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2-(2-Haloalkenyl)-aryl Halides as Substrates for Palladium-Catalysed Tandem C–N Bond Formation: Efficient Synthesis of 1-Substituted Indoles

Michael C. Willis,[a,*] Gareth N. Brace,[a] Thomas J. K. Findlay,[a] Ian P. Holmes[b]

[a] Department of Chemistry, University of Bath, Bath, BA2 7AY, U.K
Fax: (+44)-1225-386-231, e-mail: m.c.willis@bath.ac.uk
[b] Discovery Research, GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, U.K.

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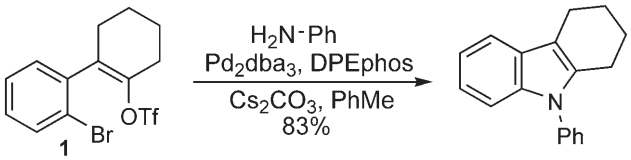
Abstract: 2-(2-Haloalkenyl)-aryl halides, conveniently prepared in a single step from the corresponding *o*-halobenzaldehydes, are combined with amines under Pd catalysis to provide 1-substituted indoles. All combinations of Br and Cl leaving groups can be employed, and a range of substituents on the arene, alkene and amine, can all be tolerated. The use of 1,3-dichloro-substituted arenes allows a third amination process to take place; these three-component processes deliver the corresponding 4-aminoindoles in good yields.

Keywords: C–N bond formation; heterocycles; homogeneous catalysis; indoles; palladium; tandem reactions

The presence of the indole heterocycle as a recurring motif in natural products and medicinal agents has resulted in sustained interest in the development of new methods for the preparation of this valuable structural unit.[1] Palladium-mediated methods are particularly prominent amongst these,[2] with the coupling of *o*-haloanilines with alkenes and alkynes remaining as a benchmark system.[3] More recently a number of syntheses based on the coupling of a nucleophilic N unit with aryl and alkenyl halides has been described.[4] In the majority of these syntheses C–N bond formation is used as the final ring-closing, indole-forming event and takes place on an acyclic substrate that incorporates the N atom. We recently reported an indole synthesis in which tandem Pd-catalysed C–N bond forming reactions, one at an alkenyl triflate,[5] the second at an aryl halide, are used to prepare the indole core (Scheme 1).[6] The ability to introduce an external N unit in the final step of the synthesis is particularly useful for the preparation of a variety of 1-functionalised indoles. Despite the success of this method there remained limitations we wished to address; although the preparation of 2,3-disubstituted products proceeded efficiently it was difficult to access the substrates required for the preparation of 2- or 3-mono-substituted structures. In addition, the alkenyl triflate substrates required a two-step synthesis from commercial compounds. In this communication we report that both these shortcomings can be overcome by the use of haloalkenylaryl halide substrates.

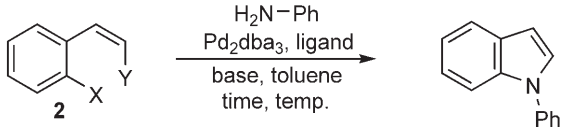


Scheme 1. Tandem Pd-catalysed C–N route in indoles.

The difficulty in accessing the 2- and 3-mono- (or non-) substituted triflates corresponding to **1** stemmed from their poor stability, and we reasoned that a triflate to halide substitution should provide more robust substrates. This proved to be the case with the required haloalkenylaryl halides being available in a single step from the corresponding aldehydes using Wittig methodology.[7] The large number of commercial *o*-halobenzaldehydes (>250)[8] was a further attractive feature of this route. To fully exploit the range of commercial starting materials we sought a catalyst that could tolerate all combinations of chloro and bromo leaving groups.[9]

We selected simple styrenes **2** as suitable test substrates and evaluated a range of ligands in coupling reactions between **2** and aniline (Table 1). With the dibromo substrate (**2a**) the ligand and base combination employed in our initial alkenyl triflate system (DPEphos **3**, Cs_2CO_3, Scheme 1) was unsuccessful; however, the

