Directed palladation: fine tuning permits the catalytic 2-alkenylation of indoles

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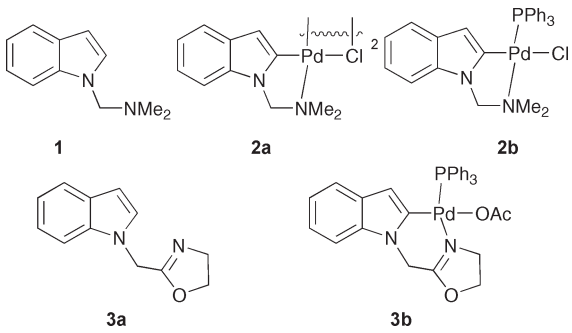
Received (in Cambridge, UK) 9th November 2004, Accepted 17th December 2004
First published as an Advance Article on the web 17th February 2005
DOI: 10.1039/b417035k

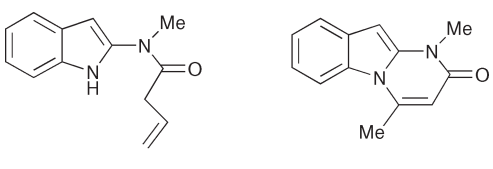
A C–H activating Pd-catalysed alkenylation of indole is regiospecific for 2-substitution when the nitrogen carries a 2-pyridylmethyl substituent.

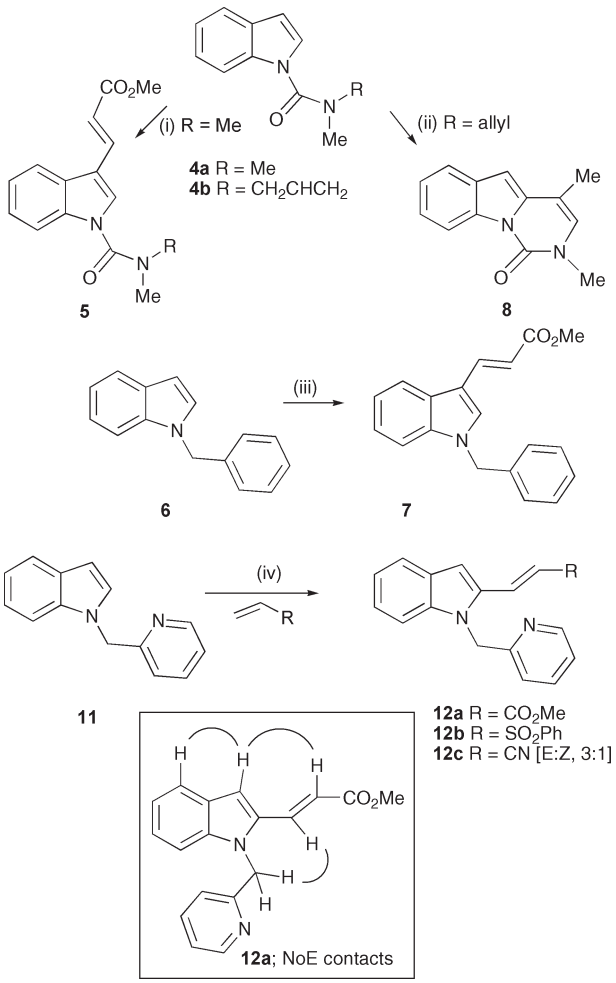
In Heck reactions and related C–C couplings, the organic reactant must be intrinsically capable of covalent transfer to palladium to initiate the catalytic cycle. This step is most commonly brought about by the (oxidative) addition of an electrophilic reactant, such as an unsaturated halide or sulfonate.[1] In an increasing number of examples, the organic reactant is a nucleophile such as an arylboronic acid, and in this case a stoichiometric amount of oxidizing agent needs to be added in order to return the catalyst to the correct oxidation state after each cycle.[2] In an ideal situation, this latter pathway can be modified by generating the critical Pd–C intermediate by C–H activation, removing the need for a C–B bond at the reaction site.[3] The potential for combining C–H activation with an alkene-coupling step has received much recent attention, not confined to Pd catalysis. Indeed, the application of Pd catalysts is pre-dated the early work of Fujiwara, in which the palladation step in a coupling catalytic cycle occurs by electrophilic substitution of an aromatic C–H bond,[4] and by Murai's demonstration of the directed activation and C–H ortho-substitution of arenecarbonyl compounds catalysed by simple ruthenium complexes.[5] An inherent problem in chemoselective synthesis is engendered by the lack of regiochemical control in C–H activation, unless it is substituent-directed.

