Heterocycle Synthesis

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Cascade Palladium-Catalyzed Direct Intramolecular Arylation/Alkene Isomerization Sequences: Synthesis of Indoles and Benzofurans**

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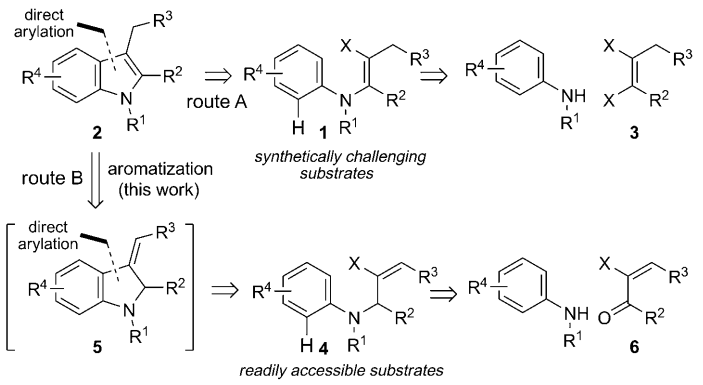
The development of metal-catalyzed direct arylation reactions between activated aromatic rings, most usually aryl halides, and a non-activated aromatic coupling partner has had a tremendous impact on the synthesis of biaryl carbon–carbon bonds.[1–3] The direct functionalization of heteroaromatic molecules features prominently among these reactions.[4] Although less general, variations of these methods to include the direct union of an aromatic ring with alkenyl- or alkylhalide coupling partners are becoming more common.[5,6] Indeed, if opportunities for further elaboration of the coupled products are considered, then direct arylation of alkenyl substrates is particularly attractive as the transformations deliver styryl units featuring a reactive alkenyl functional group. Herein we exploit the ready formation of styryl units through a direct arylation approach and illustrate how, when combined with a simple isomerization step, a common route to both indoles and benzofurans can be developed.



Scheme 1. Routes based on alkenyl halide direct arylation to give 2,3-disubstituted indoles.

Although palladium-catalyzed direct arylation, alkenylation, and alkylation reactions have been extensively applied to heteroaromatic systems, it is usually in the context of decorating existing aromatic scaffolds.[7] Less common is the use of similar methods for the construction of heteroaromatic molecules, particularly benzo-fused five-membered aromatic rings.[8,9] One reason for this is the difficulty in accessing suitable cyclization substrates in short sequences from simple starting materials. For example, route A in Scheme 1 illustrates an indole retrosynthesis in which the C3–C3a bond is formed by a direct arylation procedure (**1**→**2**); however, such a synthesis requires an *N*-aryl-2-haloenamine cyclization substrate (**1**), and although similar systems are known, for example by a metal-catalyzed coupling of an aniline with a 1,2-dihaloalkene (**3**),[10,11] the preparation of a library of these substrates in a straightforward and efficient manner is not trivial. As one of the primary motivations for employing direct arylation methods is to streamline syntheses, both in terms of step count and waste generation, the use of a direct arylation reaction on a step-intensive substrate is counterproductive. Despite these difficulties, the advantages to be gained from developing a direct arylation route to biologically important heterocycles, such as indoles and benzofurans, are considerable. In particular, the ability to employ readily available building blocks (e.g. anilines) directly in a synthetic route is an attractive proposition. Route B in Scheme 1 presents our solution to these challenges, set in the framework of an indole retrosynthesis: the C3–C3a direct arylative bond construction is maintained (**4**→**5**); however, to deliver readily available substrates, the target structure from the key C–C bond-forming reaction is no longer the heteroaromatic molecule, but rather the isomerized, non-aromatic, congener **5**. We reasoned that isomerization from the *exo*-alkene **5** to the aromatic indole **2** should be a facile transformation and may even take place during the arylative step. Then, *N*-aryl-2-haloallylic amines become the cyclization substrates, thus reducing the synthesis to the combination of two readily available building blocks: anilines and α-haloenones **6**.[12]

To evaluate the feasibility of the synthesis described in Scheme 1 (route B) we elected to study the conversion of bromoalkene **7a** into indole **8a** (Table 1). Based on literature precedent we focused on the use of the electron-rich, diphenyl-backbone-based phosphine ligands pioneered by Buchwald.[13] Treatment of bromoalkene **7a** with a catalyst generated from $Pd(OAc)_2$ and amino-substituted ligand **9a**, using Cs_2CO_3 as the base in DME, delivered 4% of the desired indole (Table 1, entry 1). Changing the ligand to the dimethoxy variant **9b** increased the yield to 62% (Table 1, entry 2), while the triisopropyl-substituted ligand **9c** provided the indole in 86% yield (Table 1, entry 3). The reaction

