colourless oil (107.7 mg, 0.640 mmol, 64%). δ_H (400 MHz, $CDCl_3$): 2.48 (3H, s, CH_3), 7.22 (1H, m, Ar*H*), 7.39 (2H, m, Ar*H*), 7.47 (4H, m, Ar*H*), 7.64 (2H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 21.7, 124.4, 127.3, 128.1, 128.8, 128.9, 138.5, 141.4, 141.5. IR (NEAT) ν = 615, 696, 750, 1481, 1599, 2918, 3030. *m/z* (APCI) calcd for $C_{13}H_{12}$ $[M]^+$: 168.0934, found: 168.0930.

Substrate: 3-iodotoluene 30, Additive: 1,4-dibenzylpiperazine-2,5-dione 8 (Table 1, Entry 22)
3-Iodotoluene **30** (0.218 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methyl-1,1′-biphenyl **42** as a colourless oil (95.9 mg, 0.570 mmol, 57.0%). NMR spectra details as above.

Substrate: 3-iodotoluene 30, Additive: 1,4-diphenethylpiperazine-2,5-dione 9 (Table 1, Entry 23)
3-Iodotoluene **30** (0.218 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **9** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methyl-1,1′-biphenyl **42** as a colourless oil (117.8 mg, 0.700 mmol, 70.0%). NMR spectra details as above.

Substrate: 3-iodotoluene 30, Additive: 1,4-bis(3-phenylpropyl)-piperazine-2,5-dione 10 (Table 1, Entry 24)
3-Iodotoluene **30** (0.218 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **10** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methyl-1,1′-

biphenyl **42** as a colourless oil (112.7 mg, 0.670 mmol, 67.0%). NMR spectra details as above.

Substrate: 4-iodotoluene 31, Additive: 1,4-diphenylpiperazine-2,5-dione 7 (Table 1, Entry 25)
4-Iodotoluene **31** (0.218 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.026 g, 0.1 mmol), KO*t*Bu (0.337 mg, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **43** as a colourless solid (100.9 mg, 0.060 mmol, 60%). M.Pt: 45-47 °C (lit. 46-47 °C).[39] δ_H (400 MHz, $CDCl_3$): 2.41 (3H, s, CH_3), 7.26 (2H, m, Ar*H*), 7.33 (1H, m, Ar*H*), 7.43 (2H, m, Ar*H*), 7.51 (2H, m, Ar*H*), 7.59 (2H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 21.2, 127.1, 128.8, 129.6, 137.2, 138.5, 141.3. IR (NEAT) ν = 688, 752, 821, 1037, 1377, 1485, 2856, 2916, 3030. *m/z* (APCI) calcd for $C_{13}H_{13}$ $[M+H]^+$: 169.1012, found: 169.1011.

Substrate: 4-iodotoluene 31, Additive: 1,4-dibenzylpiperazine-2,5-dione 8 (Table 1, Entry 26)
4-iodotoluene **31** (0.218 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **43** as a colourless solid (100.9 mg, 0.600 mmol, 60.0%). NMR spectra details as above.

Substrate: 4-iodotoluene 31, Additive: 1,4-diphenethylpiperazine-2,5-dione 9 (Table 1, Entry 27)
4-iodotoluene **31** (0.218 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **9** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-me thyl-1,1'-biphenyl **43** as a colourless solid (131.2 mg, 0.780 mmol, 78.0%). NMR spectra details as above.

Substrate: 4-iodotoluene 31, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 10 (Table 1, Entry 28)
4-iodotoluene **31** (0.218 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **10** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **43** as a colourless solid (114.4 mg, 0.680 mmol, 68.0%). NMR spectra details as above.

Substrate: bromobenzene 32, Additive: 1,4-diphenylpiperazine-2,5-dione 7 (Table 2, Entry 1)
Bromobenzene **32** (0.157 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.026 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **37** as a white solid (21.6 mg, 0.140 mmol, 14.0%). NMR spectra details as above.

Substrate: bromobenzene 32, Additive: 1,4-dibenzylpiperazine-2,5-dione 8 (Table 2, Entry 2)
Bromobenzene **32** (0.157 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **37** as a white solid (104.9 mg, 0.680 mmol, 68.0%). NMR spectra details as above.