The potential synthetic value of a catalytic route to 2-substituted indoles has been widely recognized in recent work, but the means to achieve this (arylation or carbonylation) have required forcing conditions.[6] There is precedent for the promotion of cyclopalladation at the 2-position of indoles by polar 3-substituents,[7] encouraging the alternative approach of *N*-substitution. We considered that a suitable indole *N*-substituent could provide activation of the 2-position *via* cyclopalladation, and were surprised not to find any evidence for this in the literature. In initial experiments the isogramine complex **2a** was prepared, (compound **1**, Li_2PdCl_4, AcONa, EtOH, RT, 1 h, 80%). The X-ray structure of the corresponding PPh_3 complex **2b** has been obtained,[8] comparable to related N, C palladacycles.[9] Although this complex was an efficient catalyst for the Suzuki reaction ($PhB(OH)_2$, PhI, C_7H_8, reflux 1.5 h, 200 turnovers),[10] isogramine **1** is itself unreactive to *catalytic* activation under a variety of conditions designed to encourage oxidative Heck reaction. This could be due to the stability of the palladocycle; by analogy with directed C–H activations in the benzene series,[3] a weaker Pd–C bond in the intermediate state could be desirable. A number of simple *N*-substituted indoles were prepared, but none was successful in inducing catalytic C–H activation-driven Heck reactions. Among this group the oxazoline **3a**[11] was readily converted into a structurally characterized palladocycle **3b** ($Pd(OAc)_2$, AcONa, AcOH, 50 °C, 1 h, then RT, 24 h, 96%, then Ph_3P, CH_2Cl_2, 2h, RT, 56%).possessing a six-membered ring with a C–Pd–N angle of 87.9° quite distinct from the value of 80.7° in **2b**. As expected on the precedence from reactant **1**, the oxazole **3a** was not able to participate in catalytic C–H activation.



These experiments indicate that our stable palladocycles do not function as intermediates in catalytic Heck coupling. A further clue to progress was obtained by observing that compound **4a** did not form a palladacycle under standard conditions. This reactant provided the first evidence for an oxidative Heck reaction, but the product was exclusively the 3-substituted ester **5** (Scheme 1). That this was the normal non-directed pathway was further verified by treatment of *N*-benzylindole **6** under the same conditions whereupon a clean, albeit slow reaction took place giving the 3-isomer **7** exclusively. Literature precedent indicates that electrophilic palladation occurs selectively at the 3-position in the absence of directing groups.[12] In contrast, the *N*-allyl amide **4b** underwent smooth coupling to give the heterocycle **8** in excellent yield under the same conditions. This indicates the possibility that the palladation step occurs reversibly but further reaction requires both its efficient interception, and an equilibrium disfavouring the palladacycle. Notably, it has been reported that the 2-substituted analogue **9** gives the isomeric compound **10** by Pd-catalysed NH-activation, but with a different Pd-catalyst cyclisation to the 3-position occurs.[13]

