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

Florimond Cumine,* Shengze Zhou,* Tell Tuttle,* and John. A. Murphy* |

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 peptides21 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.
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).

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 reported19 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.

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 optimization25-26 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-

![Diagram](https://example.com/diagram.png)

**Figure 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**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl Halide</th>
<th>DKP</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 X = I, R = H</td>
<td>7</td>
<td>37 R = H</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>25 X = I, R = H</td>
<td>8</td>
<td>37 R = H</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>25 X = I, R = H</td>
<td>9</td>
<td>37 R = H</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>25 X = I, R = H</td>
<td>10</td>
<td>37 R = H</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>26 X = I, R = o-OMe</td>
<td>7</td>
<td>38 R = o-OMe</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>26 X = I, R = o-OMe</td>
<td>8</td>
<td>38 R = o-OMe</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>26 X = I, R = o-OMe</td>
<td>9</td>
<td>38 R = o-OMe</td>
<td>59</td>
</tr>
<tr>
<td>8</td>
<td>26 X = I, R = o-OMe</td>
<td>10</td>
<td>38 R = o-OMe</td>
<td>64</td>
</tr>
<tr>
<td>9</td>
<td>27 X = I, R = m-OMe</td>
<td>7</td>
<td>39 R = m-OMe</td>
<td>61</td>
</tr>
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<td>8</td>
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<td>7</td>
<td>40 R = p-OMe</td>
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<tr>
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<td>8</td>
<td>40 R = p-OMe</td>
<td>64</td>
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<tr>
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<tr>
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<td>8</td>
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<td>44</td>
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<tr>
<td>19</td>
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<td>9</td>
<td>41 R = o-OMe</td>
<td>57</td>
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<td>29 X = I, R = o-OMe</td>
<td>10</td>
<td>41 R = o-OMe</td>
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<td>7</td>
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<td>8</td>
<td>42 R = m-OMe</td>
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<td>23</td>
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<td>9</td>
<td>42 R = m-OMe</td>
<td>70</td>
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<td>10</td>
<td>42 R = m-OMe</td>
<td>67</td>
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<tr>
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<td>7</td>
<td>43 R = p-OMe</td>
<td>60</td>
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<tr>
<td>26</td>
<td>31 X = I, R = p-OMe</td>
<td>8</td>
<td>43 R = p-OMe</td>
<td>60</td>
</tr>
<tr>
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<td>31 X = I, R = p-OMe</td>
<td>9</td>
<td>43 R = p-OMe</td>
<td>78</td>
</tr>
<tr>
<td>28</td>
<td>31 X = I, R = p-OMe</td>
<td>10</td>
<td>43 R = p-OMe</td>
<td>68</td>
</tr>
</tbody>
</table>

*a* Isolated yield
Table 2: Coupling reaction of aryl bromides with benzene initiated by diketopiperazines

| Entry | Aryl Halide | DKP | Product | Yield* (%)
|-------|-------------|-----|---------|-------------
| 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        |

* 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\cite{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\cite{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.

The ability of aryl halides to generate benzyynes\cite{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 was used under the same conditions and formed tert-butoxybenzene 48.