Substrate: bromobenzene 32, Additive: 1,4-diphenethylpiperazine-2,5-dione 9 (Table 2, Entry 3)
Bromobenzene **32** (0.157 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **9** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **37** as a white solid (49.3 mg, 0.320 mmol, 32.0%). NMR spectra details were as above.

Substrate: bromobenzene 32, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 10 (Table 2, Entry 4)
Bromobenzene **32** (0.157 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **10** (0.035 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **37** as a white solid (49.3 mg, 0.320 mmol, 32.0%). NMR spectra details as above.

Substrate: 2-bromoanisole 33, Additive: 1,4-diphenylpiperazine-2,5-dione 7 (Table 2, Entry 5)
2-Bromoanisole **33** (0.184 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.026 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1'-biphenyl **38** as a colourless oil (66.3 mg, 0.360 mmol, 36.0%). NMR spectra details as above.

Substrate: 2-bromoanisole 33, Additive: 1,4-dibenzylpiperazine-2,5-dione 8 (Table 2, Entry 6)
2-bromoanisole **33** (0.184 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1'-biphenyl **38** as a colourless oil (92.1 mg, 0.500 mmol, 50.0%). NMR spectra details as above.

Substrate: 2-bromoanisole 33, Additive: 1,4-diphenethylpiperazine-2,5-dione 9 (Table 2, Entry 7)
2-Bromoanisole **33** (0.184 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **9** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1'-biphenyl **38** as a colourless oil (88.4 mg, 0.480 mmol, 48.0%). NMR spectra details as above.

Substrate: 2-bromoanisole 33, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 10 (Table 2, Entry 8)
2-Bromoanisole **33** (0.184 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **10** (0.035 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1'-biphenyl **38** as a colourless oil (108.7 mg, 0.590 mmol, 59.0%). NMR spectra details as above.

Substrate: 3-bromoanisole 34, Additive: 1,4-diphenylpiperazine-2,5-dione 7 (Table 2, entry 9)
3-Bromoanisole **34** (0.184 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.026 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1'-biphenyl **39** as a colourless oil (3.7 mg, 0.020 mmol, 2.0%). NMR spectra details as above.

Substrate: 3-bromoanisole 34, Additive: 1,4-dibenzylpiperazine-2,5-dione 8 (Table 2, Entry 10)
3-Bromoanisole **34** (0.184 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1'-

biphenyl **39** as a colourless oil (3.7 mg, 0.020 mmol, 2.0%). NMR spectra details as above.

Substrate: 3-bromoanisole 34, Additive: 1,4-diphenethylpiperazine -2,5-dione 9 (Table 2, Entry 11)
3-Bromoanisole **34** (0.184 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **9** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1'-biphenyl **39** as a colourless oil (3.7 mg, 0.020 mmol, 2.0%). NMR spectra details as above.

Substrate: 3-bromoanisole 34, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 10 (Table 2, Entry 12)
3-Bromoanisole **34** (0.184 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **10** (0.035 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1'-biphenyl **39** as a colourless oil (3.7 mg, 0.020 mmol, 2.0%). NMR spectra details as above.

Substrate: 4-bromoanisole 35, Additive: 1,4-diphenylpiperazine-2,5-dione 7 (Table 2, Entry 13)
4-Bromoanisole **35** (0.184 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.026 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1'-biphenyl **40** as a white solid (23.9 mg, 0.130 mmol, 13.0%). NMR spectra details as above.

Substrate: 4-bromoanisole 35, Additive: 1,4-dibenzylpiperazine-2,5-dione 8 (Table 2, Entry 14)
4-Bromoanisole **35** (0.184 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1'-biphenyl **40** as a white solid (103.2 mg, 0.560 mmol, 56.0%). NMR spectra details as above.

Substrate: 4-bromoanisole 35, Additive: 1,4-diphenethylpiperazine -2,5-dione 9 (Table 2, Entry 15)
4-bromoanisole **35** (0.184 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **9** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1'-biphenyl **40** as a white solid (38.7 mg, 0.210 mmol, 21.0%). NMR spectra details as above.

