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Tandem indole C–H alkenylation/arylation for tetra-substituted alkene synthesis†

Laura Lopez Suarez and Michael F. Greaney*

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Alkynyl indoles undergo a novel sequence of Pd-catalysed indole C–H activation/alkyne carbopalladation/arylation, with diaryliodonium salts providing the aryl components. An array of functionalised indole alkenes have been prepared in good to excellent yield, with the reaction being selective for the Z-alkene.

Transition metal-catalysed hydroarylation of alkynes using C–H activation is a highly atom economic route for stereocontrolled alkene synthesis. The reaction was pioneered by Fujiwara, who established that electron poor propiolates would react with electron rich arenes, such as mesitylene, under Pd(II) catalysis.[1] The alkene products (**2**) formally arise from arene C–H activation[2] and carbopalladation affording alkenyl palladium **1**, followed by protonolysis (Scheme 1). Fujiwara's initial reaction system has since been shown to have excellent generality and been extended to a variety of C–H components, alkynes and catalyst systems.[3,4]

Our interests in catalytic C–H activation chemistry[5] led us to study this reaction with the aim of capturing the alkenylpalladium intermediate **3** for an additional C–C bond-forming step. Whilst protonolysis of **3** affords useful di- or tri-substituted alkynes, we reasoned that the addition of a third component could add significant value to the transformation. Such a tandem process would represent a versatile, one step route to tetra-substituted alkenes, **4**, important compounds in medicinal and materials chemistry that are usually prepared over several steps.[6] We planned to explore the proposed transformation using Pd(II)/Pd(IV) catalysis.[7] Such cycles frequently operate under mild and simple reaction conditions relative to the analogous Pd(0)/Pd(II) systems,[8,9] potentially affording an alkene synthesis with enhanced substrate scope that could function close to room temperature.

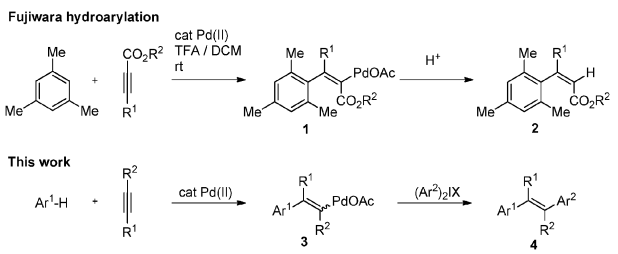
With these considerations in mind we designed indole **5a** as our primary substrate. By installing both C–H and alkyne components in the same molecule, we hoped to facilitate the first step and focus our efforts on developing the second intermolecular arylation. We chose diaryliodonium salts as the arylating agents, as these compounds are known to oxidise organo-Pd(II) species to the Pd(IV) complexes.[10] We were pleased to find that treatment of **5a** with 1.2 equiv of diphenyliodonium tetrafluoroborate, **6a**, in trifluoroethanol at 80 °C gave the expected 6-*exo*-dig alkene product **7a** in 47% yield as a 5 : 1 *Z*/*E* mixture (Table 1, entry 1).

Table 1 Optimisation data

Entry	Ligand (10 mol%)	Base	Solvent	*T*/°C	Yield of **7a** (%)[a]
1	—	—	CF_3CH_2OH	80	47 (5 : 1)
2	—	—	CF_3CH_2OH	rt	57
3	SIMes.HCl	Cs_2CO_3	CF_3CH_2OH	rt	62
4[b,c]	SIMes.HCl	Cs_2CO_3	chloro-benzene	30	86

Conditions: Indole **5a** (1 equiv), diaryliodonium salt **6a** (1.2 equiv), catalytic $Pd(OAc)_2$ (5 mol%), plus additives where indicated in solvent (3 mL). Reactions were carried out on a 0.3 mmol scale for 24 h in a sealed tube.[a] Isolated yields. Ratio shown in brackets indicates **7a** isolated as a *Z*/*E* mixture, with ratio determined by ^{1}H NMR. [b] 1.05 equiv of **6a** used. [c] Reaction time of 2 h. SIMes.HCl = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene.

Characterisation of **7a** was complicated by the fact that *Z*/*E* interconversion appeared facile, with NMR samples of *Z*/*E*-**7a** in $CDCl_3$ undergoing equilibration over the course of a day. Furthermore, the indole C3 proton of the major isomer was significantly shielded, resonating at δ = 5.8 in the ^{1}H NMR spectrum. Subsequent X-ray analysis of the analogue prepared



Scheme 1 Fujiwara hydroarylation and proposed three component coupling reaction.

