Tandem copper-catalysed aryl and alkenyl amination reactions: the synthesis of *N*-functionalised indoles†

Roy C. Hodgkinson,[a] Jurgen Schulz[b] and Michael C. Willis*[a]

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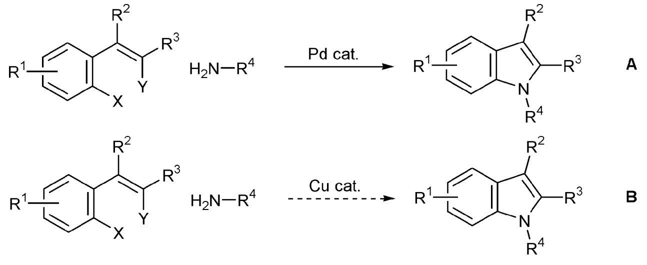
A Cu-diamine complex effectively catalyses tandem C–N bond formation on 2-(2-haloalkenyl)-aryl halide substrates, to deliver a series of *N*-functionalised indoles. Anilines, amides and carbamates are all effective coupling partners under the developed conditions.

The development of palladium catalysed aryl C–N coupling reactions employing aryl halides as substrates has had an enormous impact on synthetic chemistry. The wide range of *N*-based coupling partners, the ability to employ iodo-, bromo-, chloro- and sulfonate-substituted arenes as substrates, together with the availability of commercial catalysts are all responsible for the popularity and utility of this class of transformation.[1] More recently, copper-based methods to achieve the same bond constructions have emerged as alternatives to the palladium catalysed reactions.[2] Although the substrate scope, with respect to both the *N*-nucleophile and the aryl halide components, is more limited than with the corresponding palladium-based methods, there are situations when the use of the copper catalysed process may be attractive.[3] For example, the cost of palladium salts are significantly higher than the corresponding copper sources used in these processes. In addition, the palladium based methods usually partner the metal with a phosphine ligand; the most common ligands for the copper based reactions are diamines, diketones, and phenanthrolines. In general, the phosphine ligands again attract a higher cost. These factors must be balanced against the amount of catalyst needed in the respective reactions, with significantly lower catalyst loadings usually being achievable with the palladium based reactions. An additional cost consideration is the type of aryl halide substrate that can be employed in the reaction under consideration; there are now many examples of aryl chlorides being used in combination with palladium catalysts,[4] however the equivalent copper-catalysed examples are less common.[5] These simple economic arguments must be balanced against the differences in reactivity and selectivity possible with the two metals, considerations that are at least as important from a synthetic perspective. In this Communication we demonstrate that a tandem copper-catalysed amination process allows the efficient preparation of a range of *N*-functionalised indoles, and also document important reactivity differences when compared to an analogous palladium catalysed process.

The abundance of indole ring systems in natural products and particularly in designed medicinal agents has resulted in the development of a wide range of synthetic methods,[6] with transition metal catalysed approaches being particularly well represented.[7,8] We have previously shown that 2-(2-haloalkenyl)-aryl halides can undergo tandem palladium catalysed coupling reactions, one intermolecular, one intramolecular, to deliver a variety of 1-functionalised indole products (Reaction A, Scheme 1).[9] Although the process could incorporate a variety of *N*-nucleophiles, including amines, anilines and carbamates, we were not able to effectively prepare *N*-acyl indoles using this process.[9b] This limitation, resulting from the poor reactivity of amide coupling partners in the developed reaction, together with potential economic advantages, prompted us to explore a copper-catalysed variant of the same indole-forming transformation (Reaction B, Scheme 1).[10,11]



Scheme 1 Pd- and Cu-catalysed tandem amination routes to indoles.

We evaluated the effectiveness of a range of Cu-based conditions in the coupling of dibromo styrene **1** and *ᵗ*Bu-carbamate, to generate indole **2**, as a test reaction (Table 1). We initially explored the use of the four ligands **3–6**, known to be effective systems for simple Cu-catalysed arylation reactions,[12] in combination with CuI; the simple diamine **3** was most effective, delivering 48% of the required indole (entries 1–4). Variation of the copper:ligand proportions established that a 1:2 ratio employing 10 mol% copper for a 24 h reaction was optimal (entries 5–8). Alternative Cu-sources could also be employed, with both CuOAc and CuTC (copper(I) thiophene-2-carboxylate)[13] both effective, although with reduced efficiency compared to CuI (entries 9 and 10). Finally, we also found that the base could be varied from K_2CO_3 to K_3PO_4 and an effective system still maintained, particularly when used in combination with CuOAc (entries 11 and 12).

