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# A novel catalytic one-pot synthesis of carbazoles *via* consecutive amination and C–H activation†

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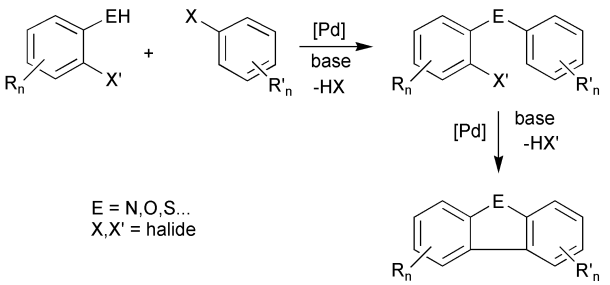
**Sequential palladium catalysed amination and C–H activation reactions occur between 2-chloro-*N*-alkylated anilines and aryl bromides to give carbazoles in one pot.**

The ability to perform two sequential catalytic transformations in one pot allows for the potential fabrication of a large number of compounds from relatively simple precursors. Such methodologies are attractive because of their possible application to parallel synthesis programmes. We were interested to see whether it is feasible to combine a palladium-catalysed C–heteroatom bond forming reaction with a catalytic C–H activation process to generate dibenzo[*b*,*d*]-fused heterocycles (Scheme 1). The second step, namely the electrophilic ring closing process, has previously been shown to occur to give examples of carbazoles and dibenzo[*b*,*d*]furans when X′ = I or Br.[1]

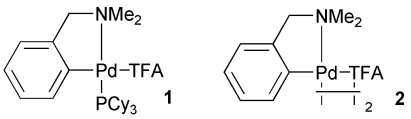



**Scheme 1** Formation of dibenzo[*b*,*d*]-fused heterocycles *via* sequential catalytic C-heteroatom coupling and C–H activation.

In order for the proposed 'double coupling' methodology to work efficiently and cleanly, the rate of oxidative addition of the C–X group in the C–heteroatom coupling step must be considerably greater than that of the aryl–X′ function in the C–H activation process. We considered that the easiest way of achieving this would be if X = Br and X′ = Cl. It may also be achievable if X = I and X′ = Br, however this is less attractive because there are far fewer available precursors.

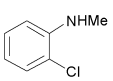
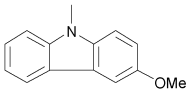
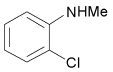
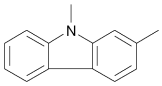
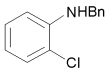
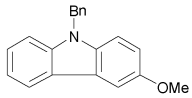
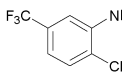
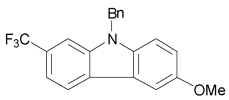
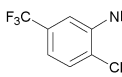
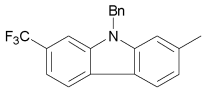
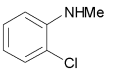
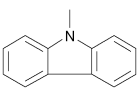
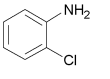
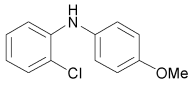
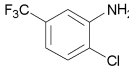
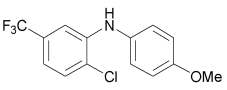
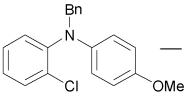
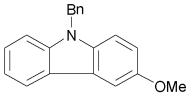
We decided to concentrate here on the coupling of anilines as catalytic amination is now a thoroughly studied, well understood process.[2] Brief optimisation studies were performed for the 'double coupling' of *N*-methyl-2-chloroaniline with 4-bromoanisole. The catalysts studied were complex **1**,[3] and the catalysts formed *in situ* from either dimer **2**,[3] [$Pd_2(dba)_3$] or palladium acetate and the phosphines $PR_2$(*o*-biphenyl) (R = Cy, $^t$Bu)[4] and $P^tBu_3$,[5] all of which have been shown to give good activity in aryl chloride coupling reactions. The best system proved to be that based on palladium acetate and 1.25–1.4 equivs. of $P^tBu_3$ using $NaO^tBu$ as base in toluene.