School of Chemistry, University of Edinburgh, King's Buildings, West Mains Rd, Edinburgh, EH9 3JJ, UK.
E-mail: Michael.Greaney@ed.ac.uk

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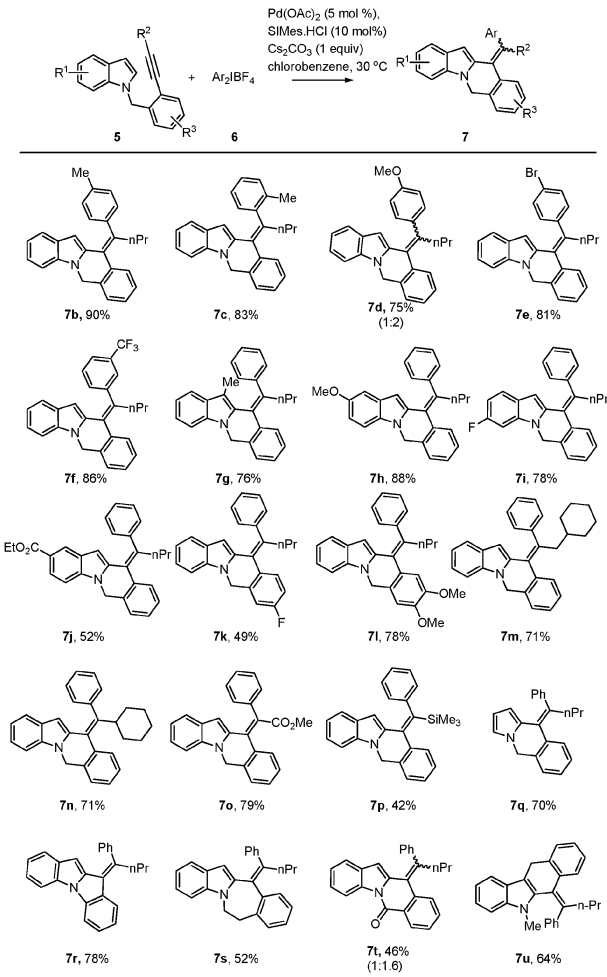


Scheme 2 Substrate scope.

from di(*p*-tolyl)iodonium tetrafluoroborate revealed the C3 indole proton pointing towards the face of the tolyl group, in the shielded zone of the aromatic ring (supporting information).

The reaction proved to be viable at room temperature (entry 2), and that under these mild conditions we could isolate the *Z*-isomer exclusively in 57% yield. A screen of various Pd salts and phosphine ligands failed to improve on the ligandless $Pd(OAc)_2$ system (supporting information). The N-heterocyclic carbene (NHC) ligand generated from SIMes.HCl, however, offered an improved yield of 62% in the presence of 1 equivalent of Cs_2CO_3 (entry 3).[11] The yield could be increased further through solvent optimisation, with chlorobenzene delivering the product **7a** in a very good 86% yield as a single isomer, after just 2 h at 30 °C (entry 4).

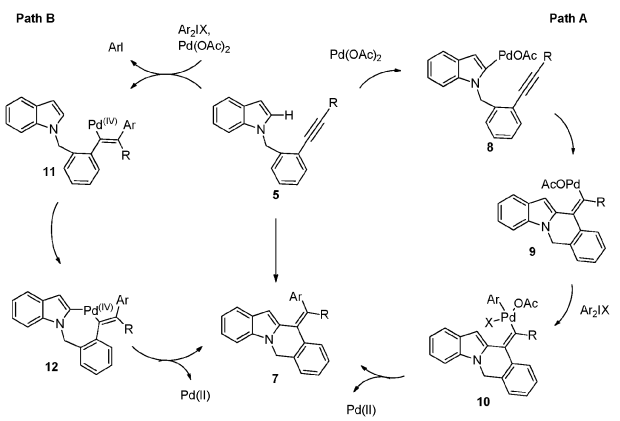
With this optimised process in hand, we first attempted to establish whether the *Z*-selectivity was intrinsic to the reaction or a consequence of equilibration under the reaction conditions. Exposure of a 2 : 1 *Z*/*E* mixture of **7a** to the optimised reaction conditions (which are *Z*-selective) gave no change in the isomer ratio over 24 h, indicating that the *Z*-isomer is a kinetic product of the reaction. We then examined the reaction scope for each component in more detail (Scheme 2).

Alternative iodonium salts were viable with the electron rich *p*- and *o*-tolyl, anisyl and bromo derivatives participating in high yield (**7b–7e**). The most electron rich alkene **7d** (anisyl) was isolated as an inseparable *E*/*Z* mixture. The electron poor *m*-CF_3 salt by contrast gave the alkene **7f** in 86% yield as a single *Z*-isomer. Strongly electron withdrawing groups such as nitro gave very poor yields in the reaction.