Substrate: 4-bromoanisole 35, Additive: 1,4-bis(3-phenylpropyl)-piperazine-2,5-dione 10 (Table 2, Entry 16)
4-Bromoanisole **35** (0.184 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **10** (0.035 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1'-biphenyl **40** as a white solid (53.4 mg, 0.290 mmol, 29.0%). NMR spectra details as above.

Substrate: 4-bromotoluene 36, Additive: 1,4-diphenylpiperazine-2,5-dione 7 (Table 2, Entry 17)
4-Bromotoluene **36** (0.171 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.026 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **43** as a colourless solid (62.2 mg, 0.370 mmol, 37.0%). NMR spectra details as above.

Substrate: 4-bromotoluene 36, Additive: 1,4-dibenzylpiperazine-2,5-dione 8 (Table 2, Entry 18)
4-bromotoluene **36** (0.171 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **43** as a colourless solid (79.1 mg, 0.470 mmol, 47.0%). NMR spectra details as above.

Substrate: 4-bromotoluene 36, Additive: 1,4-diphenethyl-piperazine-2,5-dione 9 (Table 2, Entry 19)
4-Bromotoluene **36** (0.171 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **9** (0.032 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **43** as a colourless solid (48.8 mg, 0.290 mmol, 29.0%). NMR spectra details as above.

Substrate: 4-bromotoluene 36, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 10 (Table 2, Entry 20)
4-Bromotoluene **36** (0.171 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **10** (0.035 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **43** as a colourless solid (62.2 mg, 0.370 mmol, 37.0%). NMR spectra details as above.

Benzyne Formation and *tert*-Butoxide Nucleophilic Addition (Scheme 5)

General Reaction Conditions
All reactions were performed on a 1.0 mmol scale of the aryl halide. The mixture of the aryl halide (1.0 mmol), additive (0.1 mmol) and potassium *tert*-butoxide (337 mg, 3.0 mmol) in 10 mL of benzene was sealed in a 15 mL pressure tube in glovebox. The tube was removed from the glovebox and heated at indicated temperature for indicated amount of time behind a shield. After cooling to room temperature, the reaction was quenched by water (30 mL). The mixture was extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. 1,3,5-trimethoxybenzene was added to the crude product as an internal standard and ^{1}H NMR of the resulting crude reactuion mixture was used to quantify the yields of the reactions.

Substrate: 4-bromoanisole 35, Additive: 1,4-dibenzylpiperazine-2,5-dione 8
4-bromoanisole **35** (0.184 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL). Crude ^{1}H NMR showed formation of 4-methoxy-1,1'-biphenyl **40** (0.620 mmol, 62.0%), NMR spectra details as above, 1-(*tert*-butoxy)-3-methoxybenzene **44** (0.093 mmol, 9%, δ_H (400 MHz, $CDCl_3$): 1.36 (9H, s, $OC(CH_3)_3$), 3.78 (3H, s, OCH_3), 6.55 (1H, t, J = 2.0 Hz, Ar*H*), 6.60 (2H, m, Ar*H*), 7.15 (1H, t, J = 8.0 Hz, Ar*H*)) and 1-(*tert*-butoxy)-4-methoxybenzene **46** (0.10 mmol, 10%, δ_H (400 MHz, $CDCl_3$): 1.31 (9H, s, $OC(CH_3)_3$), 3.78 (3H, s, OCH_3), 6.79 (2H, m, Ar*H*), 6.92 (2H, m, Ar*H*), data in accordance with literature for both isomers).[40]

Substrate: 4-bromoanisole 35, Additive: 1,4-dibenzylpiperazine-2,5-dione 8

4-bromoanisole **35** (0.184 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL). Crude ^{1}H NMR showed formation of 4-methoxy-1,1'-biphenyl **40** (0.290 mmol, 29.0%), 1-(*tert*-butoxy)-3-methoxybenzene **44** (0.10 mmol, 10%) and 1-(*tert*-butoxy)-4-methoxybenzene **46** (0.11 mmol, 11%). NMR spectra details as above.