These conditions were then used for the rest of the catalytic studies, the results of which are summarised in Table 1. As can be seen, the double coupling reaction proceeds smoothly, generating the carbazole products when *N*-substituted-2-chloroanilines are used as substrates (entries 1–6). GC/MS analysis




indicated that all of the aryl bromide substrate is consumed during these reactions. The coupling works not only with aryl bromides that are electronically non-activated with respect to

**Table 1** Catalytic synthesis of carbazoles from 2-chloranilines and aryl bromides, $BrC_6H_4R$.[a]

| Entry | 2-haloaniline | R | Coupled product | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  | 4-OMe |  | 47 (73) |
| 2 |  | 3-Me |  | 57 (75)[c] |
| 3 |  | 4-OMe |  | 40 (91) |
| 4 |  | 4-OMe |  | 27 (50) |
| 5 |  | 3-Me |  | 51 (69) |
| 6 |  | H |  | 61 (85) |
| 7 |  | 4-OMe |  | 100 |
| 8 |  | 4-OMe |  | 85 (100) |
| 9 |  | — |  | 63 (80) |

[a] *Reaction conditions*: 2-Haloaniline (1.30 mmol), aryl bromide (1.22 mmol), $NaO^tBu$ (6.10 mmol), $Pd(OAc)_2$ (4–5 mol%), $P^tBu_3$ (5–7 mol%), toluene (13 ml), reflux, 24 h (reaction time not optimised). [b] Non-optimised isolated yields, GC yields given in parentheses. [c] Total conversion including 4-isomer ~90%.

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b2/b207712b/

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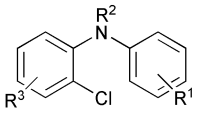
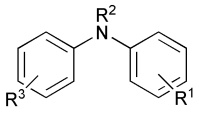
oxidative addition such as bromobenzene and 3-bromotoluene but also for the deactivated substrate 4-bromoanisole. When 3-bromotoluene is used as the substrate then, in principle, two possible isomers can form. Indeed GC/MS analysis of the crude product mixture obtained from the reaction showed the presence of both the 2-methyl isomer (shown in entry 2) and the 4-methyl isomer in a 5:1 ratio. By contrast when *N*-benzyl-2-chloro-5-trifluoromethylaniline is used as a substrate there was no evidence for the formation of the second isomer.

By contrast with the *N*-alkylated-2-chloroanilines, simple unsubstituted 2-chloroanilines gave no or, under considerably more forcing conditions (10 mol% catalyst, 60 h), trace amounts of the desired carbazoles. In these cases the main product observed was the corresponding 2-chloroaryl(aryl)amines **3** ($R^2$ = H).



