Nitrogen Heterocycles

Palladium-Catalyzed Tandem Alkenyl and Aryl C–N Bond Formation: A Cascade N-Annulation Route to 1-Functionalized Indoles**

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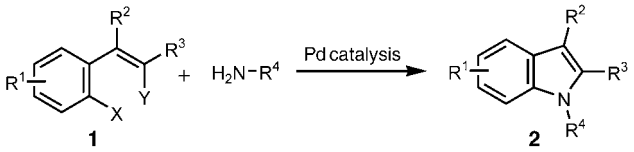
Indoles are preeminent amongst the heterocyclic motifs found in both designed medicinal agents and in natural products, and accordingly there exists a large and varied selection of methods for their preparation.[1] The majority of syntheses incorporate the key nitrogen atom of the indole nucleus early in the synthetic route. This can be problematic if systematic variation of the *N*-substituent is required without recourse to functionalization of the relatively non-nucleophilic indole N–H group. Herein we describe a tandem palladium-catalyzed process that allows installation of a diverse range of functionalized N units in a cascade indole-forming event that combines the introduction of the nitrogen atom with cyclization.

Palladium catalysis has had a major impact on indole synthesis;[2] arguably, the most important of the many reported methods are those based on Pd-catalyzed coupling of *o*-haloanilines with unsaturated carbon units.[3] Syntheses based on intra- and intermolecular Pd-catalyzed aryl–C–N bond formation,[4] the preparation of intermediates used in Fischer indole syntheses,[5] together with the use of Pd catalysis to functionalize intact indole rings[6] have all been the subjects of recent interest. To effect the desired cascade process, we focused on the introduction of functionalized nitrogen derivatives to an acyclic carbon framework **1** under the action of Pd catalysis; tandem alkenyl C–N and aryl C–N formation would then provide the indole structure (Scheme 1). Palladium-catalyzed aryl C–N bond formation



1 **2**

Scheme 1. A cascade *N*-annulation route to indoles.

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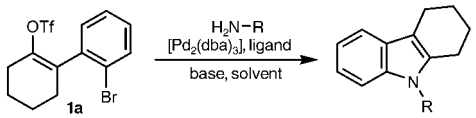
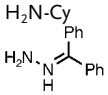
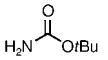
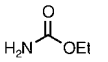
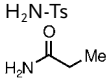
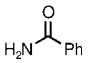
is now a well-established synthetic tool[7] and alkenyl C–N systems are also beginning to appear.[8] However, to the best of our knowledge, no examples of such a tandem process have been reported.[9]

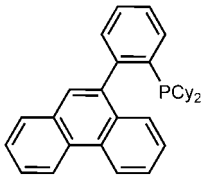
The biological relevance of *N*-arylated indoles,[10] together with the steric and electronic challenges associated with aniline nucleophiles, prompted us to select the union of triflate **1a**[11] with aniline as a platform to evaluate our proposed synthesis. Literature precedents suggested that for Pd-catalyzed C–N bond-forming processes, ligand choice is highly dependent on the electronic and steric properties of both the nucleophilic and electrophilic reaction components,[7] suggesting that identification of a catalyst capable of mediating both aryl and alkenyl C–N bond formation would present a challenge; in the event, phenanthrene ligand **3**[12] and dpephos (**4**)[13] were the most successful.[14] Dpephos has the advantage that it is commercially available

Table 1: Synthesis of *N*-substituted indoles.[a]



Entry	H_2N-R	Ligand	Base	Solvent	*T* [°C]	*t* [h]	Yield [%]
1	H_2N-Ph	**4**	Cs_2CO_3	toluene	100	20	83
2	H_2N-4-$MeOC_6H_4$	**4**	Cs_2CO_3	toluene	100	20	86
3	H_2N-4-ClC_6H_4	**4**	Cs_2CO_3	toluene	100	20	51
4	H_2N-2-ClC_6H_4	**4**	Cs_2CO_3	toluene	100	40	75
5	H_2N-Bu	**4**	NaO*t*Bu	toluene	100	16	62
6	H_2N-Bn	**4**	Cs_2CO_3	toluene	100	24	70
7	H_2N-Cy	**4**	NaO*t*Bu	toluene	100	24	46
8		**5**	Cs_2CO_3	toluene	115	21	82
9		**5**	Cs_2CO_3	dioxane	115	24	61
10		**5**	Cs_2CO_3	dioxane	115	25	70
11	H_2N-Ts	**5**	Cs_2CO_3	toluene	120	23	63
12		**5**	Cs_2CO_3	dioxane	115	24	79
13[c]		**5**	Cs_2CO_3	dioxane	115	24	80[c]
14		**5**	Cs_2CO_3	dioxane	115	26	66