Substrate: bromobenzene 32, Additive: 1,4-dibenzylpiperazine-2,5-dione 8

Bromobenzene **32** (0.157 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL). Crude ^{1}H NMR showed formation of biphenyl **37** (0.70 mmol, 70%), NMR spectra details as above, and *tert*-butoxybenzene **48** as a colourless liquid (0.08 mmol, 8%, δ_H (400 MHz, $CDCl_3$): 1.35 (9H, s, $OC(CH_3)_3$), 6.99 (2H, m, Ar*H*), 7.05 (1H, m, Ar*H*), 7.26 (2H, m, Ar*H*) data in accordance with literature).[40]

Substrate: bromobenzene 32, Additive: 1,4-dibenzylpiperazine-2,5-dione 8

Bromobenzene **32** (0.157 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL). Crude ^{1}H NMR showed formation of biphenyl **37** (0.46 mmol, 46%) and *tert*-butoxybenzene **48** (0.10 mmol, 10%). NMR spectra details as above.

Substrate: chlorobenzene 49, Additive: 1,4-dibenzylpiperazine-2,5-dione 8

Chlorobenzene **49** (0.112 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL). Crude ^{1}H NMR showed only formation of *tert*-butoxybenzene **48** (0.32 mmol, 32%). NMR spectra details as above.

Substrate: 4-chloroanisole 50, Additive: 1,4-dibenzylpiperazine-2,5-dione 8

4-chloroanisole **50** (0.142 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL). Crude ^{1}H NMR showed only formation of 1-(*tert*-butoxy)-3-methoxybenzene **44** (0.18 mmol, 18%) and 1-(*tert*-butoxy)-4-methoxybenzene **46** (0.17 mmol, 17%). NMR spectra details as above.

Substrate: 4-iodoanisole 28, Additive: 1,4-diphenylpiperazine-2,5-dione 7

4-iodoanisole **28** (0.234 g, 1.0 mmol) was treated with 1,4-diphenyl-piperazine-2,5-dione **7** (0.026 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL). Crude ^{1}H NMR showed formation of 4-methoxy-1,1'-biphenyl **40** (0.740 mmol, 74.0%), 1-(*tert*-butoxy)-3-methoxybenzene **44** (0.02 mmol, 2%) and 1-(*tert*-butoxy)-4-methoxybenzene **46** (0.02 mmol, 2%).

Coupling Reactions of 4-halobenzonitriles with Benzene (Scheme 6)

General Reaction Conditions

All reactions were performed on a 1.0 mmol scale of the aryl halide. The mixture of the aryl halide (1.0 mmol), additive (0.1 mmol) and potassium *tert*-butoxide (337 mg, 3.0 mmol) in 10 mL of benzene was sealed in a 15 mL pressure tube in glovebox. The tube was removed from the glovebox and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the reaction was quenched by water (30 mL). The mixture was extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography eluting with Et_2O (10%) in hexane.

Substrate: 4-iodobenzonitrile 51, Additive: 1,4-diphenylpiperazine-2,5-dione 7

4-iodobenzonitrile **51** (0.229 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.027 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded [1,1'-biphenyl]-4-carbonitrile **53** as a white solid (122.0 mg, 0.681 mmol, 68.1%). M.Pt: 83-86 °C (lit. 83-85 °C).[41] δ_H (400 MHz, $CDCl_3$): 7.42 (1H, m, Ar*H*), 7.48 (2H, m, Ar*H*), 7.59 (2H, m, Ar*H*), 7.72 (4H, m, Ar*H*). δ_C (100MHz, $CDCl_3$): 111.1, 119.1, 127.4, 127.9, 128.8, 129.3, 132.8, 139.4, 145.9. IR (NEAT) ν = 2224, 1602, 1481, 1065, 1041, 769, 697. *m/z* (EI) calcd for $C_{13}H_9N$ [M]: 179.1, found: 179.1.