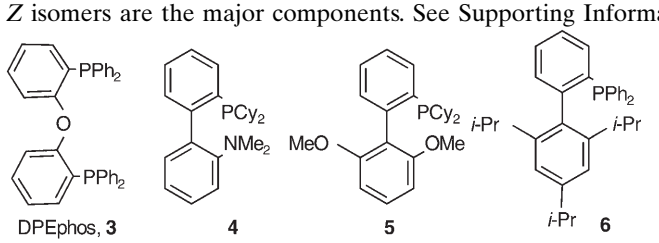
Table 1. Ligand optimization.[a]



Entry	Substrate[b] X, Y	Ligand	Base	Temp. [°C]	Time [h]	Yield[c] [%]
1	**2a** Br, Br	**3**	Cs_2CO_3	100	20	0
2	**2a** Br, Br	**3**	NaO-*t*-Bu	100	20	71
3	**2b** Cl, Br	**3**	NaO-*t*-Bu	100	20	25
4	**2b** Cl, Br	**4**	NaO-*t*-Bu	100	5	70
5	**2b** Cl, Br	**4**	NaO-*t*-Bu	80	5	76
6	**2c** Br, Cl	**4**	NaO-*t*-Bu	80	5	80
7	**2d** Cl, Cl	**4**	NaO-*t*-Bu	80	5	76
8	**2d** Cl, Cl	**4**	Cs_2CO_3	100	20	0
9	**2a** Br, Br	**4**	NaO-*t*-Bu	100	20	59
10	**2a** Br, Br	**5**	NaO-*t*-Bu	80	5	85
11	**2b** Cl, Br	**5**	NaO-*t*-Bu	80	5	64

[a] *Reaction conditions:* substrate (1.0 equiv.), aniline (1.2 equivs.), $Pd_2(dba)_3$ (2.5 mol %), ligand (7.5 mol %), base (2.5 equivs.), toluene.

[b] *Z* isomers are the major components. See Supporting Information for details.



[c] Yields of isolated products.

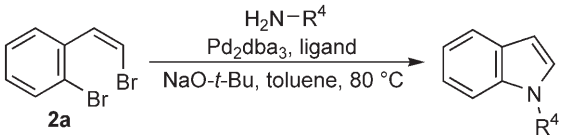
same ligand used in combination with NaO-*t*-Bu delivered the required indole in 71% yield (entries 1 and 2). When this combination was applied to the chloroarene-bromoalkene substrate (**2b**) the indole was delivered in a modest 25% (entry 3). The development of more effective supporting ligands has had a significant impact on the efficiency of Pd-catalysed aryl halide amination reactions,[10] with Buchwald's biphenyl backbone-based phosphines being particularly effective.[11] Application of the 2′-dimethylamino-2-dicyclohexylphosphine variant **4** using NaO-*t*-Bu as base delivered the indole in 70% yield (entry 4). This could be increased to 76% by lowering the reaction temperature to 80 °C, presumably due to slight product degradation occurring at the higher temperature (entry 5).

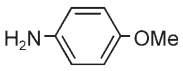
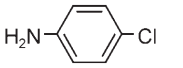
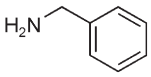
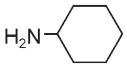
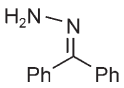
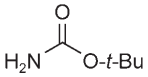
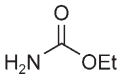
The same reagent combination was also effective on the bromoarene-chloroalkene, and the dichloride substrate, delivering the indoles in excellent yields (entries 6 and 7). An attempt to use the weaker base Cs_2CO_3 was ineffective (entry 8). The use of ligand **4** with the original dibromo substrate delivered the indole in only 59% yield (entry 9), however the use of the dimethoxy-substituted ligand (**5**) was more effective and provided the indole in an excellent 85% yield (entry 10). The dimethoxy-substituted ligand was less effective for the chloro-containing substrates (entry 11). The optimized conditions for any of the chloro-containing substrates comprise the dimethylamino-susbtituted ligand (**4**) in combination with NaO-*t*-Bu, while for the dibromo substrate, the dimethoxy-substituted ligand (**5**) performs best.