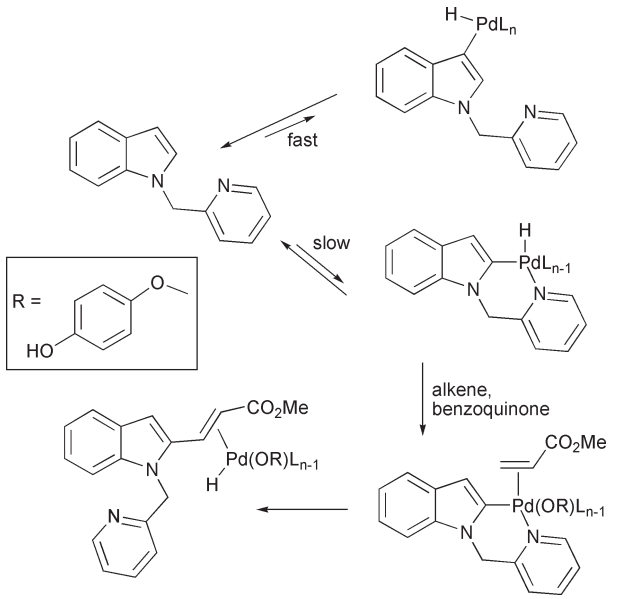




Scheme 1 (i) Me acrylate, 10 mol% $PdCl_2(MeCN)_2$, benzoquinone, THF, DMF, 80 °C, 18 h, 54%; (ii) as (i), no alkene, 95%; (iii) Me acrylate, 10 mol% $PdCl_2$, $2Cu(OAc)_2$, MeCN, 14 h, 60 °C, 95%; (iv) 10 mol% $PdCl_2$, $2Cu(OAc)_2$, MeCN, 14 h, 60 °C, 99% conversion; for **12a**, 99% conversion with 2 mol% $PdCl_2$ after 2 h; benzoquinone may replace $Cu(OAc)_2$.

The design of a directing group for catalysis should engender only weak reversible association between the ligating atom and palladium. It was verified that compound **11** did not form a palladocycle under standard conditions. This reacted smoothly with methyl acrylate to give the corresponding methyl 2-indolylethenyl ester, **12a** with complete regiospecificity under conditions where $Cu(OAc)_2$ was present as an oxidising agent in stoichiometric amount. The structure of the product was verified by ^1H and ^{13}C NMR, for which the ^1H NOESY contacts proved important in distinguishing the product from the 3-isomer. In a range of related reactions the scope of the C–H activation/substitution reaction was extended, although limited at this stage to electrophilic alkenes and to providing products **12b** and **12c** (Scheme 1).†

A tentative mechanism (Scheme 2) that explains these findings is as follows. A catalytically active Pd-complex is engaged in an activation step that is essentially an electrophilic substitution. This may of course occur at the more activated 3-position as well as at the 2-position, but only in the latter case can ligation occur to increase the lifetime of the Pd–C intermediate. Oxidation of the



Scheme 2 Possible reaction pathway.

Pd–H at this stage can prevent the reductive elimination which regenerates the reactants. The arylpalladium species can undergo insertion of a co-coordinated alkene to give a transient alkylpalladium that in turn collapses to product, hydroquinone and the starting Pd-complex. With $Cu(OAc)_2$ as the oxidant, a related catalytic cycle generates two molecules of AcOH.

These preliminary results demonstrate the potential of directing group participation in Pd-complex catalysed C–H activation. They further indicate the importance of lability in the cyclopalladated intermediate, since in those cases where this complex could be isolated, no catalytic turnover occurred. The generality of this principle is being actively explored in related C–H activating reactions, in which ease of regeneration of the parent heterocycle will be emphasised.

We thank the EC for support of an FP5 Network (HPRN-CT-2001-00172; JMB, AR) and for support of Oxford as a Marie Curie Training Site (HPRT-CT-2001-00317, awarded to E. C.). Johnson Matthey kindly provided a loan of Pd salts. Dr A. Suarez made early contributions to the problem.

We recently learned from Dr Matthew Gaunt, Cambridge (paper pending) of his related work on regioselective palladium-catalysed Heck reactions of *N*-unsubstituted indoles, and thank him for a full exchange of information.

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Notes and references

† After submission, we discovered improved conditions for Scheme 1 (iv) [$Pd(OAc)_2$, $Cu(OAc)_2$, AcOH, dioxane, 70 °C] that extend the scope.

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