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Rapid and Efficient Microwave-Assisted Synthesis of Aryl Aminobenzophenones Using Pd-Catalyzed Amination

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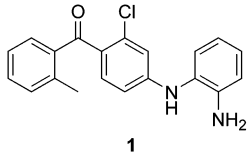
Substituted aryl aminobenzophenone p38 MAP kinase inhibitors were synthesized in good to excellent yields using palladium-catalyzed aryl amination under conditions of microwave irradiation. Various ligands have been screened, and the reaction conditions were optimized. These coupling reactions are suitable for various anilines and aryl bromides that bear a variety of functional groups. Some leaving groups (iodides, chlorides, triflates, and tosylates) other than bromides have also been investigated. By this method, a large number of aryl aminobenzophenone p38 MAP kinase inhibitors were prepared in short order.

Introduction

Activation of the p38 MAP kinase cascade has been implicated in the production of the proinflammatory cytokines interleukin 1β (Il-1β) and tumor necrosis factor α (TNF-α).[1] In response to this discovery, structurally diverse p38 MAP kinase inhibitors have been sought for the treatment of a variety of inflammatory diseases such as rheumatoid arthritis.[2] Aryl aminobenzophenones represent a new class of p38 MAP kinase inhibitors (Figure 1).[3] EO-1221 (**1**) was found to have a high affinity for p38α MAP kinase isoform and displayed effective inhibition of TNF-α and Il-1β release from human peripheral blood mononuclear cells stimulated by LPS.

In an ongoing project with the aim of preparing this type of inhibitor, an efficient amination of aryl halides was required (Scheme 1). Toward this end two methods have been used, the simplest being direct nucleophilic substitution of aryl halides with anilines in the presence of base, giving aryl aminobenzophenones. However, aryl fluorides are very inert to nucleophiles under normal conditions, except in cases where there are sustituents of -M type (e.g., nitro or nitrile) in the ortho or para position with respect to the fluorine atom. A more general method is transition-metal-catalyzed amination of aryl halides with anilines.

In recent years, the Pd-catalyzed amination of aryl halides (or their equivalents such as triflates and tosylates), which was independently developed by the groups of Buchwald and Hartwig, has emerged as a "power tool"

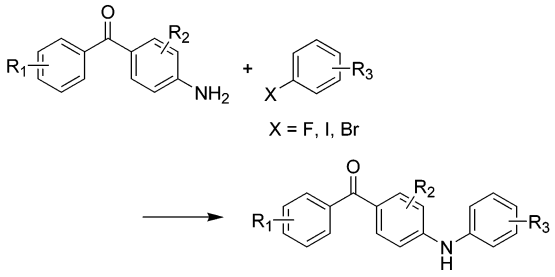


1

assay	IC_{50} in nM
TNF-α	6
Il -1β	14
p38α	10

FIGURE 1. Structure of EO-1221(**1**) and its biological data.

SCHEME 1



† Technical University of Denmark.

(1) (a) Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T. F.; Kumar, S.; Green, D.; McNulty, D.; Blumenthal, M. J.; Heys, J. R.; Landvatter, S. W.; Strickler, J. E.; Mclaughlin, M. M.; Siemens, I. R.; Fisher, S. M.; Livi, G. P.; White, J. R.; Adams, J. L.; Young, P. R. *Nature* **1994**, *372*, 739−746. (b) Gallagher, T. F.; Seibel, G. L.; Kassis, S.; Laydon, J. T.; Blumenthal, M. J.; Lee, J. C.; Lee, D.; Boem, J. C.; Fier-Thompson, S. M.; Abt, J. W.; Sorensen, M. E.; Smietana, J. M.; Hall, R. F.; Garigipati, R. S.; Bender, P. E.; Erhard, K. F.; Krog, A. J.; Hofmann, G. A.; Sheldrake, P. L.; McDonnell, P. C.; Kumar, S.; Young, P. R.; Adams, J. L. *Bioorg. Med. Chem.* **1997**, *5*, 49−64. (c) Adams, J. L.; Badger, A. M.; Kumar, S.; Lee, J. C. *Prog. Med. Chem.* **2001**, *38*, 1−60.

(2) For recent reviews, see: (a) Kumar, S.; Boehm, J.; Lee, J. C. *Nat. Rev. Drug Discov.* **2003**, 717−726. (b) Pargellis, C.; Regan, J. *Curr. Opin. Invest. Drugs* **2003**, *4*, 566−571. (c) Chakravarty, S.; Dugar, S. *Ann. Rep. Med. Chem.* **2002**, *37*, 177−186. (d) Jackson, P. F.; Bullington, J. L. *Curr. Top. Med. Chem.* **2002**, *2*, 1011−1020. (e) Boehm, J. C.; Adams, J. L. *Expert Opin. Ther. Patents* **2001**, *10*, 25−37.

(3) Ottosen, E. R.; Sørensen, M. D.; Björkling, F.; Skak-Nielsen, T.; Fjording, M. S.; Aaes, H.; Binderup, L. *J. Med. Chem.* **2003**, *46*, 5651−5662.

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for the synthesis of substituted anilines.[4] This methodology is now widely used in synthetic chemistry programs in both academic and industrial settings. However, in our hands, these Pd-catalyzed aminations typically required reaction times from several hours to several days. In a high-throughput synthetic context, it would obviously be more attractive to have reaction times in the order of minutes. Recently, high-speed microwave-assisted synthesis has been applied successfully in many fields of synthetic organic chemistry,[5] the hallmark of performing reactions under microwave irradiation conditions being the significant rate enhancements and the higher product yields that are frequently observed. These features have been particularly welcomed in medicinal chemistry research.

Although several reports of microwave-assisted Pd-catalyzed aryl amination have appeared,[6] these examples were limited to amination of simple aromatic systems that bear just a limited number of functional groups. Moreover, palladium-catalyzed amination of aryl triflates and tosylates under microwave-irradiation has not been described so far. Herein we report our efforts to systematically optimize microwave-assisted synthesis of aryl aminobenzophenones and the use of this technique in the preparation of some p38 MAP kinase inhibitors.

Results and Discussion

To optimize conditions for preparation of aryl aminobenzophenones, the amination of bromobenzene with 4-aminobenzophenone was initially selected as a model reaction for investigating the effects of various ligands, Pd sources, solvents, bases, and temperatures.

First, effects of phosphine ligands on the reactivity were examined. In a typical experiment, a mixture of 4-aminobenzophenone (1 equiv) and bromobenzene (1.2 equiv) in 1,4-dioxane was heated by microwave irradiation at 100 °C for 10 min in the presence of Cs_2CO_3 (1.4 equiv), $Pd_2(dba)_3$ (1 mol %), and phosphine ligand (4 mol %). The results of ligand screening are summarized in Figure 2, and it can be seen that the extent of the amination was dependent on the ligand used. Of the six ligands screened, the highest yield (18%) was achieved by using ligand **B** (X-Phos), while the other ligands gave much lower yields. Buchwald and co-workers reported

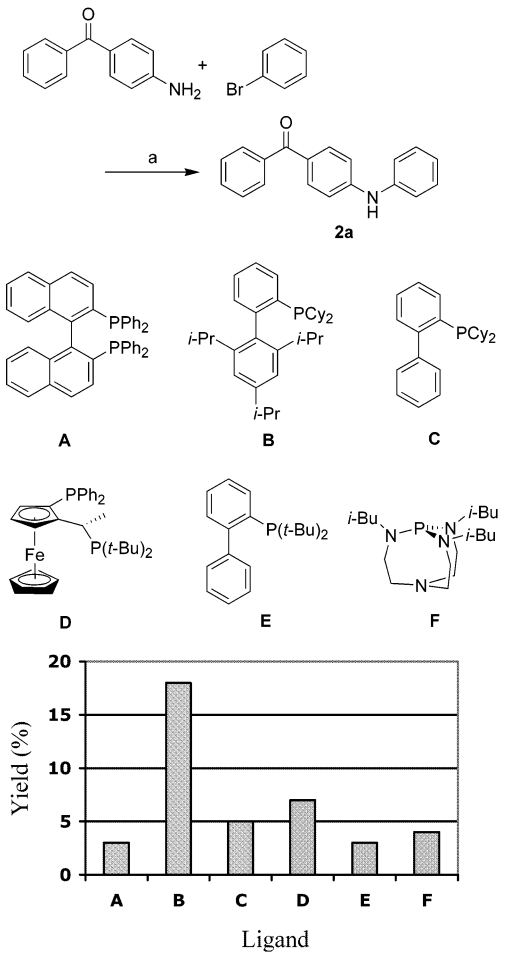


FIGURE 2. Ligand effects on palladium-catalyzed amination reaction of bromobenzene with 4-aminobenzophenone. Bromobenzene (1.2 equiv), 4-aminobenzophenone (1.0 equiv), Cs_2CO_3 (1.4 equiv), $Pd_2(dba)_3$ (1 mol %), ligand (4 mol %), 1,4-dioxane, MW 150 W, 100 °C, 10 min.

that the catalyst system based on ligand **B** exhibits both dramatically increased activity and stability relative to those based on simpler biaryl phosphine ligands.[7] Recent studies suggest that the high activity of catalyst systems based on bulky phosphines results from their ability to promote the formation of monophosphine complexes (L_1Pd^0).[8] However, our best result was still only 18% yield, so we proceeded to further optimize the reaction by varying other parameters: Pd source, solvent system, base, and temperature.