[a] Conditions: triflate (1.0 equiv), amine (1.2 equiv), $[Pd_2(dba)_3]$ (2.5 mol%); dpephos (6 mol%) or xantphos (7.5 mol%), base (2.5 equiv). [b] Yields of isolated products. [c] Free indole isolated following addition of KOH, H_2O, EtOH for 2 h. Ts = *p*-toluenesulfonyl, Tf = trifluoromethanesulfonyl, Cy = cyclohexyl, dba = dibenzylideneacetone.



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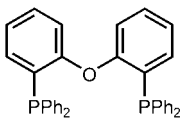
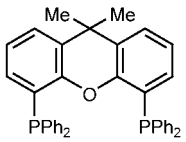


4 dpephos

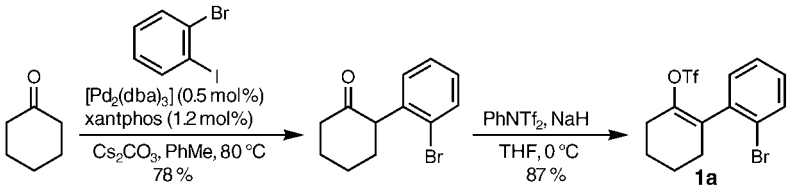


5 xantphos

and was selected for further application. Under optimized conditions ($[Pd_2(dba)_3]$, dpephos, Cs_2CO_3, PhMe, 100 °C, 20 h) the coupling of triflate **1a** with aniline delivered the required indole in 83% yield (Table 1, entry 1).

The scope of the process with respect to the N fragment was found to be broad and allowed good yields of indoles for a varied range of coupling partners (Table 1). Substituted aryl, alkyl, and benzyl amines all performed well, although the steric hindrance associated with the cyclohexyl group resulted in a lower reactivity (Table 1, entries 1–7). The use of 4- and 2-chloroanilines is notable as it allows the potential for product functionalization by subsequent palladium catalysis.[15] Hydrazine functionality could be readily incorporated, with the resultant protected 1-aminoindole being produced in high yield (Table 1, entry 8). For electron-poor nucleophiles, the use of xantphos (**5**)[13] as ligand was optimal. Under these modified conditions carbamate, sulfonamide, and amide functionalities were all incorporated in good yields (Table 1, entries 9–14). The use of propionamide has the benefit of also allowing efficient access to the free indole NH function; addition of ethanolic KOH prior to workup delivers the deprotected indole in 80% yield (Table 1, entry 13).

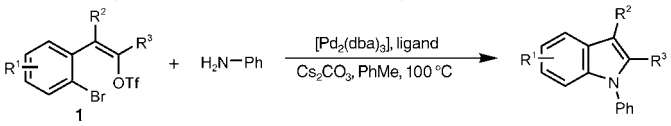
The required bis-activated carbon frameworks **1** could be conveniently prepared by triflate formation on the corresponding arylated ketones,[14] which in turn were readily available by Pd-catalyzed arylation of the parent ketone with a 1,2-dihaloarene.[16,17] For example, triflate **1a** was prepared from the arylation of cyclohexanone with 2-bromo-iodobenzene in the presence of a $[Pd_2(dba)_3]$/xantphos catalyst system followed by triflate formation with $PhNTf_2$ (Scheme 2).