Table 3: Energies of electron transfer reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Initiator</th>
<th>$\Delta G^*$</th>
<th>$\Delta G_{rel}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 $X = I, R = H$</td>
<td>20</td>
<td>31.3</td>
<td>22.9</td>
</tr>
<tr>
<td>2</td>
<td>25 $X = I, R = H$</td>
<td>21</td>
<td>28.6</td>
<td>18.5</td>
</tr>
<tr>
<td>3</td>
<td>25 $X = I, R = H$</td>
<td>22</td>
<td>27.7</td>
<td>17.0</td>
</tr>
<tr>
<td>4</td>
<td>25 $X = I, R = H$</td>
<td>23</td>
<td>27.0</td>
<td>15.1</td>
</tr>
<tr>
<td>5</td>
<td>28 $X = I, R = p$-OMe</td>
<td>20</td>
<td>35.7</td>
<td>27.7</td>
</tr>
<tr>
<td>6</td>
<td>28 $X = I, R = p$-OMe</td>
<td>21</td>
<td>32.9</td>
<td>23.4</td>
</tr>
<tr>
<td>7</td>
<td>28 $X = I, R = p$-OMe</td>
<td>22</td>
<td>31.9</td>
<td>21.8</td>
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<tr>
<td>8</td>
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<td>31.2</td>
<td>20.0</td>
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<td>20</td>
<td>31.1</td>
<td>22.8</td>
</tr>
<tr>
<td>10</td>
<td>32 $X = Br, R = H$</td>
<td>21</td>
<td>28.4</td>
<td>18.5</td>
</tr>
<tr>
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<td>32 $X = Br, R = H$</td>
<td>22</td>
<td>27.4</td>
<td>16.9</td>
</tr>
<tr>
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<td>32 $X = Br, R = H$</td>
<td>23</td>
<td>26.8</td>
<td>15.0</td>
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<tr>
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<td>20</td>
<td>34.3</td>
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<tr>
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<td>35 $X = Br, R = p$-OMe</td>
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<td>35 $X = Br, R = p$-OMe</td>
<td>23</td>
<td>30.0</td>
<td>17.1</td>
</tr>
</tbody>
</table>

*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.

On the other 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.

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 5

For this reaction, 53 was recovered in an inseparable mixture with the benzyne adducts (see experimental details for more information).
(Scheme 7). The strong attractive inductive effect of the trifluoromethyl group²⁴ must result in an increased acidity of the protons ortho to the halide thus in an easier benzyne formation.

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 (¹H) spectra was recorded at 400 MHz on a Bruker DPX 400 spectrometer. Carbon NMR (¹³C) spectra were recorded at 100 MHz. The chemical shifts are quoted in parts per million (ppm) by taking tetramethylsilsane 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 Vertical 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 NaHCO₃ (100 ml). The organic phase was dried over Na₂SO₄, filtered and concentrated to afford 2-chloro-N-phenylacetamide 16 as a brown/yellow solid (10.52 g, 62.02 mmol, 96.25%).

The organic phase was dried over Na₂SO₄, 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).¹¹ δH (400 MHz, CDCl₃): 4.19 (2H, s, CH₂), 7.17 (1H, m, ArH), 7.36 (2H, m, ArH), 7.55 (2H, m, ArH), 8.23 (1H, bs, NH). δC (101MHz, CDCl₃): 43.0, 120.3, 125.4, 129.3, 136.8, 163.9. IR (NEAT) v = 688, 748, 856, 1249, 1342, 1442, 1496, 1556, 1600, 1668, 3097, 3143, 3207, 3265 cm⁻¹. m/z (APCI) calcd for C₁₅H₁₃NO [M+H⁺]: 243.0734, found: 243.0733.

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. 266-270 °C).¹³ δH (400 MHz, CDCl₃): 4.55 (4H, s, C=N), 7.44-7.49 (4H, m, ArH), 7.32-7.38 (6H, m, ArH). δC (100MHz, CDCl₃): 53.6, 125.1, 127.7, 129.6, 139.7, 164.1. IR (NEAT) v = 690, 754, 1141, 1251, 1334, 1431, 1450, 1469, 1496, 1591, 1651, 2947, 3059 cm⁻¹. m/z (APCI) calcd for C₁₇H₁₂N₂O₂ [M+H⁺]: 297.0915, found: 297.0923.

Preparation of 1,4-dibenzylpiperazine-2,5-dione 8 [R=CH₂Ph]
To a solution of benzylamine 7 (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 NaHCO₃ (20 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated to afford the product 2-chloro-N-phenylacetamide 17 as a yellow solid (1.380 g, 7.52 mmol, 80.5%). M.pt: 87-90 °C (lit. 91-92 °C). 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 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 solids 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-Dibenzyliperazine-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). After addition, the mixture was stirred at 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 solids 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%).