As the Pd source has been previously shown to affect the amination,[9] two different Pd sources were investigated, and the results are listed in Table 1. All cases successfully provided amination products, but the use of $Pd(OAc)_2$ gave **2a** in 40% yield instead of only 27% yield when using $Pd_2(dba)_3$ under the same reaction conditions (Table 1, entries 1 and 2). As a result of the copious precipitation of inorganic salts, the magnetic stir bar was trapped during the reaction, which caused elongation of

(4) For reviews, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem*. **2002**, *219*, 131−209. (b) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000; pp 195−262. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem*. **1999**, *576*, 125−146. (d) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res*. **1998**, *31*, 805−818. (e) Hartwig, J. F. *Angew. Chem., Int. Ed*. **1998**, *37*, 2046−2067.

(5) For reviews, see: (a) Perreux, L.; Loupy, A.; *Tetrahedron* **2001**, *57*, 9199−9223. (b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem*. **2002**, *4*, 95−105. (d) Santagada, V.; Perissutti, E.; Caliendo, G. *Curr. Med. Chem*. **2002**, *9*, 1251−1283. (e) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res*. **2002**, *35*, 717−727.

(6) For examples of microwave-assisted Pd-catalyzed aryl aminations, see: (a) Weigand, K.; Pelka, S. *Mol. Diver*. **2003**, *7*, 181−184. (b) McCarroll, A. J.; Sandham, D. A.; Titcomb, L. R.; Lewis, A. K. de K; Cloke, F. G. N.; Davies, B. P.; de Santana, A. P.; Hiller, W.; Caddick, S. *Mol. Diversity* **2003**, *7*, 115−123. (c) Maes, B. U. W.; Loones, K. T. J.; Lemiere, G. L. F.; Dommisse, R. A. *Synlett* **2003**, 1822−1825. (d) Wang, T.; Magnin, D. R.; Hamann, L. G. *Org. Lett*. **2003**, *5*, 897−900. (e) Wan, Y.; Alterman, M.; Hallberg, A. *Synthesis* **2002**, 1597−1600. (f) Sharifi, A.; Hosseinzadeh, R.; Mirzaei, M. *Monatsh. Chem*. **2002**, *133*, 329−332.

(7) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2003**, *125*, 6653−6654.

(8) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc*. **2003**, *125*, 13978−13980.

(9) Wolfe, J.; Buchwald, S. L. *J. Org. Chem*. **2000**, *65*, 1144−1157.

TABLE 1. Pd Source Effects on Palladium-Catalyzed Amination Reaction of Bromobenzene with 4-Aminobenzophenone[a]

entry	Pd source	temp (°C)	time (min)	yield (%)[b]
1	$Pd_2(dba)_3$	100[c]	20	27
2	$Pd(OAc)_2$	100[c]	20	40
3	$Pd(OAc)_2$	140[d]	25	68
4	$Pd(OAc)_2$	140[d]	25	84[e]

[a] Reagents: bromobenzene (1.2 equiv), 4-aminobenzophenone (1.0 equiv), Cs_2CO_3 (1.4 equiv), Pd(0) (1 mol %) or Pd(II) (2 mol %), ligand **B** (4 mol %), 1,4-dioxane. [b] Isolated yield based on 4-aminobenzophenone. [c] MW, 150 W. [d] MW, 200 W. [e] The reaction was performed in the presence of Celite [Cs_2CO_3/Celite 2/1 (w/w)].

TABLE 2. Solvent Effects on Palladium-Catalyzed Amination Reaction of Bromobenzene with 4-Aminobenzophenone[a]

entry	solvent	yield (%)[b]
1	1,4-dioxane	48
2	toluene	38
3	*t*-butanol	54
4	toluene/*tert*-butyl alcohol 1:1	58
5	toluene/*tert*-butyl alcohol 5:1	65
6	toluene/*tert*-butyl alcohol 10:1	42

[a] Reagents and conditions: bromobenzene (1.2 equiv), 4-aminobenzophenone (1.0 equiv), Cs_2CO_3 (1.4 equiv), $Pd(OAc)_2$ (2 mol %), ligand **B** (4 mol %), MW 150 W, 100 °C, 20 min. [b] Isolated yield based on 4-aminobenzophenone.

TABLE 3. Base Effects on Palladium-Catalyzed Amination Reaction of Bromobenzene with 4-Aminobenzophenone[a]

entry	base	yield (%)[b]
1	K_3PO_4	29
2	K_2CO_3	13
3	Cs_2CO_3	65
4	NaO*t*-Bu	78

[a] Reagents and conditions: bromobenzene (1.2 equiv), 4-aminobenzophenone (1.0 equiv), base (1.4 equiv), $Pd(OAc)_2$ (2 mol %), ligand **B** (4 mol %), *tert*-butyl alcohol/toluene (1/5), MW 200 W, 100 °C, 20 min. [b] Isolated yield based on 4-aminobenzophenone.

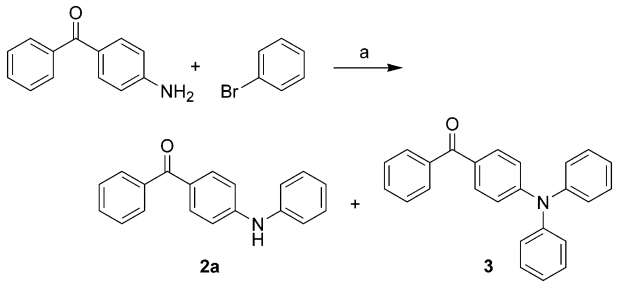
reaction time (Table 1, entry 3). To alleviate this situation, Celite was added and this indeed provided a better yield in the same time period (Table 1, entry 4).

We also explored several solvent systems: 1,4-dioxane and toluene are two common solvents used for the aryl amination, while *tert*-butyl alcohol and *tert*-butyl alcohol/toluene have been used for the amination of aryl sulfonates by Buchwald et al.[8] Our results are summarized in Table 2. It was found that *tert*-butyl alcohol was superior to 1,4-dioxane and toluene (Table 2, entries 1−3). However, the combination of toluene/*tert*-butyl alcohol was found to be even more effective, the best yield (65%) being achieved when a 5:1 ratio of toluene/*tert*-butyl alcohol was used (Table 2, entries 4−6).

The use of other bases, for example, K_3PO_4, K_2CO_3, and NaO*t*-Bu, was then investigated, and the results are presented in Table 3. Using K_3PO_4 and K_2CO_3, **2a** was obtained in 29% and 13% yield, respectively (Table 3, entries 1 and 2), whereas using NaO*t*-Bu gave higher yield (78%) than when using Cs_2CO_3 (65%) (Table 3, entries 3 and 4).

Finally, we explored the temperature effect (Table 4). The reaction was carried out under the standard set of

TABLE 4. Temperature Effects on Palladium-Catalyzed Amination Reaction of Bromobenzene with 4-Aminobenzophenone[a]



entry	temp (°C)	time (min)	PhBr (equiv)	**2a**:**3**	yield (%)[b]
1	100	10	1.2	72:2[c]	72[d]
2	120	5	1.2	73:20	73
3	120	10	1.2	67:25	67
4	140	10	1.2	nd[e]	64
5	160	10	1.2	nd	62
6	120	10	1.0	nd	88
7	120	3	1.0	nd	89
8	120	1	1.0	nd	81[f]

[a] Reagents and conditions: bromobenzene, 4-aminobenzophenone (1.0 equiv), NaO*t*-Bu (1.4 equiv), $Pd(OAc)_2$ (2 mol %), ligand **B** (4 mol %), *tert*-butyl alcohol/toluene (1/5), MW 200 W. [b] Isolated yield for **2a** based on 4-aminobenzophenone. [c] The ratio was calculated on the basis of the isolated products. [d] 22% of 4-aminobenzophenone was isolated. [e] nd = not determined. [f] The reaction was not complete according to TLC control.

conditions (1.2 equiv of bromobenzene, 1.0 equiv of 4-aminobenzophenone, 1.4 equiv of NaO*t*-Bu, 2 mol % of $Pd(OAc)_2$, 4 mol % of ligand **B**, MW 200 W) at various temperatures and reaction times. When run at 100 °C for 10 min, the reaction was incomplete and the desired product **2a** was obtained in 72% yield together with 22% of recovered 4-aminobenzophonone and 2 % of diarylation byproduct **3** (Table 4, entry 1). However, raising the temperature resulted in a significant amount of **3** and decreased the yields of **2a** (Table 4, entries 2−5). The low yield of **2a** was clearly caused by the presence of the excess bromobenzene, and decreasing the ratio of 4-aminobenzophenone and bromobenzene to 1:1 greatly affected the ratio of **2a** and **3**. Use of a 1:1 ratio of coupling partners led to **2a** in 89% yield under optimized conditions (1.0 equiv of bromobenzene, 1.0 equiv of 4-aminobenzophenone, 1.4 equiv of NaO*t*-Bu, 2 mol % of $Pd(OAc)_2$, 4 mol % of ligand **B**, MW 200 W) after 3 min (Table 4, entries 6 and 7). In the last entry of Table 4, total conversion was not achieved after 1 min, giving relatively lower yield (Table 4, entry 8).