Substrate: 4-bromobenzonitrile 52, Additive: 1,4-diphenylpiperazine-2,5-dione 7

4-bromobenzonitrile **52** (0.182 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.027 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded an inseparable mixture of [1,1'-biphenyl]-4-carbonitrile **53** (14.4%) NMR spectra details as above, 4-(*tert*-butoxy)benzonitrile (8.5%), δ_H (400 MHz, $CDCl_3$): 1.42 (9H, s, $OC(CH_3)_3$), 7.04 (2H, m, Ar*H*), 7.56 (2H, m, Ar*H*), and 3-(*tert*-butoxy)benzonitrile (9.9%), δ_H (400 MHz, $CDCl_3$): 1.37 (9H, s, $OC(CH_3)_3$), 7.21 (1H, m, Ar*H*), 7.27 (1H, m, Ar*H*), 7.35 (2H, m, Ar*H*).

Substrate: 4-iodobenzonitrile 51, Additive: 1,4-dibenzylpiperazine-2,5-dione 8

4-iodobenzonitrile **51** (0.229 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded [1,1'-biphenyl]-4-carbonitrile **53** as a white solid (135.0 mg, 0.753 mmol, 75.3%). NMR spectra details as above.

Substrate: 4-bromobenzonitrile 52, Additive: 1,4-dibenzylpiperazine-2,5-dione 8

4-bromobenzonitrile **52** (0.182 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol), KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded [1,1'-biphenyl]-4-carbonitrile **53** as a white solid (96.0 mg, 0.536 mmol, 53.6%). NMR spectra details as above.

Reactions of 4-halobenzotrifluorides with KO*t*Bu (Scheme 7)

General Reaction Conditions

All reactions were performed on a 1.0 mmol scale of the aryl halide. The mixture of the aryl halide (1.0 mmol), additive (0.1 mmol) and potassium *tert*-butoxide (337 mg, 3.0 mmol) in 10 mL of benzene was sealed in a 15 mL pressure tube in glovebox. The tube was removed from the glovebox and heated at 130 °C for 18 h behind a shield. After cooling to room temperature, the reaction was quenched by water (30 mL). The mixture was extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography eluting with Et_2O (1%) in hexane.

Substrate: 4-iodobenzotrifluoride 54, Additive: 1,4-diphenylpiperazine-2,5-dione 7

4-iodobenzotrifluoride **54** (0.272 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.027 g, 0.1 mmol) and KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded an inseparable mixture of 4-(*tert*-butoxy)benzotrifluoride **56** (0.216 mmol, 21.6%, δ_H (400 MHz, $CDCl_3$): 1.39 (9H, s, $OC(CH_3)_3$), 7.06 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.53 (2H, d, *J* = 8.4 Hz, Ar*H*)) and 3-(*tert*-butoxy)benzotrifluoride **57** (0.196 mmol, 19.6%, δ_H (400 MHz, $CDCl_3$): 1.37 (9H, s, $OC(CH_3)_3$), 7.15 (1H, m, Ar*H*), 7.23 (1H, m, Ar*H*), 7.36 (2H, m, Ar*H*), data in accordance with literature for both isomers).[40]

Substrate: 4-bromobenzotrifluoride 55, Additive: 1,4-diphenylpiperazine-2,5-dione 7

4-bromobenzotrifluoride **55** (0.225 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **7** (0.027 g, 0.1 mmol) and KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded an inseparable mixture of 4-(*tert*-butoxy)benzotrifluoride **56** (0.171 mmol, 17.1%) and 3-(*tert*-butoxy)benzotrifluoride **57** (0.150 mmol, 15.0%). NMR spectra details as above.

Substrate: 4-iodobenzotrifluoride 54, Additive: 1,4-dibenzylpiperazine-2,5-dione 8

4-iodobenzotrifluoride **54** (0.272 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol) and KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded an inseparable mixture of 4-(*tert*-butoxy)benzotrifluoride **56** (0.214 mmol, 21.4%) and 3-(*tert*-butoxy)benzotrifluoride **57** (0.166 mmol, 16.6%). NMR spectra details as above.