Preparation of 1,4-diphenylpiperazine-2,5-dione 9 [R = (CH₃)₂Ph]
To a solution of 3-phenypropyl)piperazine-2,5-dione 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 HCI in water (20 mL) and with a saturated solution of NaHCO₃ (20 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated to afford the product 2-chloro-N-(3-phenylpropyl)piperazine-2,5-dione 19 as an orange oil (1.167 g, 5.51 mmol, 74.5%). M.pt: 201 °C (lit. 210 °C). To a solution of 3-phenypropyl)piperazine-2,5-dione 15 (1.0 equiv, 1.167 g, 5.51 mmol) in dry DCM (30 mL) was slowly added chloroacetyl chloride (1.1 equiv, 0.65 mL, 8.12 mmol). 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 (97%/3%).

Preparation of 1,4-diphenylpiperazine-2,5-dione 9 [R = (CH₃)₂Ph]
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 NaHCO₃ (20 mL). The organic phase was dried over Na₂SO₄, 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). 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 NaHCO₃ (20 mL). The organic phase was dried over Na₂SO₄, 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). After addition, the mixture was stirred at 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 solids 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%).
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 × 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 Et2O (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), KOtBu (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%). δ (400 MHz, CDCl3): 7.35 (2H, m, ArH), 7.47 (4H, m, ArH). δ (100MHz, CDCl3): 127.3, 127.5, 128.8, 129.8, 141.4. IR (NEAT) ν = 694, 725, 902, 1404, 1475, 2924, 3034, 3061. m/z (APCI) calcd for C12H11 [M+H]+: 155.0855, found: 155.0851.

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

Iodobenzene 25 (0.204 g, 1.0 mmol) was treated with 1,4-dibenzyloxyphenylpiperazine-2,5-dione 8 (0.029 g, 0.1 mmol), KOtBu (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), KOtBu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl 37 as a white solid (111.6 mg, 0.610 mmol, 61.0%). 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), KOtBu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl 37 as a white solid (108.7 mg, 0.590 mmol, 59.0%). NMR spectra details as above.

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

2-Iodoanisole 27 (0.234 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione 7 (0.026 g, 0.1 mmol), KOtBu (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 27, Additive: 1,4-dibenzyloxyphenylpiperazine-2,5-dione 8 (Table 1, Entry 6)

2-Iodoanisole 26 (0.234 g, 1.0 mmol) was treated with 1,4-dibenzyloxyphenylpiperazine-2,5-dione 8 (0.029 g, 0.1 mmol), KOtBu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1’-biphenyl 38 as a colourless oil (111.6 mg, 0.610 mmol, 61.0%). NMR spectra details as above.

Substrate: 2-iodoanisole 27, 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), KOtBu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1’-biphenyl 38 as a colourless oil (129.0 mg, 0.700 mmol, 70.0%). NMR spectra details as above.

Substrate: 2-iodoanisole 27, 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), KOtBu (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), KOtBu (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 (400 MHz, CDCl3): 3.88 (3H, s, CH3), 6.92 (1H, m, ArH), 7.15 (1H, m, ArH), 7.20 (1H, m, ArH), 7.35-7.39 (2H, m, ArH), 7.45 (2H, m, ArH), 7.61 (2H, m, ArH). δ (100MHz, CDCl3): 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 C13H13O [M+H]+: 184.0883, found: 184.0878.

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

3-Iodoanisole 27 (0.234 g, 1.0 mmol) was treated with 1,4-dibenzyloxyphenylpiperazine-2,5-dione 8 (0.029 g, 0.1 mmol), KOtBu (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-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), KOTBu (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%). NMR spectra details as above.

Substrate: 4-iodoanisole 28, Additive: 1,4-dibenzyloppiperazine-2,5-dione 7 (Table 1, Entry 13)
4-iodoanisole 28 (0.234 g, 1.0 mmol) was treated with 1,4-dibenzyloppiperazine-2,5-dione 7 (0.026 g, 0.1 mmol), KOTBu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1′-biphenyl 40 as a white solid (112.4 mg, 0.610 mmol, 61%). M.Pt: 84-85 °C (lit. 84-85 °C). δH (400 MHz, CDCl3): 3.86 (3H, s, CH3), 6.98 (2H, m, ArH), 7.30 (1H, m, ArH), 7.42 (2H, m, ArH), 7.51-7.57 (4H, m, ArH). δC (100MHz, CDCl3): 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) v = 700, 725, 746, 773, 1439, 1479. m/z (APCI) calcd for C36H27O [M]+: 515.2; found: 515.2.