Having now changed so many reaction parameters, we wished to determine whether ligand **B** was still the best for the model reaction, so we reinvestigated the effect of ligands. Two more ligands were screened. The results are outlined in Figure 3. The reactions were run for 3 min, and all the ligands gave better yields than in the original screening. Although ligand **B** was still found to perform very efficiently, ligand **C** now proved to be equally effective, giving **2a** in 91% yield. The use of ligands **A**, **D**, and **F** gave moderate to good yields, and ligands **E**, **G** and **H** were found to be the least effective. Recently, methods for direct amination of aryl halides and triflates with amines and anilines under microwave irradiation

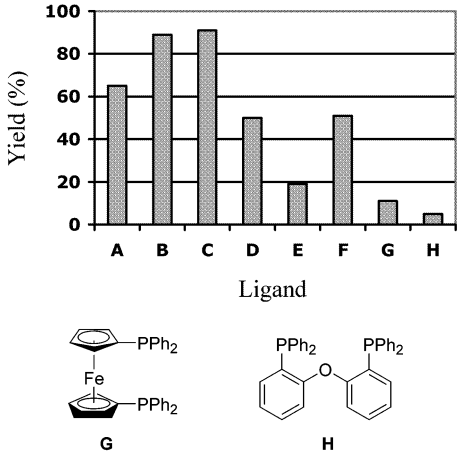


FIGURE 3. Ligand effects on palladium-catalyzed amination reaction of bromobenzene with 4-aminobenzophenone.

without a transition-metal catalyst have been reported.[10] To rule out this possible mechanism shift, the amination reaction was carried out in the absence of Pd catalyst and ligand **B** under otherwise identical conditions. No reaction occurred, thus demonstrating that the catalyst was indeed necessary. The same reaction using ligand **B** was also carried out using an oil bath to heat the reaction mixture under the same conditions as for the microwave-assisted reaction. As expected, a much longer reaction time (70 min) was needed for the same degree of conversion.

The above systematic investigations suggested that ligands **B** and **C** are highly effective for the amination of bromobenzene with 4-aminobenzophenone in the presence of NaO*t*-Bu. With optimized conditions in hand, we subsequently explored the substrate scope of the reaction with various aryl bromides, chlorides, triflates,[11] and tosylates.[7,12] Considering its high activity in all cases, ligand **B** was our choice for further experimentation, and the results (summarized in Table 5) show that a variety of aryl bromides can be coupled to differently substituted anilines. Both electron-neutral and electron-rich aryl bromides reacted efficiently under the optimized conditions, giving the desired arylamines in high isolated yields (Table 5, entries 1−6). When electron-rich aryl bromides were aminated, higher temperature was needed (Table 5, entries 7 and 8). Selective substitution of Br over Cl can be achieved in the coupling of 2-bromo-1-chlorobenzene with 4-aminobenzophenone (Table 5, entry 9). Amination of 3-bromopyridine turned out to be a slow reaction even at higher temperature (Table 5, entry 10). The reason is probably that nonchelating triarylphosphines can be displaced from the metal by the pyridine substrate, leading to catalyst deactivation.[12] Aryl and pyridyl chlorides can also be aminated in high yields (Table 5, entries 11 and 12). For aryl bromides bearing base-sensitive functional groups such as nitro and nitrile, the reactions turned out to be less effective. Buchwald et al. found out that by using Cs_2CO_3, the reaction conditions are sufficiently mild to tolerate the presence of nitrile and nitro groups, which are incompatible with reaction conditions that employ NaO*t*-Bu as the stoichiometric base.[13] We thus examined the amination of aryl bromides bearing nitro and nitrile functional groups using Cs_2CO_3 as base and found that higher yields could indeed be achieved for the amination of 1-bromo-3-nitrobenzene and 4-bromobenzonitrile, respectively (Table 5, entries 15 and 16). Amination of aryl triflates with NaO*t*-Bu as base gave only low yields (Table 5, entry 14), which is attributable to cleavage of the triflate by attack of NaO*t*-Bu on sulfur, leading to the formation of sodium phenoxide.[11a,c] However, the use of Cs_2CO_3 in place of NaO*t*-Bu led to much higher yield (Table 5, entry 18). Amination of aryl tosylates turned out to be more difficult even if Cs_2CO_3 was used as base (Table 5, entries 13 and 17). First, even using Cs_2CO_3 might not effectively prevent cleavage of the tosylate, and second excessive precipitation caused incomplete (vide supra).

We then explored the more challenging coupling of aryl bromides with 4-amino-2-chloro-2′-methylbenzophenone;[3] the results are outlined in Table 6. Two byproducts (**5a** and **6a**) were observed (Table 6, entry 1), **6a** arising from amination of 4-amino-2-chloro-2′-methylbenzophenone by another molecule of 4-amino-2-chloro-2′-methylbenzophenone. This gave two problems: (i) to form one molecule of **6a**, two molecules of 4-amino-2-chloro-2′-methylbenzophenone are required, thus lowering the yield (71%) of the desired product (Table 6, entry 1); (ii) as a result of the similar polarities of **4a** and **6a**, it was difficult to separate the desired product by chromatography. To suppress the undesired reaction, the amount of aryl bromide was increased, and when 1.5 equiv of aryl bromide was used, a higher yield of the desired product (79%) was achieved (Table 6, entry 2). Under these conditions, some aryl bromides bearing various functional groups were chosen for the amination reaction (Table 6, entries 3−11). All of the reactions were complete within 3 min, with good yields. Amination of 4-iodotoluene expectedly turned out to be a fast reaction as well, giving **4k** in 75% yield (Table 6, entry 12). Considering the issue of compatibility of functional groups, the base was again switched from NaO*t*-Bu to Cs_2CO_3 for amination of aryl bromides bearing nitro and nitrile groups (Table 6, entries 14 and 15). As expected, longer reaction times were needed, but the yields are comparable. Entry 15 of Table **6** shows a more complicated situation: besides the two above-mentioned byproducts **5** and **6**, a third byproduct, trione **7**, was observed (Scheme 2). The structure of **7** was deduced from ^{1}H and ^{13}C NMR spectroscopy in combination with HRMS. Clearly, trione **7** was formed by further amination of **6k** with 4-amino-2-chloro-2′-methylbenzophenone, implying that the aryl triflate substrate is not as reactive as the corresponding aryl iodide or bromide.

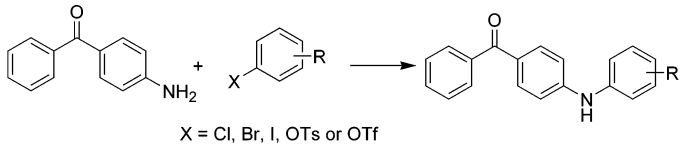
(10) For microwave-assisted direct amination of halides and triflate, see: (a) Shi, L.; Wang, M.; Fan, C.; Zhang F.; Tu, Y. *Org. Lett.* **2003**, *5*, 3515. (b) Brown, G. R.; Foubister, A. J.; Roberts, C. A.; Wells, S. L.; Wood, R. *Tetrahedron Lett.* **2001**, *42*, 3917. (c) Xu, G.; Wang, Y. *Org. Lett.* **2004**, *6*, 985−987.

(11) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264−1267. (b) Louie, L.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268−1273. (c) Åhman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6363−6366.

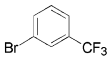
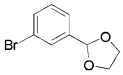
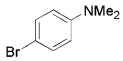
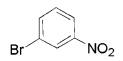
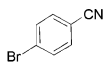
(12) (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370. (b) Bolm, C.; Hildebrand, J. P.; Rudolph, J. *Synthesis* **2000**, 911−913.

(13) (a) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359−6362. (b) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560−2565.

TABLE 5. Reactions of Aryl Bromides, Aryl Chlorides, Aryl Tosylate, and Aryl Triflate with Aminobenzophenone

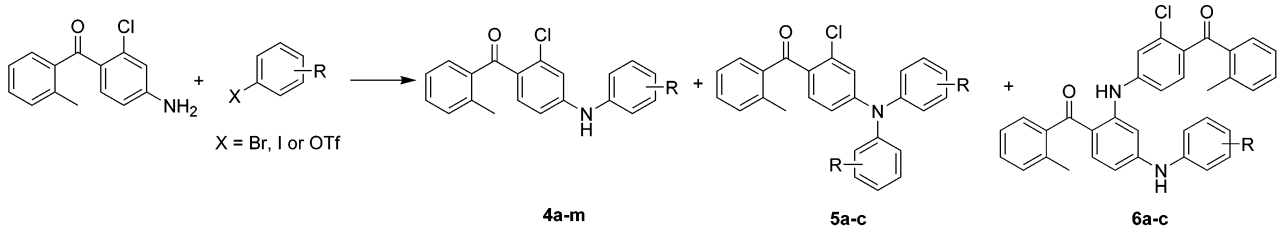


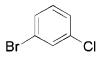
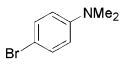
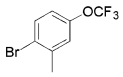
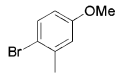
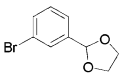
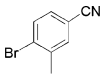
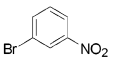
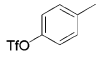
2a-m

entry	ArX	base	MW (W)	temp (°C)	time (min)	product	yield (%)[b]
1		NaO*t*-Bu	200	120	3	**2a**	89
2		NaO*t*-Bu	200	120	12	**2b**	91
3		NaO*t*-Bu	200	120	6	**2c**	96
4		NaO*t*-Bu	200	120	9	**2d**	84
5		NaO*t*-Bu	200	120	10	**2e**	88
6		NaO*t*-Bu	200	120	6	**2f**	84
7		NaO*t*-Bu	300	160	15	**2g**	85
8		NaO*t*-Bu	300	160	10	**2h**	89
9		NaO*t*-Bu	200	160	10	**2i**	82
10		NaO*t*-Bu	300	160	20	**2j**	91
11		NaO*t*-Bu	300	160	10	**2k**	91
12		NaO*t*-Bu	300	160	20	**2j**	89
13		NaO*t*-Bu	300	160	30	**2k**	22
14		NaO*t*-Bu	300	160	30	**2k**	45
15		Cs_2CO_3[c]	300	160	20	**2l**	80
16		Cs_2CO_3[c]	300	160	20	**2m**	84
17		Cs_2CO_3[c]	300	160	30	**2k**	27
18		Cs_2CO_3[c]	300	160	20	**2k**	91

[a] Reagents: bromobenzene (1.0 equiv), 4-aminobenzophenone (1.0 equiv), base (1.4 equiv), $Pd(OAc)_2$ (2 mol %), ligand **B** (4 mol %), *tert*-butyl alcohol/toluene (1/5). [b] Isolated yield based on 4-aminobenzophenone. [c] The reaction was performed in the presence of Celite.