With reagent combinations available for all arrangements of chloro and bromo leaving groups on the simple test substrate, we next explored the scope of the process (Table 2).[7] We first evaluated the range of N units that could be introduced; substituted anilines, benzyl- and cyclohexylamine all delivered the expected indoles in good yields (entries 1–5). Access to 1-aminoindoles was possible by the use of the protected hydrazine derivative shown in entry 6. Ethyl and *tert*-butyl carbamates could also be introduced, allowing potential access to the indole N−H systems (entries 7 and 8). It was necessary to employ the triisopropyl-substituted ligand **6** in order to achieve good conversions with the carbamate substrates.

The wide availability of variously substituted *o*-halobenzaldehydes allowed a variety of substituents around the aryl unit to be introduced (Table 3); using a variety of dibrominated substrates the 6-methyl-, 5-fluoro- and 5,6-dioxolane-substituted indoles were all available

Table 2. Scope of the N substituent.[a]



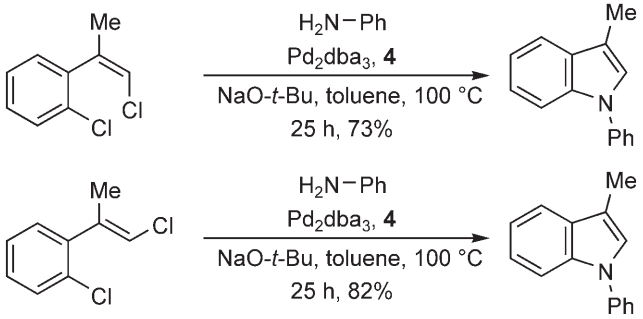
Entry	N Unit	Ligand	Time [h]	Yield [%][b]
1	H_2N-Ph	**5**	5	85
2		**5**	6	75
3		**5**	5	77
4[c]		**3**	20	70
5[c]		**3**	20	63
6		**5**	6	62
7[d]		**6**	10	68
8[d]		**6**	24	54

[a] Reaction conditions; substrate (1.0 equiv.), *N*-unit (1.2 equivs.), $Pd_2(dba)_3$ (2.5 mol %), ligand (7.5 mol %), NaO-*t*-Bu (2.5 equivs.), toluene, 80 °C. Alkene used as a 9:2 mixture of *Z*:*E* isomers.
[b] Yields of isolated products.
[c] At 100 °C.
[d] At 110 °C, Cs_2CO_3 as base, dioxane as solvent.

in good yields (entries 1–3). The 4-chloroindole originated from the corresponding 1,3-dichloro-arene-bromoalkene substrate (entry 4). Aryl chloride-substituted ketones (as opposed to aldehydes) also served well as substrates, with the methyl and phenyl ketones delivering the corresponding 3-substituted indoles as expected (entries 5 and 6).

2-Substituted indoles could be accessed using two methods; the first involved the use of a substituted Wittig reagent to prepare the methyl-substituted cyclisation substrate (entry 7). The second employed an initial Suzuki coupling on the corresponding 1,1-dibromoalkene to introduce a 2-aryl-substituent on the indole precursor (entries 8 and 9).[7] The substrates prepared using either route delivered the indoles in an efficient manner. The lower yield obtained in entry 9 is compensated for by the presence of the synthetically useful 2-(4-chlorophenyl)-substituent in the product.[9]

Several of the examples in Table 3 suggested that the geometry of the starting alkenyl halide is unimportant to the success of the transformation and that an isomerisation process was taking place. To investigate this the two isomers of the vinyl chloride substrates employed in entry 5 were independently subjected to the reaction conditions; the separate isomers performed almost identically (Scheme 2). No isomerisation of the vinyl chloride substrates was observed, rather isomerisation of the initially formed enamine intermediates is thought to account of the funnelling of the isomer mixtures to a single indole product. A similar isomerisation has been reported in the preparation of enamides from vinyl triflates.[12] From a synthetic perspective the ability to use either geometrical isomer (or mixtures of the two) of a substrate is attractive as it allows the complications of producing geometrically pure starting materials to be avoided.