Having established that we could achieve the required tandem amination sequence employing Cu-catalysis, we turned our attention to exploring the scope of the *N*-coupling partner. We again employed the simple dibromo styrene **1** as our test substrate (Table 2).‡

Extending from the *ᵗ*Bu-carbamate employed in our optimisation studies we found that both Et- and Bn-carbamates were

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[a] *Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, UK OX1 3TA. E-mail: michael.willis@chem.ox.ac.uk; Fax: +44 1865 285002; Tel: +44 1865 285126*
[b] *Schering Plough Corporation, Newhouse, UK ML1 5SH*

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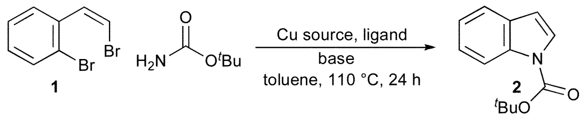
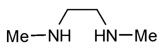
Table 1 Evaluation of Cu-catalysts in the conversion **1** → **2**[a]



entry	Cu source (mol%)	ligand	metal:ligand	base	time	yield (%)[b]
1	CuI (10)	**3**	1:1	K_2CO_3	24 h	48
2	CuI (10)	**4**	1:1	K_2CO_3	24 h	0
3	CuI (10)	**5**	1:1	K_2CO_3	24 h	0
4	CuI (10)	**6**	1:1	K_2CO_3	24 h	0
5	CuI (10)	**3**	1:2	K_2CO_3	24 h	85
6	CuI (10)	**3**	1:4	K_2CO_3	24 h	54
7	CuI (5)	**3**	1:2	K_2CO_3	24 h	60
8	CuI (5)	**3**	1:2	K_2CO_3	48 h	27
9	CuOAc (10)	**3**	1:2	K_2CO_3	24 h	76
10[c]	CuTC (10)	**3**	1:2	K_2CO_3	24 h	68
11	CuI (10)	**3**	1:2	K_3PO_4	24 h	61
12	CuOAc (10)	**3**	1:2	K_3PO_4	24 h	88

[a] Reaction conditions: dihalide (1.0 equiv.), carbamate (2.0 equiv.), K_2CO_3 (3.0 equiv.), toluene, 110 °C, 24 h. [b] Isolated yields. [c] CuTC = copper(I) thiophene-2-carboxylate.



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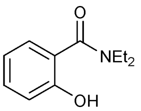

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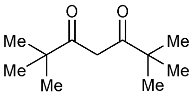

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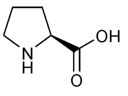

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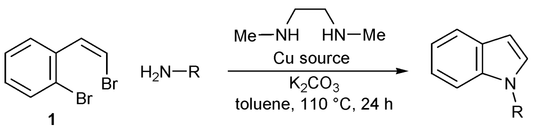
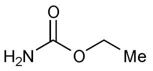
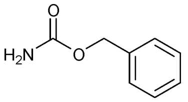
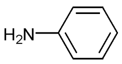
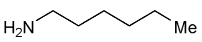
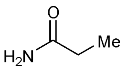
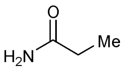
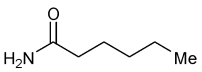
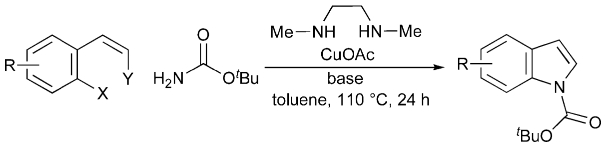
Table 2 Variation of *N*-coupling partner[a]

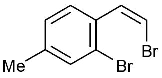
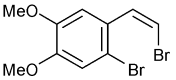
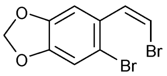
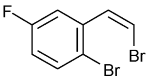
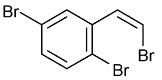
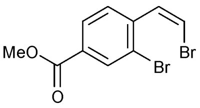
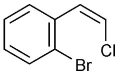
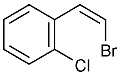


entry	Cu source	*N*-substrate	yield (%)[b]
1	CuI		81
2	CuI		84
3	CuI		80
4	CuI		21
5	CuI		80[c]
6	CuTC		89
7	CuTC		87

[a] Reaction conditions: dihalide (1.0 equiv.), *N*-substrate (2.0 equiv.), K_2CO_3 (3.0 equiv.), Cu source (10 mol%), ligand **3** (20 mol%), toluene, 110 °C, 24 h. [b] Isolated yields. [c] Isolated along with 13% of the *N*-H indole.