TABLE 6. Reaction of Aryl Bromides, Aryl Iodide, and Aryl Triflate with 4-Amino-2-chloro-2′-methylbenzophenone[a]

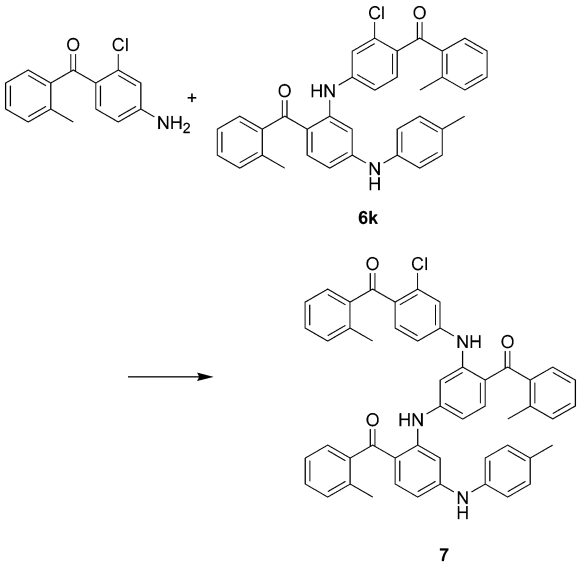


entry	ArX	equiv	base	time (min)	ratio **4**:**5**:**6**	main product	yield (%)[b]
1		1.0	NaO*t*-Bu	3	90:4:6	**4a**	71
2		1.5	NaO*t*-Bu	3	87:10:3	**4a**	79
3		1.5	NaO*t*-Bu	3	94:3:3	**4b**	79
4		1.5	NaO*t*-Bu	3	nd	**4c**	78
5		1.5	NaO*t*-Bu	3	nd	**4d**	80
6		1.5	NaO*t*-Bu	3	nd	**4e**	77
7		1.5	NaO*t*-Bu	3	nd	**4f**	78
8		1.5	NaO*t*-Bu	3	nd	**4g**	75
9		1.5	NaO*t*-Bu	3	nd	**4h**	76
10		1.5	NaO*t*-Bu	3	nd	**4i**	73
11		1.5	NaO*t*-Bu	3	nd	**4j**	79
12		1.5	NaO*t*-Bu	3	nd	**4k**	75
13		1.5	Cs_2CO_3[c]	15	nd	**4l**	74
14		1.5	Cs_2CO_3[c]	15	nd	**4m**	75
15		1.5	Cs_2CO_3[c]	15	nd	**4k**	51

[a] Reagents and conditions: bromobenzene (1.0 equiv), 4-aminobenzophenone (1.0 equiv), base (1.4 equiv), $Pd(OAc)_2$ (2 mol %), ligand **B** (4 mol %), *tert*-butyl alcohol/toluene (1/5), MW 250 W, 150 °C. [b] Isolated yield based on 4-aminobenzophenone. [c] The reaction was performed in the presence of Celite.

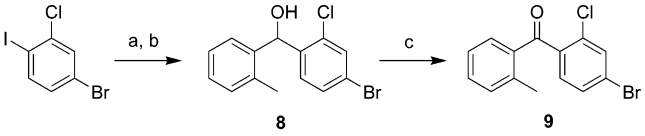
We were also interested in performing the aryl amination in an alternative mode, because of the large number of readily available anilines. Therefore, we examined the coupling of substituted 4-bromobenzophenones with various anilines, the starting material (**9**) being readily prepared in three steps (Scheme 3). Ac-

SCHEME 2 [a]



[a] Reagents and conditions: see reagents and conditions for Table 6, entry 15.

SCHEME 3 [a]



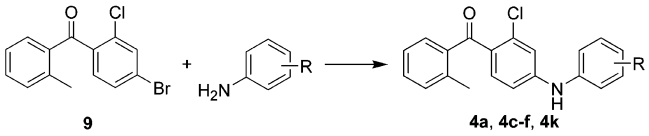
[a] Reagents and conditions: (a) isopropylmagnesiumchloride, THF, −60 °C, 2 h; (b) 2-methylbenzaldehyde, THF, rt, 2 h (92% over two steps); (c) Dess−Martin periodinane, CH_2Cl_2, rt, 30 min (94%).

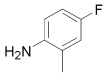
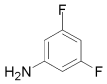
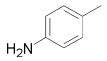
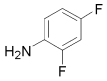
cording to Knochel's protocol,[14,15] a functionalized aryl iodide was reacted with *i*-PrMgCl in THF at −60 °C for 2 h, leading to halogen-metal exchange. Reaction of the newly formed Grignard reagent with 2-methylbenzaldehyde at room temperature for 2 h then furnished alcohol **8** in 92% yield. Finally, oxidation of **8** with the Dess−Martin periodinane provided benzophenone **9** in 94% yield.

Substrate **9** was then subjected to amination with several different anilines; the results are presented in Table 7. The reaction was first carried out by using NaO*t*-Bu as base, which led to a complicated product distribution and isolation of only 24% of the desired product **4a** (Table 7, entry 1). Fortunately, replacement of NaO*t*-Bu by Cs_2CO_3 led to a much higher yield (79%), although a longer reaction time was required (Table 7, entry 2). Coupling of other anilines also gave good yields under the same conditions (Table 7, entries 3−7).

In summary, we have developed a convenient protocol for the rapid and efficient preparation of aryl aminobenzophenones from the corresponding anilines and aryl halogens (or triflates). Amination of an electronically diverse array of aryl halides with a variety of anilines was realized with good to excellent yields, and it was not necessary to work under an inert atmosphere. Unfortunately, coupling of aryl tosylates under conditions of microwave irradiation turned out to be sluggish, and in some cases the chemoselectivity of the process was not satisfactory. However, in general, the procedure is suitable for the preparation of a large number of aryl aminobenzophenones and also for automated library production. High-throughput medicinal chemistry efforts are currently under way using this technique.

TABLE 7. Amination of 9 with Various Anilines[a]



entry	$ArNH_2$	base	time (min)	product	yield (%)[b]
1		NaO*t*-Bu	6	**4a**	24
2		Cs_2CO_3	20	**4a**	79[c]
3		Cs_2CO_3	20	**4c**	78[c]
4		Cs_2CO_3	20	**4d**	79[c]
5		Cs_2CO_3	20	**4e**	71[c]
6		Cs_2CO_3	20	**4k**	73[c]
7		Cs_2CO_3	20	**4f**	70[c]

[a] Reagents and conditions: **9** (1.0 equiv), aniline (1.0 equiv), base (1.4 equiv), $Pd(OAc)_2$ (2 mol %), ligand **B** (4 mol %), *tert*-butyl alcohol/toluene (1/5), MW 250 W, 150 °C. [b] Isolated yield based on (4-bromo-2-chlorophenyl)(2-methyl)methanone. [c] The reaction was performed in the presence of Celite.

Experimental Section

{4-[(4-Fluorophenyl)amino]phenyl}(phenyl)methanone (2b). General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 2-bromo-4-fluorobenzene (175.0 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol). The reaction was conducted under microwave irradiation (200 W) at 120 °C for 12 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to yield 264.1 mg (91%) of the title compound as a yellow solid: mp 155−157 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77−7.72 (m, 4H), 7.54−7.51 (ddt, J = 1.1, 5.7, 7.1 Hz, 1H) 7.47−7.45 (m, 2H), 7.19−7.14 (m, 2H), 7.07−7−01 (m, 2H), 6.92−6.88 (dt, J = 2.7, 7.1 Hz, 2H), 6.14 (s, 1H);

(14) Varchi, G.; Ricci, G.; Gahiez, G.; Knochel, P. *Tetrahedron* **2000**, *56*, 2727−2731.

(15) For a review, see: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302−4320.

^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 195.2, 159.3 148.9, 138.7, 136.5, 132.8, 131.6, 129.6, 128.4, 128.1, 123.6, 116.3, 113.7; HRMS (EI) (M^+) calcd for $C_{20}H_{17}NO$ 291.1059, found 291.1053.

[4-(2-Methylphenylamino)phenyl](phenyl)methanone (2c). General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 2-bromotoluene (171.0 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol). The reaction was conducted under microwave irradiation (200 W) at 120 °C for 6 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to yield 274.4 mg (96%) of the title compound as a yellow solid: mp 133−134 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77−7.72 (m, 4H), 7.56−7.50 (tt, J = 1.5, 7.3 Hz, 1H), 7.47−7.42 (m, 2H), 7.31−7.21 (m, 3H), 7.12−7.09 (dt, J = 1.2, 7.3 Hz, 1H), 6.83−6.80 (dt, J = 1.9, 8.9 Hz, 2H), 5.85 (s, 1H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 195.2, 149.4, 138.8, 138.7, 132.8, 132.0, 131.4, 131.3, 129.5, 128.1, 128.0 127.0, 124.9, 123.3, 113.8, 17.9; HRMS (EI) (M^+) calcd for $C_{20}H_{17}NO$ 287.1310, found 287.1324.