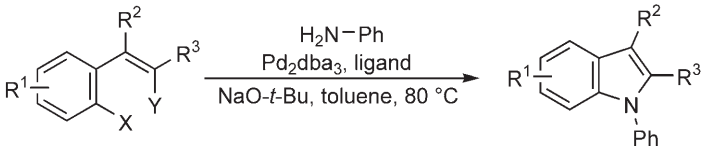


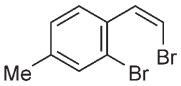
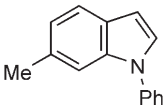
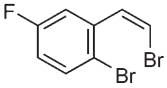
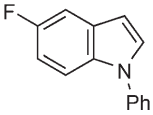
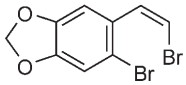
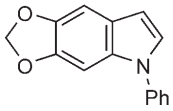
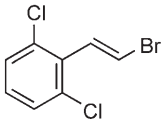
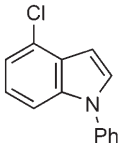
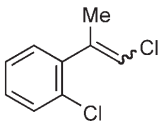
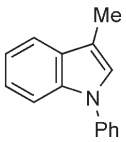
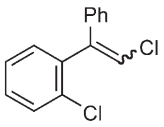
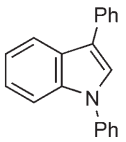
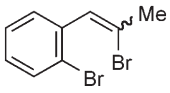
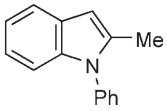
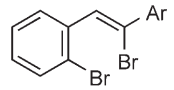
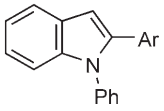
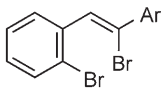
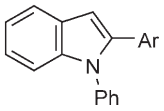
Scheme 2. Utility of *E* and *Z* alkenes.

As well as allowing mixtures of alkene isomers to be employed as substrates, the greater reactivity of the alkenyl halide site to the amination conditions allowed sequential amination processes to be explored. For example, the use of an extra equivalent of aniline in the coupling employing the 1,3-dichloro substrate allowed indole formation to be followed by a third C–N bond formation to introduce an aniline substituent at the indole 4-position (Scheme 3). More usefully, provided thirty minutes had elapsed from the start of the reaction, a second amine could be successfully introduced. For example, the 5-morpholino- and 5-*N*-methyl-aniline substituted *N*-phenylindoles were both obtained in good yields (Scheme 3).

In conclusion, we have demonstrated that the haloalkenylaryl halides are efficient substrates for tandem Pd-catalysed C–N bond formation and deliver a variety of *N*-functionalised indoles in good yields. The majority of substrates used in these reactions are available in a single step from commercial compounds. The use of readily available starting materials allows access to 1-, 2-, 3-, 4-, 5- and 6-substituted indoles. By careful choice of the halide leaving group it is possible to construct se-