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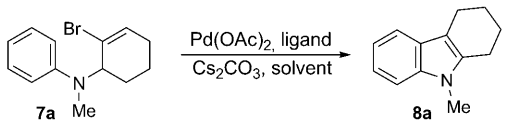
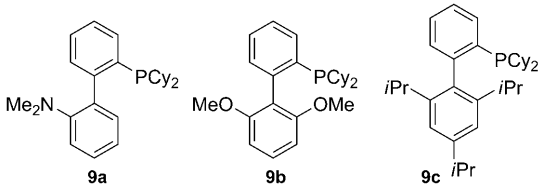
Table 1: Reaction evaluation for the formation of indole **8a**.[a]



Entry	Solvent	Ligand	Yield [%][b]
1	DME	**9a**	4
2	DME	**9b**	62
3	DME	**9c**	86
4	toluene	**9c**	0
5	MeCN	**9c**	0
6	DMF	**9c**	0[c]

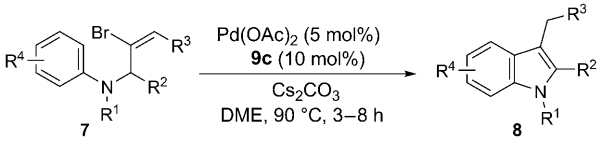
[a] Reaction conditions: bromoalkene (1.0 equiv), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), base (1.5 equiv), 90°C, 17 h. [b] Yield of isolated product. [c] Diphenylmethylamine isolated as the sole reaction product. Cy = cyclohexyl, DME = 1,2-dimethoxyethane, DMF = *N*,*N*-dimethylformamide.

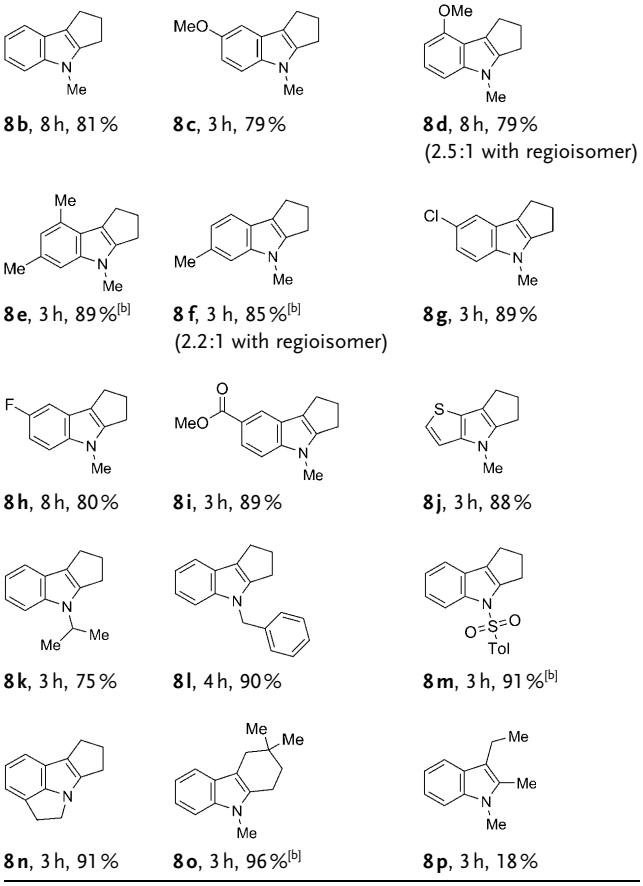


displayed a dramatic solvent effect, with experiments performed in toluene and acetonitrile resulting in the recovery of the starting material (Table 1, entries 4 and 5). When the reaction was performed in DMF, only diphenylmethylamine was isolated as the product (Table 1, entry 6). Importantly, the non-aromatic *exo*-alkene, corresponding to **5**, was not isolated in any of the optimization experiments.

We next explored the scope of this new indole-forming process (Table 2). Employing the optimized reaction conditions allowed the efficient formation of the cyclopentane-fused indole **8b** in 81% yield. This cyclopentane framework was employed for the majority of the scoping studies: Both *para*- and *meta*-methoxy-substituted aniline components could be incorporated and delivered indoles **8c** and **8d** in good yields. Di- and mono-methyl substituents could also be readily introduced (indoles **8e** and **8f**). However, in these two examples the indoles were formed as mixtures along with their non-aromatic *exo*-alkene isomers; in these cases it was found that simple treatment of the reaction mixtures with *p*TSA before work-up allowed complete isomerization to the aromatic systems.[14] Halogen substituents were also readily incorporated (indoles **8g** and **8h**). The introduction of a resonance electron-withdrawing group, an ester in this example, was readily achieved, although acid-catalyzed isomerization was again needed (indole **8i**). The final variation of the aromatic group was to introduce a thienyl unit, thus generating the unusual 5,5,5-fused ring system **8j** as a single regioisomer. The next four examples, indoles **8k**–**n**, illustrate successful variation of the *N*-substituent; the *N*-Ts derivative (**8m**) required acid-catalyzed isomerization. The final two examples show further variation of the α-bromoenone starting materials; dimethyl derivative **8o** was obtained in good yield; however, the acyclic variant, **8p**, was obtained