(4-{[3-(Trifluoromethyl)phenyl]amino}phenyl)(phenyl)methanone (2d). General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 3-bromotrifluoromethylbenzene (225.1 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol). The reaction was conducted under microwave irradiation (200 W) at 120 °C for 9 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to give 282.2 mg (84%) of the title compound as a yellow solid: mp 169−171 °C; ^{1}H NMR (DMSO, 300 MHz) δ 9.19 (s, 1H), 7.76−7.52 (m, 9H), 7.45 (s, 1H), 7.30−7.29 (m, 1H), 7.21 (d, J = 8.8 Hz, 2H); ^{13}C NMR (DMSO, 75.4 MHz) δ 193.8, 147.3, 142.3, 138.2, 132.2, 131.7, 130.5, 130.1 129.0, 128.3, 128.0, 124.1, 121.8, 117.6 114.9, 114.6; HRMS (EI) (M^+) calcd for $C_{20}H_{14}F_3NO$ 341.1027, found 341.1013.

[4-(2,4-Difluorophenylamino)phenyl](phenyl)methanone (2e). General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 2,4-difluorobromobenzene (193.0 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol). The reaction was conducted under microwave irradiation (200 W) at 120 °C for 10 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to yield 272.5 mg (88%) of the title compound as a yellow solid: mp 147−149 °C; ^{1}H NMR (DMSO, 300 MHz) δ 8.63 (s, 1H), 7.67−7.33 (m, 9H), 7.14−7.07 (m, 1H), 6.89 (s, 1H), 6.86 (s, 1H); ^{13}C NMR (DMSO, 75.4 MHz) δ 193.7, 160.1, 157.1, 154.0, 149.4, 138.4, 132.1, 131.5, 128.6, 126.7, 126.1, 124.8, 113.1, 111.8, 104.9; HRMS (EI) (M^+) calcd for $C_{19}H_{13}F_2NO$ 309.0965, found 309.0951.

{4-[3-(1,3-Dioxolan-2-yl)phenylamino]phenyl}(phenyl)methanone (2f). General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 2-(3-bromophenyl)-1,3-dioxolane (229.1 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol). The reaction was conducted under microwave irradiation (200 W) at 120 °C for 6 min. The crude material was purified by flash column chromatography (ethyl acetate/CH_2Cl_2 1:20), to yield 290.8 mg (84%) of the title compound as a yellow solid: mp 147−149 °C; ^{1}H NMR (DMSO, 300 MHz) δ 8.96 (s, 1H), 7.70−7.51 (m, 7H), 7.35 (t, J = 7.7 Hz, 1H), 7.26−7.23 (m, 2H), 7.12−7.05 (m, 3H), 5.73 (s, 1H), 4.07−3.90 (m, 4H); ^{13}C NMR (DMSO, 75.4 MHz) δ 194.5, 149.3, 142.0, 140.4, 139.3, 133.2, 132.4, 130.1, 129.8, 129.2, 127.8, 121.1, 120.7, 118.3, 114.8, 103.4, 65.6; HRMS (EI) (M^+) calcd for $C_{22}H_{19}NO_3$ 345.1365, found 345.1370.

(4-{[4-(Dimethylamino)phenyl]amino}phenyl)(phenyl)methanone (2g). General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 4-bromo-*N*,*N*-dimethylaniline (200.1 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol). The reaction was conducted under microwave irradiation (300 W) at 160 °C for 15 min. The crude material was purified by flash column chromatography (ethyl acetate/CH_2Cl_2 1:20), to yield 269.8 mg (85%) of the title compound as a yellow solid: mp 129−131 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.67−7.63 (m, 4H), 7.56−7.45 (m, 3H), 7.11−7.08 (m, 2H), 6.86−6.79 (m, 4H), 2.94 (s, 6H); ^{13}C NMR (CD_3OD, 75.4 MHz) δ 197.4, 153.3, 149.6, 140.5, 134.2, 132.6, 132.1, 130.4, 129.3, 126.9, 125.2, 115.4, 113.5, 41.6; HRMS (EI) (M^+) calcd for $C_{21}H_{20}N_2O$ 316.1576, found 316.1566.

{4-[(2-Methoxyphenyl)amino]phenyl}(phenyl)methanone (2h).[18] General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 2-bromoanisole (187.0 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol). The reaction was conducted under microwave irradiation (300 W) at 160 °C for 10 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to yield 275.4 mg (91%) of the title compound as a yellow solid: mp 93−95 °C (lit.[18] mp 130 °C); ^{1}H NMR (DMSO, 300 MHz) δ 8.27 (s, 1H), 7.67−7.52 (m, 7H), 7.33−7.30 (m, 1H), 7.11−7.09 (m, 2H), 6.97−6.94 (m, 3H), 3.81 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 193.5, 151.9, 149.7, 138.6, 132.0, 131.3, 129.1, 128.9, 128.2, 126.0, 124.3, 122.3, 120.5, 113.3, 112.0, 55.4; HRMS (EI) (M^+) calcd for $C_{20}H_{17}NO_2$ 303.1259, found 303.1247.

[4-(2-Chlorophenylamino)phenyl](phenyl)methanone (2i). General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 2-chloro-bromobenzene (191.5 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol). The reaction was conducted under microwave irradiation (200 W) at 160 °C for 15 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to yield 252.1 mg (82%) of the title compound as a yellow solid: mp 123−125 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82−7.75 (m, 4H), 7.56 (dt, J = 1.5, 7.3 Hz, 1H), 7.50−7.40 (m, 4H), 7.25 (m, 1H), 7.14 (t, J = 2.3 Hz, 1H), 7.11 (t, J = 1.9 Hz, 1H), 6.97−6.96 (dt, J = 1.5, 8.0 Hz, 1H), 6.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 195.2, 146.6, 138.4, 137.9, 132.5, 131.8, 130.1, 130.1 129.7, 128.2, 127.5, 124.2, 123.0, 119.1, 116.0; HRMS (EI) (M^+) calcd for $C_{19}H_{14}ClNO$ 307.0769, found 307.0779.

[4-(Pyridin-3-ylamino)phenyl](phenyl)methanone (2j). General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 3-bromopyridine (158.0 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol). The reaction was conducted under microwave irradiation (300 W) at 160 °C for 20 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:1), to yield 250.3 mg (91%) of the title compound as a yellow solid: mp 108−110 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.41 (d, J = 2.7 Hz, 1H), 8.15 (dd, J = 1.5, 4.9 Hz, 1H), 7.75−7.67 (m, 5H), 7.59 (dt, J = 1.5, 7.3 Hz, 1H), 7.51 (m, 2H), 7.35 (dd, J = 4.9, 8.4 Hz, 1H), 7.14 (t, J = 2.3 Hz, 1H), 7.11 (t, J = 2.3 Hz, 1H); ^{13}C NMR (CD_3OD, 75.4 MHz) δ 197.3, 149.4, 143.2, 141.9, 140.4, 139.8, 133.8, 133.1, 130.6, 130.0 129.4, 127.7, 125.6, 115.8; HRMS (EI) (M^+) calcd for $C_{18}H_{14}N_2O$ 274.1106, found 274.1103.

2j. General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 3-chloropyridine (113.6 mg, 1.00 mmol, using ligand **B** (17.1 mg, 0.04 mmol). The reaction was conducted under microwave irradiation (300 W) at 160 °C for 20 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:1), to give 250.3 mg (91%) of the title compound as a yellow solid. The spectroscopic data are identical with those described above for **2j**.

{4-[(4-Methylphenyl)amino]phenyl}(phenyl)methanone (2k).[19] General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 4-chlorotoluene (126.6 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol).

(16) Kamikawa, K.; Sugimoto, S.; Uemura, M. *J. Org. Chem.* **1998**, *63*, 8407−8410.

(17) Staskun, B. *J. Org. Chem.* **1968**, *33*, 3031−3036.

(18) Bhavsar, M. D.; Saraiya, P. N. *Man-Made Text. India* **1986**, *29*, 224−230. In this literature the compound **2h** was not fully characterized. Only IR data and melting point for **2h** were found.

(19) Birchall, J. M.; Clark, M. T. *J. Chem. Soc., Perkin. Trans. 1* **1973**, 1259−1263.

The reaction was conducted under microwave irradiation (300 W) at 160 °C for 10 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to give 260.6 mg (91%) of the title compound as a yellow solid: mp 128−130 °C (lit.[19] mp 126−127 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77−7.72 (m, 4H), 7.53 (dt, J = 1.5, 7.3 Hz, 1H), 7.47−7.41 (m, 2H), 7.17−7.08 (m, 4H), 6.95 (t, J = 2.3 Hz, 1H), 6.92 (t, J = 1.5 Hz, 1H), 6.11 (s, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 195.1, 149.0, 138.8, 137.9, 133.4, 132.8, 131.5, 130.1, 129.6, 128.2, 128.1, 121.6, 113.8, 60.4; HRMS (EI) (M^+) calcd calcd for $C_{20}H_{17}NO$ 287.1310, found 287.1305.

2k. General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 4-tolyl 4-toluenesulfonate (262.3 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol). The reaction was conducted under microwave irradiation (300 W) at 160 °C for 30 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to give 62.8 mg (22%) of the title compound as a yellow solid. The spectroscopic data are identical with those described above for **2k**.

2k. General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 4-tolyl triflate (240.2 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol). The reaction was conducted under microwave irradiation (300 W) at 160 °C for 30 min. The crude was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to give 129.9 mg (45%) of the title compound as a yellow solid. The spectroscopic data are identical with those described above for **2k**.