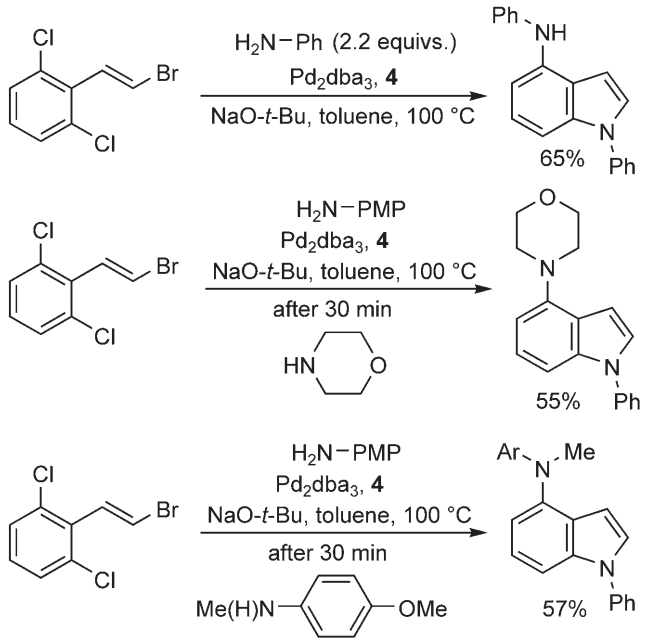
Table 3. Substrate scope.[a]



Entry	Substrate	$Z:E$[b]	Ligand	Product	Yield [%][c]
1		9:1	**5**		73
2		9:1	**5**		59
3		4:1	**5**		67
4[d]		1:20	**4**		80
5[d]		1:1	**4**		78
6[d]		7:2	**4**		94
7		1:1	**5**		79
8[d]	 Ar = 4-MeO-C_6H_4	20:1	**5**		81
9[d]	 Ar = 4-Cl-C_6H_4	20:1	**5**		51

[a] Reaction conditions; substrate (1.0 equiv.), aniline (1.2 equivs.), $Pd_2(dba)_3$ (2.5 mol %), ligand (7.5 mol %), NaO-*t*-Bu (2.5 equivs.), toluene, 80 °C.
[b] Determined by ^1H NMR spectroscopy.
[c] Yield of isolated products.
[d] At 100 °C.

quential reactions to introduce further amine functionality *via* a third C–N bond formation. Studies applying similar strategies to the synthesis of alternative heterocycles are under way.



PMP = *p*-methoxyphenyl

Scheme 3. Sequential amination reactions.

Experimental Section

Tandem Palladium Catalysed C–N Bond Formation to form the Indole Nucleus. General Procedure, Exemplified by 1-Phenylindole from 1-Bromo-2-(2-bromovinyl)benzene (Table 2, Entry 1)

Sodium *tert*-butoxide (125 mg, 1.298×10^{-3} mol) was added to an oven-dried flask charged with $Pd_2(dba)_3$ (12 mg, 1.3×10^{-5} mol) and ligand **5** (16 mg, 3.968×10^{-5} mol) under nitrogen. The flask was flushed with nitrogen and the reagents suspended in anhydrous toluene (1.04 mL). To this, 1-bromo-2-(2-bromovinyl)benzene (136 mg, 5.192×10^{-4} mol) and aniline (58 mg, 57 μL, 6.230×10^{-4} mol) were added and the reaction mixture was heated at 80 °C for 5 hours under nitrogen. After cooling, the reaction mixture was diluted with diethyl ether (5 mL) and filtered through a celite pad, washing with diethyl ether (30 mL). The filtrate was reduced under vacuum. The product was separated *via* flash chromatography (eluant: 0.5% diethyl ether-hexane) to afford the indole as a pale amber oil; yield: 88 mg (85%): IR (liquid film): $\nu_{max} = 3055, 2924, 2854, 1597, 1515, 1497, 1456, 1331, 1233, 1213, 1135, 1014, 953, 774, 740, 695\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 6.71$ (1H, dd, $J = 3.3$ and 0.8 Hz, ArH), 7.16–7.28 (2H, m, ArH), 7.34–7.42 (1H, m, ArH), 7.37 (1H, d, $J = 3.3$ Hz, ArH), 7.52–7.55 (4H, m, ArH), 7.57–7.62 (1H, m, ArH), 7.67–7.74 (1H, m, ArH); ^{13}C NMR ($CDCl_3$): $\delta = 103.5, 110.5, 120.3, 121.1, 122.3, 124.4, 126.4, 127.9, 129.3, 129.6, 135.8, 139.8$. Data in accordance with those reported in the literature.[13]

Acknowledgements

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