Table 3 Variation of 2-(2-haloalkenyl)-aryl halides substrates[a]



entry	substrate	base	yield (%)[b]
1[c]		K_3PO_4	79
2		Cs_2CO_3	82
3[d]		Cs_2CO_3	62
4		K_3PO_4	80
5[e]		Cs_2CO_3	53
6[c]		K_3PO_4	70
7		K_3PO_4	56
8		K_3PO_4	0

[a] Reaction conditions: dihalide (1.0 equiv.), carbamate (2.0 equiv.), base (3.0 equiv.), Cu source (10 mol%), ligand **3** (20 mol%), toluene, 110 °C, 24 h. [b] Isolated yields. [c] 40 mol% ligand employed. [d] 5.0 Equivalents of carbamate used. [e] 1.75 Equivalents of carbamate used.

also good coupling partners (entries 1 and 2). Aniline could also be readily introduced, delivering the *N*-aryl indole in 80% yield (entry 3). However, simple amines were not effective coupling partners. This was demonstrated by the use of *n*-pentylamine, in which only 21% of the *N*-alkyl indole was obtained, with the balance of material being unreacted substrate (entry 4). When propionamide was employed as the nucleophile we isolated 80% of the desired *N*-acyl indole, along with 13% of the *N*-H indole (entry 5). Attempts to further exclude moisture from the reaction resulted in no improvement, with the *N*-H indole always being obtained in similar amounts. However, the use of a catalyst derived from CuTC delivered the *N*-acyl indole in 89% yield with none of the *N*-H indole byproduct (entry 6). The same conditions could also be used to couple hexamide with comparable results (entry 7). These successful reactions employing amide coupling partners are notable, as we were never able to prepare the same *N*-acyl indoles using Pd-catalysis in the corresponding transformations.[9b]

The 2-(2-haloalkenyl)-aryl halides used as substrates in the indole syntheses are readily obtained from the corresponding *o*-halo benzaldehydes using simple Wittig chemistry. Accordingly, we prepared a variety of functionalised substrates to probe the generality of the Cu-catalysed process (Table 3). ^{t}Bu-carbamate was used as the *N*-coupling partner in all examples. A catalyst derived from CuOAc was found to deliver the most consistent yields across a variety of substrates, although some variation in the choice of base was needed. Within these constraints it was possible to employ substrates featuring a variety of both electron-donating and electron-withdrawing substituents (entries 1–6). A limitation of the present method was that two Br-substituents were needed to achieve efficient reactions. For example, employing the substrate partnering an alkenyl-chloride with an aryl bromide delivered the desired indole in a yield of 56% (entry 7); significantly lower than the corresponding dibromo example (88% yield, table 1 entry 12). The aryl-chloride containing substrate was unreactive (entry 8).

In summary, we have demonstrated that tandem Cu-catalysed amination reactions employing 2-(2-haloalkenyl)-aryl halides allow the straightforward preparation of *N*-functionalised indoles. The range of *N*-coupling partners that can be used complements that achievable using Pd-catalysis, with the major advantage being the successful preparation of *N*-acyl indoles when employing the Cu-system. Conversely, couplings employing simple amines were less efficient when using the Cu-chemistry. Ultimately, the choice of Pd or Cu catalysis will be determined on a case-by-case basis, balancing economic considerations of the catalyst and other reaction components, against the reactivity and efficiency possible with the two systems.

Acknowledgements

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Notes and references

‡ General procedure for the Cu-catalyst diamination: Table 1, entry 5. Potassium carbonate (316 mg, 2.29 mmol) and *tert*-butylcarbamate (179 mg, 1.52 mmol) were added to an oven dried flask charged with CuI (14 mg, 0.08 mmol) and *N,N′*-dimethylethyldiamine (13 mg, 16 μL, 0.15 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (0.38 mL) and (*Z*)-1-bromo-2-(2-bromovinyl)benzene (200 mg, 0.76 mmol) was added. The reaction mixture was stirred for 24 hours at 110 °C and then cooled to room temperature. The reaction was diluted with ethyl acetate, filtered through celite, and reduced under *vacuo.* The product was purified by flash chromatography (10% EtOAc: Hexane) to yield *indole* (142 mg, 85%) as a yellow oil.

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