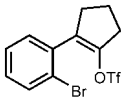
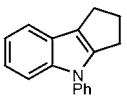
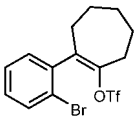
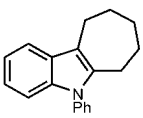
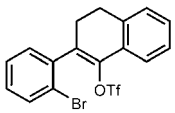
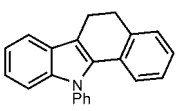
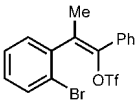
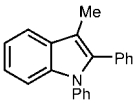
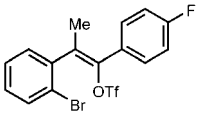
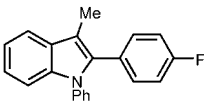
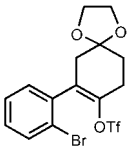
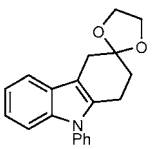
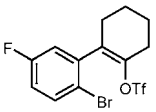
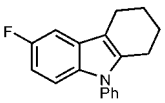
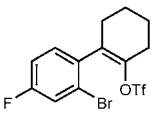
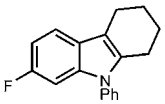
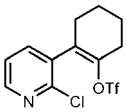
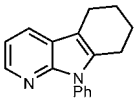


Scheme 2. Preparation of triflate **1a**.

Variations in the ketone and aryl halide components were explored with aniline as the nitrogen unit (Table 2). Indole formation was effective for a variety of architectures; five-, six-, and seven-membered cyclic ketones, simple acyclic, and aryl- and ketal-functionalized[18] ketones were all incorpo-

Table 2: Scope of the ketone and arene components.[a]



Entry	Substrate	Ligand	Product	Yield (%)[b]
1		4		71
2		4		82
3[c]		4		90
4[c]		4		74
5[c]		4		65
6[c]		4		80
7		4		81
8		4		88
9		5		84

[a] Conditions: triflate (1.0 equiv), aniline (1.2 equiv), $[Pd_2(dba)_3]$ (2.5 mol%), dpephos (6 mol%) or xantphos (7.5 mol%), base (2.5 equiv), PhMe, 100°C. [b] Yields of isolated products. [c] NaO*t*Bu used as base.

rated efficiently. Medicinally attractive fluorine-substituted arenes together with simple heterocycles could also be readily introduced.

In summary, we have developed a new palladium-catalyzed route to *N*-functionalized indoles in which the N fragments are introduced in a single-step cascade sequence onto an acyclic carbon framework. A wide range of electronically and structurally varied N fragments can be introduced through a tandem C–N bond-forming process that employs commercially available catalyst components. This new synthesis allows the nitrogen atom of the indole core to be introduced as the final synthetic operation. The cyclization precursors are assembled from the union of a ketone and a 1,2-dihaloarene; variations in both components is well tolerated and allows the efficient synthesis of structurally varied indole systems. Studies to apply similar tandem processes to alternative heterocyclic motifs are underway.

Experimental Section

General procedure (Table 1, entry 1): Cesium carbonate (420 mg, 1.30 mmol) was added to an oven-dried flask charged with $[Pd_2(dba)_3]$ (12 mg, 0.01298 mmol) and dpephos (17 mg, 0.0312 mmol) under nitrogen. The flask was evacuated and back-filled with nitrogen three times. The reagents were suspended in anhydrous toluene (1.10 mL) and 2-(2-bromophenyl)cyclohexen-1-yl triflate (200 mg, 0.519 mmol) and aniline (58 mg, 0.057 mL, 0.623 mmol) were added under nitrogen. The reaction was heated at 100°C for 20 h. After cooling, the reaction mixture was diluted with diethyl ether (≈5 mL) and water (25 mL). The product was extracted with diethyl ether (3×25 mL). The combined organic extracts were washed with HCl (1M; 2× 25 mL) and brine (20 mL) and then dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash chromatography (1% diethyl ether/petroleum ether) to yield the title compound (106 mg, 83%) as an off-white solid.

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Keywords: amination · cascade reactions · indoles · nitrogen heterocycles · palladium

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[11] Triflate **1** was prepared in 64% yield by the arylation of cyclohexanone with 1-bromo-2-iodobenzene, in the presence of a catalyst generated from $[Pd_2(dba)_3]$ and xantphos, followed by triflate formation (NaH, Tf_2NPh, Scheme 2). See Supporting Information for details.
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