Substrate: 2-iodotoluene 29, Additive: 1,4-dibenzyloppiperazine-2,5-dione 8 (Table 1, Entry 18)
2-iodotoluene 29 (0.218 g, 1.0 mmol) was treated with 1,4-dibenzyloppiperazine-2,5-dione 8 (0.029 g, 0.1 mmol), KOTBu (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%). NMR spectra details as above.

Substrate: 3-iodotoluene 30, Additive: 1,4-dibenzyloppiperazine-2,5-dione 9 (Table 1, Entry 19)
3-iodotoluene 30 (0.218 g, 1.0 mmol) was treated with 1,4-dibenzyloppiperazine-2,5-dione 9 (0.032 g, 0.1 mmol), KOTBu (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%). NMR spectra details as above.
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), KOtBu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-ethyl-1,1'-biphenyl 43 as a colourless solid (100.9 mg, 0.060 mmol, 60%). M.pt: 45-47 °C (lit. 46-47 °C). 

Substrate: bromobenzene 32, Additive: 1,4-dibenzylpiperazine-2,5-dione 8 (Table 1, Entry 26)
(0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl 42 as a colourless oil (131.2 mg, 0.780 mmol, 78.0%). NMR spectra details as above.

Substrate: 4-iodotoluene 31, Additive: 1,4-dibenzylpiperazine-2,5-dione 9 (Table 1, Entry 27)
4-iodotoluene 31 (0.218 g, 1.0 mmol) was treated with 1,4-dibenzybpiperazine-2,5-dione 9 (0.032 g, 0.1 mmol), KOtBu (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), KOtBu (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-dibenzybpiperazine-2,5-dione 8 (0.029 g, 0.1 mmol), KOtBu (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), KOtBu (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: bromobenzene 32, Additive: 1,4-bis(3-phenyloxy)propylpiperazine-2,5-dione 10 (Table 2, Entry 4)
Bromobenzene 32 (0.157 g, 1.0 mmol) was treated with 1,4-bis(3-phenyloxy)propylpiperazine-2,5-dione 10 (0.035 g, 0.1 mmol), KOtBu (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), KOtBu (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), KOtBu (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), KOtBu (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-dibenzylpiperazine-2,5-dione 10 (Table 2, Entry 8)
2-Bromoanisole 33 (0.184 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione 10 (0.035 g, 0.1 mmol), KOtBu (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), KOtBu (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.
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-diphenylpiperazine-2,5-dione -2,5-dione 9 (Table 2, Entry 11)**

3-Bromoanisole 34 (0.184 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione 9 (0.032 g, 0.1 mmol), KOTBu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-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), KOTBu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1′-biphenyl 40 as a white solid (23.9 mg, 0.130 mmol, 13.0%). NMR spectra details as above.

**Substrate: 3-bromoanisole 34, Additive: 1,4-diphenylpiperazine-2,5-dione 8 (Table 2, Entry 13)**

3-Bromoanisole 34 (0.184 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione 8 (0.029 g, 0.1 mmol), KOTBu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1′-biphenyl 40 as a white solid (103.2 mg, 0.560 mmol, 56.0%). NMR spectra details as above.

**Substrate: 3-bromoanisole 35, Additive: 1,4-diphenylpiperazine-2,5-dione 7 (Table 2, Entry 14)**

3-Bromoanisole 35 (0.184 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione 7 (0.026 g, 0.1 mmol), KOTBu (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: 3-bromoanisole 35, Additive: 1,4-diphenylpiperazine-2,5-dione 9 (Table 2, Entry 15)**

3-Bromoanisole 35 (0.184 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione 9 (0.032 g, 0.1 mmol), KOTBu (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: 3-bromoanisole 35, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 10 (Table 2, Entry 16)**

3-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), KOTBu (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: 3-bromoanisole 35, Additive: 1,4-diphenylpiperazine-2,5-dione 8 (Table 2, Entry 17)**

3-Bromoanisole 35 (0.184 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione 8 (0.029 g, 0.1 mmol), KOTBu (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-diphenethylpiperazine-2,5-dione 8 (Table 2, Entry 18)**

4-Bromotoluene 36 (0.171 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione 8 (0.029 g, 0.1 mmol), KOTBu (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-diphenethylpiperazine-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), KOTBu (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), KOTBu (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 1H NMR of the resulting crude reaction mixture was used to quantify the yields of the reactions.