We used the *p*-tolyl arylating agent to investigate the effects of varying the iodonium salt structure. Mixed salts containing a dummy ligand such as mesityl were productive,[11,12] affording **7b** in the slightly reduced 75% yield. The alternative triflate salt was equally effective as the tetrafluoroborate, producing **7b** in an identical 90% yield (supporting information).

We could display additional functionality on both the indole and tethering aryl components without compromising the efficiency of the reaction. 3-Me, 5-OMe, 5-CO_2Et and 6-F indole derivatives were all successful in the reaction (**7g–7j**), with the more electron rich substrate the most effective (**7h**, 88% yield, crystal structure available). A fluoro group in the aryl linker gave a moderate 49% yield of **7k**, whereas bismethoxy substitution afforded alkene **7l** in a good 78% yield. We were pleased to find similar substrate tolerance with the alkyne substituent, which might be expected to be more sensitive to modification given its proximity to the key bond-forming steps. Branched alkyl groups at both the α and β-positions were well tolerated (**7m** and **7n**), as was the electron poor propiolate **7o**. The versatile silane group could also be introduced, albeit in lower yield (**7p**, 42%, 71% based on recovered SM). Bis-aryl substituted (R^2 = Ar) and terminal (R^2 = H) alkynes were not good substrates for reaction.

Having established good versatility amongst the three functional components of the reaction, we extended the process to more fundamental alterations of the indole-alkene-arene structure. Pleasingly, the reaction was viable for the pyrrole series, with the annulated heterocycle **7q** being formed in a good 70% yield. We altered the tethering ring size and observed exclusive 5-*exo*-dig cyclisation in the formation of cyclopentane derivative **7r**, with no sign of the alternative 6-*endo* pathway. 7-*exo*-dig cyclisation was also feasible in the formation of **7s**. The amide derivative **7t** was formed in a lower 46% yield as a mixture of *E* and *Z* isomers, fitting the pattern of electron poor indoles being poorer substrates for the reaction. Simple indole arylation was not observed as a competing reaction for any substrate, and appears to be a slow process under the basic reaction conditions (supporting information).



Scheme 3 Mechanistic pathways.

We also altered the carbon skeleton of the substrates such that the alkyne was linked *via* the indole 3-position, rather than the N-atom. 6-*exo*-dig cyclisation proceeded as before to give the structural isomer **7u** in 64% yield as a single geometric isomer (assigned as *Z* by analogy).

A number of different mechanisms may be envisaged for the reaction. The *Z*-geometry of the alkene group for almost all substrates, however, is a key feature and implicates alkyne *syn*-carbopalladation at the heart of the C–C bond forming events. Two possible pathways are set out in Scheme 3. Path A involves direct indole palladation at C2[13,14] with $Pd(OAc)_2$ to afford **8**, which can then undergo intramolecular 6-*exo*-dig carbopalladation. Trapping of the alkenyl Pd(II) intermediate **9** with the iodonium salt then gives the *Z*-product **7**, *via* Pd(IV) intermediate **10**. This mechanism varies from that of classic Fujiwara hydroarylation, where initial S_EAr addition of the C–H component to the alkyne would afford an *E*-alkenyl Pd intermediate, something not observed in our system. However, the basic reaction conditions we employ are quite different to the acidic, ionising character of a typical Fujiwara reaction.[15]

Path B reverses the order of C–C bond formation, and begins with *intermolecular* alkyne carbopalladation using $ArPd(OAc)_2X$ to provide the *Z*-alkene intermediate **11**. Intramolecular C–H activation at the indole 2-position then gives **12**, which reductively eliminates Pd(II) to access the tetra-substituted alkene products. This sequence requires the alkyne carbopalladation to be either regioselective for **11** (Pd on the 'internal' position next to the aryl ring), or for this process to be reversible. Little is known about alkyne carbopalladation for Pd(IV) species, in contrast to the analogous reaction with ArPd(II)X complexes,[16] and further work is necessary to clarify the differences in the proposed mechanistic pathways.[17]

We have developed a novel tetra-substituted alkene synthesis that comprises a diaryliodonium salt plus alkyne and indole C–H components. The reaction proceeds under very mild conditions using Pd(II)/Pd(IV) catalysis, is highly selective for the *Z*-alkene isomer and shows excellent substrate scope around each of the reacting functional groups. Further studies to apply this reaction to biologically active targets are underway in our laboratory.

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