**3**

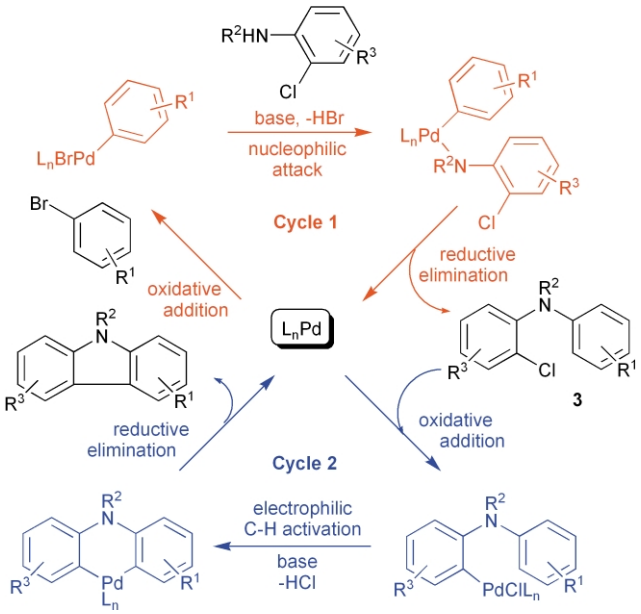


**4**

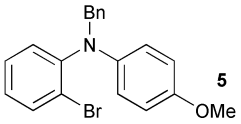
In all the cases of successful double coupling, small amounts of the hydrodehalogenated products **4** ($R^2$ = Me, Bn) are seen (GC/MS) and in the reactions shown in entries 1–3 and 6 small amounts of the compounds **3** are also observed. These latter compounds are not seen when *N*-benzyl-2-chloro-5-trifluoromethylaniline is used as a substrate, presumably because the $CF_3$ group activates the chloride with respect to oxidative addition.‡ These data indicate that, as anticipated, the amination step occurs first, followed by a ring closing process. However the presence of the hydrodehalogenation products **4** opens up the possibility that ring closure may not occur *via* the elimination of HCl but rather by the known oxidative coupling of compounds of the type **4**.[6] In order to test this possibility we subjected *N*-methyldiphenylamine to the same general catalytic conditions. No *N*-methylcarbazole was produced, despite the fact that this product is readily formed from *N*-methyl-2-chloroaniline and bromobenzene (entry 6), demonstrating that an oxidative coupling mechanism is not operative under these conditions.

In order to confirm that the 2-chloroaryl(aryl)amines **3** are indeed the intermediates that enter the second coupling step a representative example **3a** ($R^1$ = 4′-OMe, $R^2$ = Bn, $R^3$ = H) was synthesised by reacting the isolated compound **3b** ($R^1$ = 4′-OMe, $R^2$ = H, $R^3$ = H, entry 7) with *n*-butyllithium and then benzylbromide. When **3a** was subjected to the standard reaction conditions, the expected carbazole was formed in good yield (entry 9). Therefore it seems reasonable to suggest that two distinct catalytic manifolds operate; in the first cycle (cycle 1, Scheme 2) a classical amination reaction occurs to generate an intermediate **3** which then enters the second cycle by oxidative addition to Pd(0). The resultant Pd(II) complex then undergoes intramolecular C–H activation, presumably by an electrophilic displacement mechanism,[7] to give a six-membered palladacycle which subsequently yields the carbazole by reductive elimination.

Since 2-haloanilines are strongly electronically deactivated with respect to oxidative addition, we wondered whether there is sufficient disparity in reactivity between *N*-benzyl-2-chloroaniline and 4-chloroanisole for them to undergo the sequential coupling reaction. GC/MS analysis of the reaction mixture after 24 h showed that whilst some double coupling had occurred to give the desired carbazole, the major species proved to be unreacted 4-chloroanisole, with substantial amounts of the intermediate **3a** and the hydrodehalogenated species **4a** ($R^1$ = 4-OMe, $R^2$ = Bn, $R^3$ = H) also present. In this case it seems that the rate of the amination is too slow for substantial product formation and that the conversion of the intermediate **3a** to product is probably limited by catalyst longevity. When the reaction of *N*-benzyl-2-bromoaniline and 4-bromoanisole was attempted, GC/MS analysis showed that very little double coupling had occurred, with only trace amounts of the carbazole present along with substantial amounts of unreacted 4-bromoanisole (~70%). In addition small amounts of the hydrodehalogenated species **4a** and trace amounts of the 2-brominated intermediate **5** were seen. Here the low rate of amination is probably due to steric hindrance caused by the bromide in the 2-position of the aniline.




**Scheme 2** Probable catalytic pathway.



**5**

In summary we have shown that it is possible to synthesise carbazoles by a novel, sequential double coupling of 2-chloroanilines with arylbromides. This method has the potential to generate a large range of new carbazoles from simple, readily available starting materials. We are currently investigating the scope and limitations of this new methodology and its extension to other heterocyclic systems.

We thank the university of Exeter for a student bursary (to C. S. J. C.).

## Notes and references

‡ GC/MS analysis of the crude reaction mixtures obtained with this substrate showed the presence of small peaks with masses consistent with products of the general formula BnN($C_6H_4$R)($C_6H_3$-2-O$^t$Bu-5-$CF_3$) formed by catalytic etheration of the aryl chloride function of the intermediates **3** with NaO$^t$Bu.

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3 R. B. Bedford and C. S. J. Cazin, *Chem. Commun.*, 2001, 1540.
4 For examples of amination reactions of aryl chlorides with these ligands, see: J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1158.
5 For examples of amination reactions of aryl chlorides with tri-*tert*-butylphosphine, see: J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy and L. M. Alcazar-Roman, *J. Org. Chem.*, 1999, **64**, 5575.
6 For a recent example, see: H. Hagelin, J. D. Oslob and B. Åkermark, *Chem. Eur. J.*, 1999, **5**, 2413.
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