{4-[(3-Nitrophenyl)amino]phenyl}(phenyl)methanone (2l). General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 3-bromonitrobenzene (202.0 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol) and instead of NaO*t*-Bu, Cs_2CO_3 as base. The reaction was conducted under microwave irradiation (300 W) at 160 °C for 20 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to give 255.1 mg (80%) of the title compound as a yellow solid: mp 173−175 °C; ^{1}H NMR (DMSO, 300 MHz) δ 9.34 (s, 1H), 7.97 (t, J = 1.9 Hz, 1H), 7.79−7.53 (m, 7H), 7.58 (d, J = 1.9 Hz, 1H), 7.56 (d, J = 1.5 Hz, 1H), 7.53 (t, J = 1.5 Hz, 1H), 7.26 (s, 1H), 7.23 (s, 1H); ^{13}C NMR (DMSO, 75.4 MHz) δ 193.8, 148.6, 146.7, 142.9, 138.0, 132.1, 131.7, 130.6, 129.0, 128.5, 128.3, 124.0, 115.4, 115.3, 111.8; HRMS (EI) (M^+) calcd for $C_{19}H_{14}N_2O_3$ 318.1004, found 318.1016.

4-[(4-Benzoyl)phenylamino]benzonitrile (2m). General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 4-bromobenzonitrile (182.0 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol) and instead of NaO*t*-Bu, Cs_2CO_3 as base. The reaction was conducted under microwave irradiation (300 W) at 160 °C for 20 min. The crude material was purified by flash column chromatography (ethyl acetate/CH_2Cl_2 1:20), to give 251.3 mg (84%) of the title compound as a yellow solid: mp 185−187 °C; ^{1}H NMR (DMSO, 300 MHz) δ 9.44 (s, 1H), 7.79−7.67 (m, 4H), 7.66 (t, J = 2.3 Hz, 1H), 7.63 (t, J = 1.5 Hz, 1H), 7.58 (s, 1H), 7.56 (d, J = 1.2 Hz, 1H), 7.53 (t, J = 1.5 Hz, 1H), 7.31−7.29 (m, 4H); ^{13}C NMR (DMSO, 75.4 MHz) δ 193.9, 146.2, 145.8, 137.9, 133.7, 132.0, 131.8, 129.2, 129.1, 128.3, 119.5, 116.9, 116.7, 101.5; HRMS (EI) (M^+) calcd for $C_{20}H_{14}N_2O$ 298.1106, found 298.1104.

2k. General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 4-tolyl 4-toluenesulfonate (262.3 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol) and instead of NaO*t*-Bu, Cs_2CO_3 as base. The reaction was conducted under microwave irradiation (300 W) at 160 °C for 30 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum 1:8), to give 78.8 mg (27%) of the title compound as a yellow solid. The spectroscopic data are identical with those described before for **2k**.

2k. General Procedure 6 was used to couple 4-aminobenzophenone (197.2 mg, 1.00 mmol) with 4-tolyl triflate (240.2 mg, 1.00 mmol), using ligand **B** (17.1 mg, 0.04 mmol) and instead of NaO*t*-Bu, Cs_2CO_3 as base. The reaction was conducted under microwave irradiation (300 W) at 160 °C for 15 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum 1:8), to give 261.1 mg (91%) of the title compound as a yellow solid. The spectroscopic data are identical with those described before for **2k**.

{2-Chloro-4-(phenylamino)phenyl}(2-methylphenyl)methanone (4a),[3] [2-Chloro-4-(diphenylamino)phenyl](2-methylphenyl)methanone (5a), and [(2-{[2-Chloro-4-(2-methylbenzoyl)]phenylamino}-4-phenylamino)phenyl](2-methylphenyl)methanone (6a). General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)-methanone (245.7 mg, 1.00 mmol) with bromobenzene (235.5 mg, 1.50 mmol), using NaO*t*-Bu (134.5 mg, 1.40 mmol). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 3 min. The ratio of the crude products was determined by ^{1}H NMR spectroscopy. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4a** (252.8 mg, 79%) as a yellow solid, **5a** (40.1 mg) as a yellow solid and **6a** (10.1 mg) as a yellow syrup. **4a**: mp 93−95 °C (lit.[3] mp 79−82 °C). **5a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.13 (m, 15H), 6.97 (d, J = 2.3 Hz, 1H), 6.85(dd, J = 2.3, 8.8 Hz,1H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 196.5, 151.3, 146.1, 138.9, 138.2, 134.3, 132.6, 131.4, 131.0, 130.3, 129.9, 129.8, 126.1, 125.4, 125.0, 121.3, 117.7, 20.5. **6a**: ^{1}H NMR (DMSO, 300 MHz) δ 10.94 (s, 1H), 9.05 (s, 1H), 7.53−7.02 (m, 18H), 6.50 (dd, J = 1.9, 8.8 Hz, 1H), 2.39 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 197.7, 195.6, 150.4, 147.0, 144.4, 140.3, 137.9, 137.4, 137.0, 134.3, 132.5, 132.3, 131.5, 131.4, 131.3, 130.3, 129.7, 129.2, 129.0, 126.8, 125.7, 125.3, 122.8, 120.7, 120.6, 118.4, 112.7, 106.9, 98.0, 20.1, 19.0; HRMS (EI) (M^+) calcd for $C_{34}H_{27}ClN_2O_2$ 530.1761, found 530.1749.

{2-Chloro-4-[(3-chlorophenyl)amino]phenyl}(2-methylphenyl)methanone (4b),[20] (2-Chloro-4-{[di(3-chlorophenyl)]amino}phenyl)(2-methylphenyl)methanone (5b), and [(2-{[2-Chloro-4-(2-methylbenzoyl)]phenylamino}-4-[(3-chlorophenyl)amino])phenyl](2-methylphenyl)methanone (6b). General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)methanone (245.7 mg, 1.00 mmol) with 3-chloro-bromobenzene (287.2 mg, 1.50 mmol), using NaO*t*-Bu (134.5 mg, 1.40 mmol). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 3 min. The ratio of the crude products was determined by ^{1}H NMR spectroscopy. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4b** (280.6 mg, 79%) as a yellow solid, **5b** (31.8 mg) as a yellow solid and **6b** (8.0 mg) as a yellow syrup. **4b**: mp 104−106 °C; ^{1}H NMR (DMSO, 300 MHz) δ 9.08 (s, 1H), 7.42−7.27 (m, 6H), 7.21−7.03 (m, 5H), 2.35 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 195.3, 147.2, 142.5, 138.8, 136.7, 133.7, 133.3, 133.2, 131.1, 131.0, 130.9, 129.1, 128.2, 125.6, 121.7, 118.5, 117.4, 116.4, 113.2, 19.9; HRMS (EI) (M^+) calcd for $C_{20}H_{15}Cl_2NO$ 355.0531, found 355.0547. **5b**: ^{1}H NMR (DMSO, 300 MHz) δ 7.46−7.15 (m, 13H), 6.94 (d, J = 2.3 Hz, 1H), 6.90 (t, J = 1.9 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 195.5, 149.7, 146.6, 137.7, 137.5, 134.1, 132.4, 132.3, 131.6, 131.5, 131.4, 131.3, 129.9, 125.7, 125.7, 125.3, 124.3, 121.5, 119.0, 20.1; HRMS (EI) (M^+) calcd for $C_{26}H_{18}Cl_3NO$ 465.0454, found 465.0457. **6b**: ^{1}H NMR (DMSO, 300 MHz) δ 10.84 (s, 1H), 9.16 (s, 1H), 7.51−7.03 (m, 17H), 6.54 (dd, J = 2.3, 8.8 Hz, 1H), 2.39 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 197.9, 195.6, 149.3, 146.9, 144.4, 142.2, 140.1, 137.9, 137.3, 136.9, 134.4, 133.6, 132.6, 132.3, 131.5, 131.4, 131.3, 130.8, 130.4, 129.7, 129.1, 126.9, 125.7, 125.4, 122.0, 121.0, 119.3, 118.3, 118.1, 113.6, 107.4, 99.1, 20.1, 19.1; HRMS (EI) (M^+) calcd for $C_{34}H_{26}Cl_2N_2O_2$ 564.1371, found 564.1382.

{2-Chloro-4-[(2-methylphenyl)amino]phenyl}(2-methylphenyl)methanone (4c).[3] General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)methanone (245.7 mg, 1.00 mmol) with 2-bromotoluene (256.6 mg, 1.50

mmol), using NaO*t*-Bu (134.5 mg, 1.40 mmol). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 3 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4c** (262.5 mg, 78%) as a yellow solid: mp 100−102 °C (lit.[3] mp 98−99 °C).

{**2-Chloro-4-[(4-fluoro-2-methylphenyl)amino]phenyl**}**-(2-methylphenyl)methanone (4d).**[3] General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)-methanone (245.7 mg, 1.00 mmol) with 2-bromo-5-fluorotoluene (283.5 mg, 1.50 mmol), using NaO*t*-Bu (134.5 mg, 1.40 mmol). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 3 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4d** (283.4 mg, 80%) as a yellow solid: mp 153−155 °C (lit.[3] mp 151−152 °C).