Table 2: Palladium-catalyzed direct arylation/alkene isomerization preparation of indole derivatives.[a]



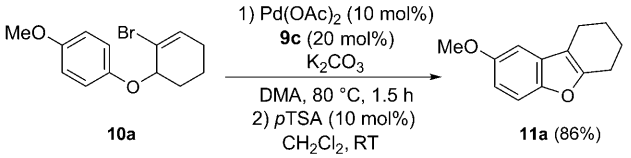


[a] Reaction conditions: bromoalkene (1.0 equiv), $Pd(OAc)_2$ (5 mol%), ligand **9c** (10 mol%), Cs_2CO_3 (1.5 equiv), DME 90°C, 3–8 h. Yields of isolated product. [b] Cs_2CO_3 (1.1 equiv) employed, and *p*TSA (1.2 equiv) added at completion of reaction and stirred for 3 h at RT. Tol = tolyl.

in only 18% yield. It is interesting to note that when *meta*-substituted anilines were employed as substrates, some regioselectivity was observed in the mixtures of indoles produced; the *meta*-methoxyaniline substrate delivered a 2.5:1 mixture of regioisomers (**8d**), and the *meta*-methyl example generated a 2.2:1 mixture (**8f**). The major isomer in these examples varies; the *meta*-methoxy example underwent preferential reaction at the position next to the OMe group, while the *meta*-methyl example favored reaction opposite to the methyl substituent.[15]

Having demonstrated an efficient route to a variety of indole derivatives, we were interested in extending the method to the preparation of alternative heterocycles. The simple exchange of the aniline reaction components for the corresponding phenols led to ether-linked substrates, which were suitable for the preparation of benzofuran compounds. We evaluated the original reaction conditions against ether-linked bromoalkene **10a** and found that a slight variation of

the conditions was needed to achieve efficient formation of the corresponding benzofuran (Scheme 2); the optimal conditions again employed ligand **9c**, but the choice of K_2CO_3 as base and DMA as solvent was beneficial. In addition, the

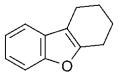
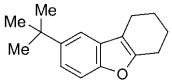
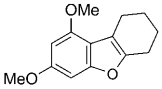
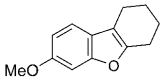
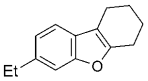
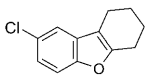
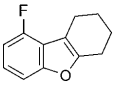
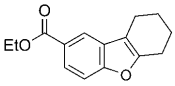
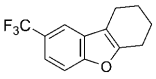
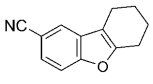
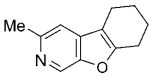
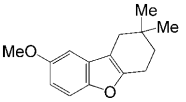
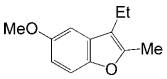
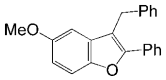
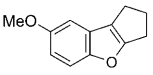


Scheme 2. Optimized benzofuran formation. DMA = *N*,*N*-dimethylacetamide, *p*TSA = toluene-*p*-sulfonic acid.

majority of benzofuran-forming reactions delivered mixtures of the aromatic and non-aromatic isomers, and so all the studied examples were subjected to acid-catalyzed aromatization.

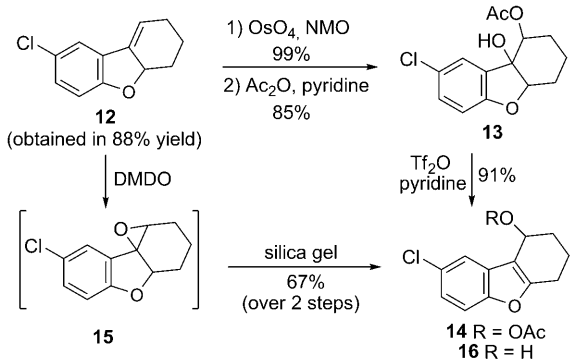
The scope of the benzofuran-forming method is shown in Table 3. The use of phenol itself delivered benzofuran **11b** in 79% yield. A variety of electron-donating substituents could be readily incorporated, thus delivering the expected benzofurans in good yields (**11c–f**). The incorporation of electron-withdrawing groups was less straightforward; although the Cl-, F-, and ester-substituted benzofurans (**11g–i**) were obtained in good yields, the trifluoromethyl- and nitrile-derivatives (**11j** and **11k**) were isolated in only 24% and 36% yields, respectively. The reason for the lower yields was not the efficiency of the direct arylation steps, which were achieved in 79% and 74% yields, but the difficulty in achieving efficient isomerization of the resultant electron-poor enol ethers. The final variation of the phenol component demonstrated the use of a simple heterocyclic derivative, with 6-azabenzofuran **11l** being obtained in 66% yield. Variation of the α-bromoenone components allowed dimethyl-derivative **11m**, as well as acyclic variants **11n** and **11o** to be prepared in reasonable yields. The strained, cyclopentane-derived benzofuran **11p** was prepared in poor yield, although the C–C bond-forming process was moderately efficient. The benzofuran-forming reactions again displayed some interesting regiocontrol; both benzofurans **11e** and **11f**, which incorporated *meta*-methoxy and *meta*-ethyl phenol, respectively, resulted from arylation at the opposite position to the substituent. However, benzofuran **11h**, derived from *meta*-F-phenol was formed from preferential arylation next to the F substituent. The implications of these selectivities on the mechanisms in operation are the subject of ongoing investigation.[15]