Substrate: 4-bromobenzotrifluoride 55, Additive: 1,4-dibenzylpiperazine-2,5-dione 8

4-bromobenzotrifluoride **55** (0.225 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **8** (0.029 g, 0.1 mmol) and KO*t*Bu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded an inseparable mixture of 4-(*tert*-butoxy)benzotrifluoride **56** (0.244 mmol, 24.4%) and 3-(*tert*-butoxy)benzotrifluoride **57** (0.196 mmol, 19.6%). NMR spectra details as above.

Acknowledgements

We thank the University of Strathclyde for funding. Mass spectrometry data were acquired at the ESPRC UK National Mass Spectrometry Facility at Swansea University.

References

1 S. Yanagasawa, K. Ueda, T. Taniguchi and K. Itami *Org. Lett.* 2008, *10*, 4673-4676.
2 Selected reviews on transition metal-free cross-coupling reactions: (a) C.-L. Sun, Z.-J. Shi, *Chem. Rev.* 2014, **114**, 9219-9280. (b) R. Narayan, K. Matcha, A. P. Antonchick, *Chem. Eur. J.* 2015, **21**, 14678-14693. (c) A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* 2016, **55**, 58-102. (d) P. Liu, G. Zhang, P. Sun, *Org. Biomol. Chem.* 2016, **14**, 10763-10777.
3 C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Hunag, S.-F. Zheng, B.-J. Li and Z.-J. Shi, *Nat. Chem.* 2010, **2**, 1044-1049.
4 W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong and A. Lei, *J. Am. Chem. Soc.* 2010, **132**, 16737-16740.
5 Y. Wu, P. Y. Choyand F. Y. Kwong, *Org. Biomol. Chem.* 2014, **12**, 6820-6823.
6 E. Shirakawa, K.-I. Itoh, T. Higashino and T. Hayashi, *J. Am. Chem. Soc.* 2010, **132,** 15537-15539.
7 M. Rueping, M. Leiendecker, A. Das, T. Poisson and L. Bui, *Chem. Commun.* 2011, **47**, 10629-10631.
8 H. Liu, B. Yin, Z. Gao, Y. Li and H. Jiang, *Chem. Commun.* 2012, **48**, 2033-2035.
9 D. S. Roman, Y. Takahashi and A. B. Charette, *Org. Lett.* 2011, **13**, 3242-3245.
10 S. De, S. Ghosh, S. Bhunia, J. A. Shiekh and A. Bisai, *Org. Lett.* 2012, **14**, 4466-4469.
11 K. Tanimoro, M. Ueno, K. Takeda, M. Kirihata and S. Tanimori, *J. Org. Chem.* 2012, **77**, 7844-7849.
12 W. Liu, F. Tian, X. Wang, H. Yu and Y. Bi, *Chem. Commun.* 2013, **49**, 2983-2985.
13 W.-C. Chen; Y.-C. Hsu, W.-C. Shih, C.-Y. Lee, W.-H. Chuang, Y.-F. Tsai, P. P.-Y. Chen and T.-G. Ong, *Chem. Commun.* 2012, **48**, 6702-6704.
14 S. Sharma, M. Kumar, V. Kumar and N. Kumar, *Tetrahedron Lett.* 2013, **54,** 4868-4871.
15 J. Cuthbertson, V. J. Gray and J. D. Wilden, *Chem. Commun.* 2014, **50**, 2575-2578.
16 H. Yi, A. Jutand and A. Lei, *Chem. Commun.* 2015, **51**, 545-548.
17 A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* 2011, **50**, 5018-5022.
18 S. Zhou, G. M. Anderson, B. Mondal, E. Doni, V. Ironmonger, M. Kranz, T. Tuttle and J. A. Murphy, *Chem. Sci.* 2014, **5**, 476-482.
19 S. Zhou, E. Doni, G. M. Anderson, R. G. Kane, S. W. MacDougall, V. M. Ironmonger, T. Tuttle and, J. A. Murphy, *J. Am. Chem. Soc.* 2014, **136,** 17818-17826.
20 J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, L. E. A. Berlouis, T. McGuire, T. Tuttle and J. A. Murphy, *J. Am. Chem. Soc.* 2016, **138**, 7402-7410.
21 C. A. G. N. Montalbetti and V. Falque, *Tetrahedron* 2005, **61**, 10827-10852.
22 Nonappa, K. Ahonen, M. Lahtinen and E. Kolehmainen, *Green Chem*. 2011, **13**, 1203-1209.
23 J. P. Barham, G. Coulthard, R. G. Kane, N. Delgado, M. P. John and J. A. Murphy, *Angew. Chem. Int. Ed.* 2016, **55**, 4492-4496.
24 E. Ceppi, W. Eckhardt and C. A. Grob, *Tetrahedron Lett.* 1973, **14**, 3627-3630.
25 Calculations were performed using the Gaussian 09 software package. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr, J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts,