{**2-Chloro-4-[(3,5-difluorophenyl)amino]phenyl**}**(2-methylphenyl)methanone (4e)**.[20] General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)-methanone (245.7 mg, 1.00 mmol) with 1-bromo-3,5-difluorobenzene (289.5 mg, 1.50 mmol), using NaO*t*-Bu (134.5 mg, 1.40 mmol). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 3 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4e** (275.2 mg, 77%) as a yellow solid: mp 86−88 °C; ^{1}H NMR (DMSO, 300 MHz) δ 9.24 (s, 1H), 7.46−7.14 (m, 5H) 7.17−7.14 (m, 2H), 6.85−6.76 (m, 3H), 2.36 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 195.4, 163.1, 146.0, 144.1, 133.0, 132.9, 131.2, 131.1, 129.3, 129.3, 101.1, 100.9, 100.8, 100.7, 96.8, 96.5, 96.1, 19.9; HRMS (EI) (M^+) calcd for $C_{20}H_{14}ClF_2NO$ 357.0732, found 357.0747.

{**2-Chloro-4-[(2,4-difluorophenyl)amino]phenyl**}**(2-methylphenyl)methanone (4f).** General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)methanone (245.7 mg, 1.00 mmol) with 2,4-difluorobromobenzene (289.5 mg, 1.50 mmol), using NaO*t*-Bu (134.5 mg, 1.40 mmol). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 3 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4f** (279.3 mg, 78%) as a yellow solid: mp 140−142 °C; ^{1}H NMR (DMSO, 300 MHz) δ 8.70 (s, 1H), 7.45−7.30 (m, 6H), 7.27 (d, J = 3.8 Hz, 1H), 7.15−7.08 (m, 1H), 6.83 (d, J = 1.5 HZ, 1H), 6.79 (dd, J = 1.5, 8.8 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 195.3, 158.8, 155.6, 149.1, 139.0, 136.5, 133.4, 133.3, 131.0, 130.7, 128.9, 127.0, 126.3, 125.6, 124.3, 114.8, 112.1, 111.8, 105.0, 19.8; HRMS (EI) (M^+) calcd for $C_{20}H_{14}ClF_2NO$ 357.0732, found 357.0728.

{**2-Chloro-4-[4-(dimethylamino)phenylamino]phenyl**}**-(2-methylphenyl)methanone (4g).** General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)-methanone (245.7 mg, 1.00 mmol) with 4-bromo-*N*,*N*-dimethylaniline (300.1 mg, 1.50 mmol), using NaO*t*-Bu (134.5 mg, 1.40 mmol). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 3 min. The crude product was separated by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4g** (274.0 mg, 75%) as a yellow solid: mp 155−157 °C; ^{1}H NMR (DMSO, 300 MHz) δ 8.58 (s, 1H), 7.42−7.24 (m, 5H), 7.07 (s, 1H), 7.04 (s, 1H), 6.78−6.71 (m, 4H), 2.88 (s, 6H), 2.28 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 194.8, 150.7, 147.6, 139.7, 136.0, 134.0, 130.8, 130.3, 128.9, 128.4, 125.5, 124.8, 123.9, 113.6, 113.2, 110.8, 40.3, 19.6; HRMS (EI) (M^+) calcd for $C_{22}H_{21}ClN_2O$ 364.1342, found 364.1345.

{**2-Chloro-4-[2-methyl-4-(trifluoromethoxy)phenylamino]phenyl**}**(2-methylphenyl)methanone (4h).** General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)methanone (245.7 mg, 1.00 mmol) with 2-methyl-4-(trifluoromethoxy)bromobenzene (382.6 mg, 1.50 mmol), using NaO*t*-Bu (134.5 mg, 1.40 mmol). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 3 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4h** (320.3 mg, 76%) as a yellow solid: mp 94−96 °C; ^{1}H NMR (DMSO, 300 MHz) δ 8.44 (s, 1H), 7.45−7.19 (m, 8H), 6.83 (d, J = 1,9 Hz, 1H), 6.77 (dd, J = 1.9, 8.4 Hz, 1H), 2.31 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 195.2, 149.5, 144.6, 139.2, 137.8, 136.4, 134.6, 133.6, 133.5, 131.0, 130.6, 128.8, 126.5, 125.6, 124.8, 123.5, 119.3, 118.4, 115.0, 111.8, 19.7, 17.6; HRMS (EI) (M^+) calcd for $C_{22}H_{17}ClF_3NO_2$ 419.0900, found 419.0897.

{**2-Chloro-4-[(4-methoxy-2-methylphenyl)amino]-phenyl**}**(2-methylphenyl)methanone (4i).** General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)methanone (245.7 mg, 1.00 mmol) with 2-bromo-5-methoxytoluene (301.6 mg, 1.50 mmol), using NaO*t*-Bu (134.5 mg, 1.40 mmol). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 3 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4i** (268.1 mg, 73%) as a yellow solid: mp 137−139 °C; ^{1}H NMR (DMSO, 300 MHz) δ 8.33 (s, 1H), 7.34−7.23 (m, 5H), 7.14 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 3.1 Hz, 1H), 6.83 (dd, J = 3.1 Hz, J = 8.8 Hz, 1H), 6.59 (d, J = 1.9 Hz, 1H), 6.55 (dd, J = 2.3, 8.4 Hz, 1H), 3.76 (s, 3H), 2.28 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 194.4, 157.0, 151.5, 139.6, 136.1, 135.5, 134.0, 130.8, 130.7, 130.3, 128.4, 127.2, 125.5, 124.8, 116.1, 113.5, 112.1, 110.6, 55.1, 19.6, 17.8; HRMS (EI) (M^+) calcd for $C_{22}H_{20}ClNO_2$ 365.1183, found 365.1148.

(4-{**[2-Chloro-3-(1,3-dioxolan-2-yl)]phenylamino**}**phenyl)(2-methylphenyl)methanone (4j).** General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)-methanone (245.7 mg, 1.00 mmol) with 2-(3-bromophenyl)-1,3-dioxolan (343.6 mg, 1.50 mmol), using NaO*t*-Bu (134.5 mg, 1.40 mmol). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 3 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4j** (312.3 mg, 79%) as a yellow solid: mp 81−83 °C; ^{1}H NMR (DMSO, 300 MHz) δ 9.01 (s, 1H), 7.43−7.22 (m, 8H), 7.12 (d, J = 7.3 Hz, 1H), 7.05 (d, J = 1.9 Hz, 1H), 7.02 (dd, J = 1.9, 8.4 Hz, 1H), 5.74 (s, 1H), 4.07 (m, 4H), 2.33 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 195.2, 148.1, 140.6, 139.6, 139.1, 136.5, 133.5, 133.4, 131.0, 130.7, 129.3, 128.9, 127.2, 125.6, 120.7, 120.2, 117.7, 115.5, 112.4, 102.4, 64.7, 19.8; HRMS (EI) (M^+) calcd for $C_{23}H_{20}ClNO_3$ 393.1132, found 393.1138.

{**2-Chloro-4-[(4-methylphenyl)amino]phenyl**}**(2-methylphenyl)methanone (4k).** General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)methanone (245.7 mg, 1.00 mmol) with 4-iodotoluene (327.1 mg, 1.50 mmol), using NaO*t*-Bu (134.5 mg, 1.40 mmol). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 3 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4k** (250.7 mg, 75%) as a yellow solid: mp 140−142 °C; ^{1}H NMR (DMSO, 300 MHz) δ 8.83 (s, 1H), 7.45−7.08 (m, 9H), 6.97 (d, J = 2.3 Hz, 1H), 6.93 (dd, J = 2.3, 8.4 Hz, 1H), 2.31 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 195.1, 149.0, 139.3, 137.7, 136.3, 133.7, 133.6, 132.1, 130.9, 130.5, 129.8, 128.7, 126.2, 125.5, 120.7, 114.8, 111.7, 20.3, 19.7; HRMS (EI) (M^+) calcd for $C_{21}H_{18}ClNO$ 335.1077, found 335.1061.

4-{**[3-Chloro-4-(2-methylbenzoyl)phenyl]amino**}**-3-methylbenzonitrile (4l).**[20] General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)methanone (245.7 mg, 1.00 mmol) with 4-bromo-3-methylbenzonitrile (294.1 mg, 1.50 mmol), using Cs_2CO_3 (456.1 mg, 1.40 mmol) and Celite (228 mg). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 15 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4l** (267.4 mg, 74%) as a yellow solid: mp 153−155 °C; ^{1}H NMR (DMSO, 300 MHz) δ 8.53 (s, 1H), 7.70 (d, J = 1.2 Hz, 1H), 7.61 (dd, J = 1.9, 8.4 Hz, 1H), 7.45−7.25 (m, 6H), 7.15 (d, J = 2.3 Hz, 1H), 7.09 (dd,

(20) Ottosen, E. R. WO 0142189, 2001.

J = 1.9, 8.4 Hz, 1H), 2.36 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 196.3, 147.5, 145.0, 139.4, 137.8, 135.5, 133.8, 133.7, 132.1, 132.0, 131.9, 130.9, 130.2, 130.0, 126.6, 120.1, 119.9, 118.9, 115.6, 104.8, 20.8, 18.4; HRMS (EI) (M^+) calcd for $C_{21}H_{18}ClNO$ 360.1029, found 360.1023.

{2-Chloro-4-[(3-nitrophenyl)amino]phenyl}(2-methylphenyl)methanone (4m). General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)methanone (245.7 mg, 1.00 mmol) with 3-bromo-nitrobenzene (303.02 mg, 1.50 mmol), using Cs_2CO_3 (456.1 mg, 1.40 mmol) and Celite (228 mg). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 15 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4m** (275.7 mg, 75%) as a yellow solid: mp 138−140 °C; ^{1}H NMR (DMSO, 300 MHz) δ 9.35 (s, 1H), 7.94 (t, J = 1.9 HZ, 1H), 7.82 (dt, J = 1.9, 7.3 Hz, 1H), 7.65−7.57 (m, 2H), 7.47−7.28 (m, 5H), 7.18 (d, J = 1.9 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 195.4, 148.6, 146.4, 142.5, 138.5, 136.9, 133.1, 131.2, 131.1, 130.7, 129.3, 129.1, 128.8, 125.7, 124.3, 116.9, 115.9, 113.9, 112.3, 19.9; HRMS (EI) (M^+) calcd for $C_{20}H_{15}ClN_2O_3$ 366.0771, found 366.0756.

