A Chemo- and Regioselective Tandem [3+2]-Heteroannulation Strategy for Carbazole Synthesis: Synergizing Two Mechanistically Distinct Bond-Forming Processes

Emma Campbell, Andrea Taladriz-Sender, Olivia I. Paisley, Alan R. Kennedy, Jacob T. Bush, Glenn A. Burley

a Department of Pure Applied Chemistry, University of Strathclyde, Thomas Graham Building, 295 Cathedral Street, Glasgow, UK, G1 1XL.
b GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, UK, SG1 2NY.

Supporting Information Placeholder

ABSTRACT: A modular approach to prepare tri- and tetracyclic carbazoles by a sequential [3+2] heteroannulation is described. First, optimization of a Pd-catalyzed Buchwald-Hartwig amination followed by C/N-arylation in a one-pot process is established. Second, mechanistic analyses identified the origins of chemo- and regioselective sequential control of both bond-forming steps. Finally, the substrate scope is demonstrated by the preparation of a range of tri- and tetracyclic carbazoles, including expedient access to several natural products and anti-cancer agents.

Carbazoles are ubiquitous N-heterocycles used throughout medicinal chemistry and the material sciences. From a pharmaceutical perspective, the carbazole core features extensively in drugs and natural products, many of which exhibit potent anti-proliferative activities (Figure 1a). The breadth of applications has inspired the development of numerous methodologies for their preparation. Pd-catalyzed processes in particular enable a [3+2] heteroannulation via a Pd(0)-catalyzed Buchwald-Hartwig amination, followed by a Pd(II)-catalyzed C-arylation at a late stage in a synthetic workflow. However, a generalized set of guidelines outlining the molecular determinants which define the chemo- and regioselective control of each C-N/C-C bond-forming reaction, and the factors which influence Pd(0) versus Pd(II) catalysis in a one-pot process has not been established. This is an important requirement for the formation of tetracyclic carbazoles where a regioselective C-H activation step is required.

In this manuscript, we establish reaction guidelines to prepare tri- and tetracyclic carbazoles by controlling the chemoselectivity of the first Pd(0)-catalyzed C-N bond-forming step, and the regioselectivity of the second Pd(II)-catalyzed C/N-arylation (Figure 1b). Our rationale was to use chloroanilines (1) to define the A-ring of a carbazole core, and heteroaryl bromides to form the C/D-rings of tricyclic and tetracyclic products.

Figure 1. A generalized approach for the synthesis of tri-tetracyclic carbazoles by Pd-catalyzed [3+2]-heteroannulation.
hough the 5-position of isoquinoline is the more nucleophilic site, the mechanistic determinants which control the regioselectivity of such a Pd(II)-catalyzed C-aryl formation are not known.

Our studies commenced with optimizing reaction conditions for the Pd(0)-catalyzed C-N bond-forming step using 4-methoxy-2-chloroaniline (1a) and 6-bromoisoquinoline (6a) as exemplar substrates (Scheme 1). An extensive screen (Table S1) identified DavePhos and K$_2$PO$_4$ as the optimal ligand/base pairing, which formed 7a in 87% yield.

With conditions for the Pd(0)-catalyzed C-N bond-forming step established, the optimization of the one-pot process was explored (Table S2). The optimal ligand/base pairing of HPCy$_4$BF$_4$ with K$_2$PO$_4$ was identified, which formed 9a from 1a and 6a in 78% yield. This highlights that the second C-H activation step is regioselective for the 7-position of 6a. To further understand how the nature of the chloroaniline and heteroaryl bromide substrates influenced the chemoselectivity of both bond-forming steps, a series of test reactions were undertaken (Scheme 2). Exchanging 6-bromoisoquinoline (6a) for isoquinoline (10) formed dimethoxyphenazine (11) and the tertiary aniline (12) in 35% and 25% isolated yield, respectively (Scheme 2a). No dihydrophenazine was isolated from the reaction, which suggests an in situ oxidation occurred. No reaction occurred when isoquinoline (10) was the coupling partner with 1-chloro-3-methoxybenzene (13, Scheme 2b). Only secondary aniline (15) was isolated when para-anisidine (14) was reacted with 6-bromoisoquinoline (6a, Scheme 2c). Taken collectively, these test reactions highlighted the following requirements for the preparation of the tetracyclic core: (i) the aryl bromide is essential and prevents dimerization of the chloroaniline, (ii) whilst the absence of a bromo substituent in the heteroaryl substrate results in C-H activation at the same site, there is little regiocontrol, (iii) a chloro substituent is essential for C-arylation.