**Substrate: 4-bromoanisole 35, Additive: 1,4-dibenzyldiphenylpiperazine-2,5-dione 8 (Table 2, Entry 17)**

4-Bromoanisole 35 (0.184 g, 1.0 mmol) was treated with 1,4-dibenzyldiphenylpiperazine-2,5-dione 8 (0.093 mmol, 9%, δH (400 MHz, CDCl3): 1.36 (9H, s, OC(CH3)3), 3.78 (3H, s, OCH3), 6.55 (1H, t, J = 2.0 Hz, ArH), 6.60 (2H, m, ArH), 7.15 (1H, t, J = 8.0 Hz, ArH)) and 1-(tert-butoxy)-4-methoxybenzene 44 (0.093 mmol, 9%, δH (400 MHz, CDCl3): 1.36 (9H, s, OC(CH3)3), 3.78 (3H, s, OCH3), 6.79 (2H, m, ArH), 6.92 (2H, m, ArH), data in accordance with literature for both isomers).
**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), KOtBu (0.337 g, 3.0 mmol) in benzene (10 mL). Crude 1H NMR showed formation of tert-butoxybenzene 48 (0.32 mmol, 32%). NMR spectra details as above.

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**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), KOtBu (0.337 g, 3.0 mmol) in benzene (10 mL). Crude 1H NMR showed formation of tert-butoxybenzene 48 (0.10 mmol, 10%). NMR spectra details as above.

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**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), KOtBu (0.337 g, 3.0 mmol) in benzene (10 mL). Crude 1H NMR showed only formation of tert-butoxybenzene 48 (0.32 mmol, 32%). NMR spectra details as above.

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**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), KOtBu (0.337 g, 3.0 mmol) in benzene (10 mL). Crude 1H NMR showed only formation of tert-butoxy-4-methoxybenzene 46 (0.17 mmol, 17%). NMR spectra details as above.

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

4-idoanisole 28 (0.234 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione 7 (0.026 g, 0.1 mmol), KOtBu (0.337 g, 3.0 mmol) in benzene (10 mL). Crude 1H 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-halobenzoazinonitriles 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 Et2O (10%) in hexane.

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

4-iodobenzenitrile 51 (0.229 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione 7 (0.027 g, 0.1 mmol), KOtBu (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%).

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

4-bromobenzenitrile 52 (0.182 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione 7 (0.027 g, 0.1 mmol), KOtBu (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%).

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

4-iodobenzenitrile 51 (0.229 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione 8 (0.029 g, 0.1 mmol), KOtBu (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded [1,1′-biphenyl]-4-carbonitrile 53 as a white solid (150.0 mg, 0.753 mmol, 75.3%). NMR spectra details as above.

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

4-bromobenzenitrile 52 (0.182 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione 8 (0.029 g, 0.1 mmol), KOtBu (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.

**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 Et₂O (1%) in hexane.

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

and 3-((tert-butoxy)benzotrifluoride)

and 3-((tert-butoxy)benzotrifluoride)

mixture of 4-((tert-butoxy)benzotrifluoride) (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%, δH (400 MHz, CDCl3): 1.39 (9H, s, OC(CH₃)₃), 7.06 (2H, d, J = 8.4 Hz, ArH), 7.53 (2H, d, J = 8.4 Hz, ArH) and 3-(tert-butoxy)benzotrifluoride 57 (0.196 mmol, 19.6%, δH (400 MHz, CDCl3): 1.37 (9H, s, OC(CH₃)₃), 7.15 (1H, m, ArH), 7.23 (1H, m, ArH), 7.36 (2H, m, ArH), data in accordance with literature for both isomers).

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 KOtBu (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.

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