R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford, CT, USA, **2009**.

26 (a) Calculations were made using the M06-2X functional. Y. Zhao, D. G. Truhlar, *Acc. Chem. Res*. 2008, **41**, 157-167. (b) Elements were modelled using the aug-cc-pvdz basis set. T. H. Dunning, *J. Chem. Phys*. 1989, **90**, 1007-1023. (c) The Conductor-like Polarizable Continuum Model, with the associated parameters of benzene as solvent, was used to model implicit solvation. V. Barone and M. Cossi, *J. Phys. Chem. A* 1998, *102*, 1995-2001. M. Cossi, N. Rega, G. Scalmani and V. Barone, *J. Comput. Chem.* 2003, **24**, 669-681.

27 (a) R. A. Marcus, *J. Chem. Phys.* 1965, **43**, 679-701. (b) S. F. Nelsen, S. C. Blackstock and Y. Kim, *J. Am. Chem. Soc.* 1987, **109**, 677-682.

28 (a) J. D. Roberts, C. W. Vaughan, L. A. Carlsmith and D. A. Semenow, *J. Am. Chem. Soc.* 1956, **78**, 611-614. (b) J. H. Wotiz and F. Huba, *J. Org. Chem.* 1959, **24**, 595-598. (c) Y. Dong, M. I. Lipschutz and T. D. Tilley, *Org. Lett.* 2016, *18*, 1530-1533.

29 E. Picazo, K. N. Houk and N. K. Garg, *Tetrahedron Lett.* 2015, **56**, 3511-3514.

30 G. B. Bajracharya, O. Daugulis, *Org. Lett.* 2008, **10**, 4625-4628.

31 S. R. Yong, A. T. Ung, S. G. Pyne, B. W. Skelton and A. H. White, *Tetrahedron Lett.* 2007, **63**, 1191-1199.

32 Y. Wen, X. Chen, H. Wen and X. Tang, *Lett. Org. Chem.* 2011, **8**, 732-736.

33 A. L. Cardoso, C. Sousa, M. S. C. Henriques, J. A. Paixo, T.M.V.D. Pinho E Melo and K. Banert, *Molecules* 2015, **20**, 22351-22363.

34 H. Morimoto, R. Fujiwara, Y. Shimizu, K. Morisaki, T. Ohshima, *Org. Lett.* **2014**, *16*, 2018-2021.

35 V. Vecchietti, G. D. Clarke, R. Colle, G. Giardina, G. Petrone and M. Sbacchi, *J. Med. Chem.* 1991, **34**, 2624-2633.

36 Murnen, A. M. Rosales, J. N. Jaworski, R. A. Segalman and R. N. Zuckermann, *J. Am. Chem. Soc.*, 2010, **132**, 16112-16119.

37 J. Zhou, S. Yu, K. Cheng and C. Qi, *J. Chem. Res.* 2012, **36**, 672-674.

38 J. Zeng, K. M. Liu and X. F. Duan, *Org. Lett.* 2013, **15**, 5342-5345.

39 C. A. Parrish and S. L. Buchwald, *J. Org. Chem*. 2001, **66**, 2498-2500.

40 D. P. DeCosta, A. Bennett, A. L. Pincock, J. A. Pincock, R. Stefanova, *J. Org. Chem.* 2000, **65**, 4162-4168.

41 Q. Di, J. Liang, Z. Zhitong, M. He, M. Fanyang, W. Xi, Z. Yan, W. Jianbo, *J. Org. Chem.* 2013, **78**, 1923-1933.