The influence of the electron-donating aniline lone pair in the direct C-arylation step was then explored. We surmised that the acetylated substrate (16) would deactivate the C-ring and render the C-arylation less efficient. This occurred as highlighted by the formation of deacetylated C-arylated regioisomers, 9a and 17, in 27% total yield (1.2:1.0 9a:17). We assume that deacetylation occurs in situ because of the high temperatures and in the presence of base in the reaction mixture. An unexpected result was the formation of the linear tetracyclic carbazole 17, which arises from C-H activation of the isoquinoline 7-position of 16. The formation of 17 suggests that C-H activation of the 7-position is favored if the acetyl group is present prior to C-arylation. In contrast, if 7a is present - presumably formed by deacetylation of 16 - C-H activation at the 5-position occurs. We speculate that the acetyl group (i.e., 16) directs C-H activation at this site via coordination of a Pd(II) species through the amide carbonyl.

This series of reactions has guided us to propose that oxidative addition of the C-Cl bond in 7a occurs first and proceeds via a Pd(II) species to form 18 (Scheme 2e). Pd(II)-catalyzed C-aryl formation forms the palladacycle (19) followed by tautomerization (20). Finally, reductive elimination produces the C-arylated product (9a).

With mechanistic knowledge of the second C-C bond-forming step established, the substrate scope of the process was investigated (Scheme 3).
The reaction conditions formed 7H-pyrido[3,4-c]carbazole analogues (9a-c). The presence of a nitro group resulted in only trace amounts of 9d formed, with the secondary aniline (7e) isolated in 79% yield. The reaction conditions also tolerated changes in the substituents in the D-ring of the heteroaryl bromide (9e-j).37 The [3+2]heteroaunnulation strategy was also compatible with the formation of carbazole-1,4-quinones (21a-f).26,38 Access to N-arylated products is also possible, forming a mixture of fused imidazoles (9k-l) via an N-arylation step, alongside tertiary anilines (22-23).

The modularity of this strategy is also exemplified by the preparation of natural products Glycozoline (9m),39 Harmane (9n)40 and Murrayafoline A (9o).41,42 In addition, preparation of 9p demonstrates that the reaction conditions tolerate functional groups bearing potential Pd-chelating sites and bulky substituents ortho to the corresponding aryl bromide.

Our [3+2]heteroaunnulation strategy was extended to the targeted synthesis of biologically-active tetracyclic carbazoles. Carbazole-1,4-quinones (e.g., 21a-f) have established anti-cancer activity via topoisomerase inhibition or by the production of reactive oxygen species.26,43 We used 21b as a key intermediary scaffold for the targeted synthesis of a deaza analogue of the natural product 9-methoxyleptophylline (Scheme 3b), producing 24 in 3 steps and in an overall yield of 20%.44 Further exemplification of our strategy was demonstrated by the preparation of alkylated 7H-pyrido-carbazoles (e.g., 9a-e) which have well-established anti-cancer activity.35-46 Previous preparative methods of this series of compounds have involved a 6-step linear synthesis affording compound 9e in 28% overall yield.45,47 Our two-step convergent strategy accessed the 7H-pyrido[4,3-c]carbazole core 9e in a single step (83%), followed by alkylation to produce mono-N-alkylated examples (25-26), and the potent anti-cancer agent ditercalinium (27).48

In summary, we have established a mechanistic framework for the preparation of fused tetracyclic carbazoles. We envisage that this convergent approach could find application in medicinal chemistry for structure-activity profiling and in broader synthetic applications which require step-efficient access to carbazole scaffolds.

ASSOCIATED CONTENT

Supporting Information
Preparation and characterization of small molecules and crystal structural information. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

* Email: glenn.burley@strath.ac.uk
**Author Contributions**

Conceptualization: G.A.B., E.C., A.T.S., O.I.P.; Methodology: E.C., O.I.P., A.T.S., J.B.; Validation: E.C., A.T.S.; Formal analysis: E.C., A.T.S.; Manuscript preparation: E.C., A.T.S., G.A.B. These authors contributed equally.

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