Table 3: Palladium-catalyzed direct arylation/alkene isomerization preparation of benzofuran derivatives.[a]

 **11b**, 79%	 **11c**, 89%	 **11d**, 91%
 **11e**, 87% (4.5:1 with regioisomer)	 **11f**, 89% (20:1 with regioisomer	 **11g**, 75%
 **11h**, 80% (4:1 with regioisomer)	 **11i**,[b] 70%	 **11j**, 24% (79% for C–C formation)
 **11k**,[b] 36% (74% for C–C formation)	 **11l**,[c] 66%	 **11m**, 73%
 **11n**, 68%	 **11o**, 45%	 **11p**, 7% (50% for C–C formation)

[a] Reaction conditions: 1) bromoalkene (1.0 equiv), $Pd(OAc)_2$ (10 mol%), ligand **9c** (20 mol%), K_2CO_3 (2.0 equiv), DMA 80°C, 1.5–24 h; 2) *p*TSA (0.1 equiv), CH_2Cl_2, RT, 3–15 h. Yields of isolated product. [b] K_2CO_3 (1.1 equiv) employed. [c] No ligand employed.

The relative stability of a number of the non-aromatic, *exo*-alkene isomers offered the possibility of accessing remotely substituted heterocycles through alkene functionalization. We briefly explored this concept with the benzofuran scaffold (Scheme 3): *exo*-alkene **12**, obtained in 88% yield from the direct arylation reaction, could be efficiently converted into mono-acetate **13** through a dihydroxylation/acetate-formation sequence. Subsequent treatment of the acetate **13** with triflic anhydride delivered acetate-substituted benzofuran **14** in good yield. Alternatively, epoxidation of *exo*-alkene **12** with DMDO generated intermediate epoxide **15**, which, when treated with silica gel, delivered the corresponding hydroxy-substituted benzofuran **16**. The adaptation of either of these sequences to enantioselective variants, or the use of enantiomerically enriched starting



Scheme 3. Preparation of functionalized benzofurans. DMDO = 2,2-dimethyldioxirane, NMO = 4-methylmorpholine *N*-oxide, Tf = trifluoromethanesulfonyl.

materials, should allow the preparation of stereochemically defined benzofuran derivatives.

In summary, we have demonstrated that the combination of simple starting materials allows the rapid assembly of substrates for palladium-catalyzed intramolecular direct arylation/isomerization sequences. In particular, the use of aniline derivatives as the nucleophilic components ultimately delivers indoles, while the use of phenols allows access to benzofurans. Both synthetic routes tolerate significant substrate variation to deliver a broad range of substituted products. The syntheses illustrate how direct arylation processes can be employed as key steps in efficient and concise routes to desirable heteroaromatic targets. The basic route disclosed here is potentially amenable to the preparation of further heterocycles by simply employing alternative nucleophilic components; for example, aryl thiols would lead to benzothiophenes, while aryl hydrazines should allow access to cinnoline derivatives. Further investigations in these directions are underway.

Experimental Section

General procedure for the preparation of indoles through a direct arylation/isomerization cascade, exemplified by the preparation of 4-methyl-1,2,3,4-tetrahydro-cyclopenta[b]indole (**8b**, Table 2, entry 1): A dry flask flushed with nitrogen was charged with the appropriate vinyl bromide (70 mg, 0.28 mmol), palladium acetate (3.1 mg, 14.00 μmol, 5 mol%), ligand **9c** (13.0 mg, 28.00 μmol, 10 mol%), caesium carbonate (130 mg, 0.42 mmol), DME (1.4 mL) and heated at 90 °C for 8 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The resultant crude product was purified by flash chromatography on silica gel (*n*-hexane) to yield the desired indole **8b** (0.04 g, 81%) as a pale yellow oil.

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