4k, (2-Chloro-4-{[di(4-methylphenyl)]amino}phenyl)-(2-methylphenyl)methanone (5k), (2-{[2-Chloro-4-(2-methylbenzoyl)phenyl]amino}-4-[(4-methylphenyl)amino]-phenyl)(2-methylphenyl)methanone (6k), and Trione 7. General Procedure 7 was used to couple (4-amino-2-chlorophenyl)(2-methylphenyl)methanone (245.7 mg, 1.00 mmol) with 4-tolyl triflate (360.3 mg, 1.50 mmol), using Cs_2CO_3 (456.1 mg, 1.40 mmol) and Celite (228 mg). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 15 min. The crude material was separated by flash column chromatography (ethyl acetate/petroleum ether 1:8), to provide **4k** (171.0 mg, 51%) as a yellow solid, **5k** (11.0 mg) as a yellow solid, **6k** (52.2 mg) as a yellow syrup, and **7** (26.2 mg) as a yellow syrup.

4k: The spectroscopic data are identical with those described above.

5k: mp 80−82 °C; ^{1}H NMR (DMSO, 300 MHz) δ 7.46−7.21 (m, 10H), 7.12 (s, 2H), 7.10 (s, 1H), 6.72 (d, J = 2.3 Hz, 1H), 6.69 (dd, J = 2.3, 8.8 Hz, 1H), 2.34 (s, 3H), 2.30 (s, 6H); ^{13}C NMR (DMSO, 75.4 MHz) δ 195.3, 151.3, 142.5, 138.6, 136.8, 135.0, 132.9, 132.8, 131.1, 131.0, 130.5, 129.1, 128.0, 126.3, 125.6, 118.0, 115.4, 20.4, 19.9; HRMS (EI) (M^+) calcd for $C_{28}H_{24}ClNO$ 425.1546, found 425.1546.

6k: ^{1}H NMR (DMSO, 300 MHz) δ 10.99 (s, 1H), 8.97 (s, 1H), 7.52−7.22 (m, 11H), 7.16−6.97 (m, 6H), 6.44 (dd, J = 1.9, 9.2 Hz, 1H), 2.40 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 197.6, 195.6, 150.9, 147.0, 144.5, 140.3, 138.0, 137.5, 137.3, 137.0, 134.3, 132.6, 132.3, 132.2, 132.0, 131.4, 131.2, 130.3, 129.7, 129.0, 126.8, 125.7, 125.3, 121.1, 120.6, 120.4, 118.3, 112.4, 106.6, 97.6, 20.4, 20.1, 19.0; HRMS (EI) (M^+) calcd for $C_{35}H_{29}ClN_2O_2$ 544.1918, found 544.1924.

7: ^{1}H NMR (DMSO, 300 MHz) δ 10.80 (s, 1H), 10.73 (s, 1H), 8.89 (s, 1H), 7.49−6.96 (m, 23H), 6.81 (dd, J = 1.9, 8.8 Hz, 1H), 6.45 (dd, J = 1.9, 8.8 Hz, 1H), 2.37 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (DMSO, 75.4 MHz) δ 198.4, 197.5, 195.5, 150.6, 147.3, 146.2, 146.2, 144.4, 140.2, 139.8, 139.6, 137.9, 137.5, 137.3, 136.8, 136.5, 134.6, 134.4, 132.7, 132.2, 132.0, 131.4, 131.3, 131.3, 130.5, 130.3, 129.7, 129.6, 129.5, 129.1, 127.1, 126.9, 125.7, 125.4, 125.3, 120.9, 120.7, 118.5, 117.2, 115.9, 113.3, 111.1, 107.0, 103.8, 99.3, 20.3, 20.1, 19.1, 19.0; HRMS (EI) (M^+) calcd for $C_{49}H_{40}ClN_3O_3$ 753.2758, found 753.2753.

(4-Bromo-2-chlorophenyl)(2-methylphenyl)methanol (8). 4-Bromo-2-chloro-iodobenzene (10.0 g, 31.511 mmol) was dissolved in dry THF (100 mL) under an argon atmosphere. Isopropylmagnesiumchloride (2 M solution in THF, 16.5 mL, 33.09 mmol) was added at −60 °C. The solution was then stirred at −60 °C for 2 h, and then 2-methylbenzaldehyde (3.786 g, 31.51 mmol) was added. The reaction solution was stirred at the same temperature for 1 h and then allowed to warm to room temperature. A saturated aqueous solution of NH_4Cl was then added, and the mixture was extracted three times with diethyl ether. The combined organic phases were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/petroleum ether 1:10), giving 9.0293 g (92%) of the title compound as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52 (d, J = 1.9 Hz, 1H), 7.40 (dd, J = 1.9, 8.4 Hz, 1H), 7.24−7.14 (m, 6H), 6.24 (s, 1H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 139.5, 139.4, 135.9, 133.9, 132.1, 130.6, 130.2, 129.8, 128.0, 126.3, 126.2, 121.7, 69.5, 19.0; HRMS (EI) (M^+) calcd for $C_{14}H_{12}BrClO$ 309.9760, found 309.9778.

(4-Bromo-2-chlorophenyl)(2-methylphenyl)methanone (9). To a solution of **8** (8.9293 g, 28.7 mmol) in CH_2Cl_2 (200 mL) was added Dess−Martin periodinane (12.1542 g, 28.7 mmol) at room temperature. The obtained mixture was stirred at the same temperature for 30 min. The mixture was then concentrated in vacuo together with silica gel and purified by flash column chromatography (ethyl acetate/petroleum ether 1:20), giving 8.3273 g (94%) of the title compound as white solid: mp 76−78 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (d, J = 1.9 Hz, 1H), 7.50 (dd, J = 1.5, 8.0 Hz, 1H), 7.45(dt, J = 1.5, 7.3 Hz, 1H), 7.32−7.17 (m, 4H), 2.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 196.3, 139.6, 138.4, 136.6, 133.0, 132.3, 132.0, 131.6, 131.2, 131.1, 130.1, 125.6, 125.0, 21.2; HRMS (EI) (M^+) calcd for $C_{14}H_{10}BrClO$ 307.9604, found 307.9620.

4a. General Procedure 8 was used to couple aniline (93.1 mg, 1.0 mmol) with **9** (309.6 mg, 1.00 mmol) using NaO*t*-Bu (134.5 mg, 1.40 mmol). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 6 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8) to provide **4a** (78.3 mg, 24%) as a yellow solid. The spectroscopic and other physical data are identical with those described above.

4a. General Procedure 8 was used to couple aniline (93.1 mg, 1.0 mmol) with 9 (309.6 mg, 1.00 mmol) using Cs_2CO_3 (456.1 mg, 1.40 mmol) and Celite (228 mg). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 20 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8) to provide **4a** (253.1 mg, 79%) as a yellow solid. The spectroscopic data are identical with those described above.

4c. General Procedure 8 was used to couple 2-methyl-aniline (107.2 mg, 1.00 mmol) with 9 (309.6 mg, 1.00 mmol) using Cs_2CO_3 (456.1 mg, 1.40 mmol) and Celite (228 mg). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 20 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8) to provide **4c** (263.5 mg, 78%) as a yellow solid. The spectroscopic data are identical with those described above.

4d. General Procedure 8 was used to couple 4-fluoro-2-methylaniline (125.2 mg, 1.00 mmol) with 9 (309.6 mg, 1.00 mmol) using Cs_2CO_3 (456.1 mg, 1.40 mmol) and Celite (228 mg). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 20 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8) to provide **4d** (280.3 mg, 79%) as a yellow solid. The spectroscopic data are identical with those described above.

4e. General Procedure 8 was used to couple 3,5-difluoro-aniline (129.1 mg, 1.00 mmol) with 9 (309.6 mg, 1.00 mmol) using Cs_2CO_3 (456.1 mg, 1.40 mmol) and Celite (228 mg). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 20 min. The crude product was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8) to provide **4e** (254.9 mg, 71%) as a yellow solid. The spectroscopic data are identical with those described above.

4k. General Procedure 8 was used to couple 4-methylaniline (107.16 mg, 1.00 mmol) with 9 (309.6 mg, 1.00 mmol) using Cs_2CO_3 (456.1 mg, 1.40 mmol) and Celite (228 mg). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 20 min. The crude product was purified by flash

column chromatography (ethyl acetate/petroleum ether 1:8) to provide **4k** (244.1 mg, 73%) as a yellow solid. The spectroscopic data are identical with those described above.

4f. General Procedure 8 was used to couple 2,4-difluoroaniline (129.1 mg, 1.00 mmol) with **9** (309.6 mg, 1.00 mmol) using Cs_2CO_3 (456.1 mg, 1.40 mmol) and Celite (228 mg). The reaction was conducted under microwave irradiation (250 W) at 150 °C for 20 min. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:8) to provide **4f** (249.5 mg, 70%) as a yellow solid. The spectroscopic data are identical with those described above.

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Supporting Information Available: General experimental procedures and ^1H and ^{13}C NMR spectra of the compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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