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Pd^{II}-Catalysed C–H Functionalisation of Indoles and Pyrroles Assisted by the Removable *N*-(2-Pyridyl)sulfonyl Group: C2-Alkenylation and Dehydrogenative Homocoupling

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Abstract: The easily installed and removed *N*-(2-pyridyl)sulfonyl group exerts complete C2 regiocontrol over the Pd^{II}-catalysed C–H alkenylation of indoles and pyrroles, affording the corresponding products in good isolated yields (typically $\geq 70\%$). A remarkable feature of this catalyst system is that it tolerates a wide variety of substituted alkenes, including conjugated electron-deficient alkenes, styrenes and 1,3-dienes, as well as conjugated 1,1- and 1,2-disubstituted olefins. The final reductive desulfonylation affords the C2-substituted, free-NH indoles and pyrroles in good yield. This *N*-(2-pyridyl)-sulfonyl-directing strategy has also been extended to the development of a protocol for the intermolecular, dehydrogenative homocoupling of indoles, providing 2,2′-biindoles. Mechanistic work based upon reactions with isotopically labelled starting materials and competitive kinetic studies of electronically varied substrates suggests a chelation-assisted electrophilic aromatic substitution palladation mechanism.

Keywords: alkenylation · C–H functionalization · nitrogen heterocycles · palladium · protecting groups

Introduction

The direct and selective transformation of an unactivated C–H bond into a C–C bond is one of the most powerful tools to introduce molecular complexity into organic molecules, taking into consideration both chemical efficiency and environmental impact.[1] Since the pioneering work by both Murai[2] and Fujiwara and Moritani[3] on C–C bond-forming reactions through the catalytic cleavage of $C(sp^2)$–H bonds, this research area has undergone rapid development, becoming an increasingly viable alternative[1] to traditional cross-coupling strategies based upon organometallic reagents. Because reactivity and regiocontrol are major challenges in C–H functionalisation, most of the reported applications rely on the use of a metal-coordinating functionality that aids the interaction with a proximal C–H bond. However, the synthetic practicality of many of the common directing groups is compromised if the target molecule does not contain such functionality. Therefore, an intensive search for easily attachable and removable directing groups that combine high reactivity and selectivity has motivated the development of very efficient protocols based upon *N*-acyl,[4] *O*-acyl,[5] *N*-carbamoyl,[6] *O*-carbamoyl,[7] carboxylic,[8] *N*-oxide,[9] cyano[10] and hydrosilane[11] directing groups, among others.[12]

A very attractive platform for developing new selective C–H functionalisation strategies is the indole skeleton, which is a key component of many pharmacophores, natural products and synthetic building blocks.[13] Driven by the biological importance of 2- and 3-arylindoles, metal-catalysed oxidative C–H arylation reactions of indole derivatives have attracted considerable attention,[14] of which some efficient cross-dehydrogenative protocols by double C–H functionalisation stand out.[15] The intermolecular, oxidative homocoupling[16] of indoles can be envisaged to be a useful tool for the preparation of biindolyl systems, which are a frequently found structural unit in pharmaceuticals and functional materials.[17] However, achieving high regiocontrol in the intermolecular, dehydrogenative homocoupling of 2,3-unsubstituted indoles is challenging and has only very recently been

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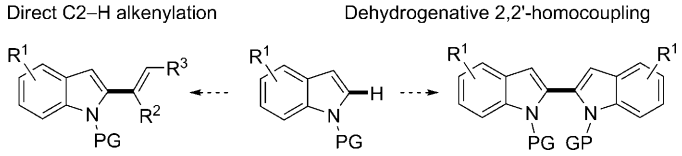
achieved. In particular, Zhang and co-workers have developed an efficient method for the assembly of 2,3′-biindolyl systems with excellent selectivity through the dimerisation of indoles under catalysis by $Pd(TFA)_2$ (5 mol%; TFA = trifluoroacetate) in combination with $Cu(OAc)_2{\cdot}H_2O$ (1.5 equiv), under mild reaction conditions.[18] However, to the best of our knowledge, the complementary catalytic synthesis of symmetrical 2,2′-biindoles[19] by regiocontrolled, intermolecular, dehydrogenative homocoupling (Scheme 1, right) remains undocumented.



Scheme 1. C2–H functionalisation reactions on C2/C3-unsubstituted indole derivatives.

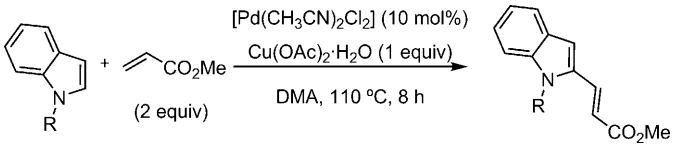
Metal-catalysed alkenylation is a very appealing strategy for the direct functionalisation of indoles. Due to the higher nucleophilic character of the C3 position in indole compared with the C2 position, C3-alkenylated indoles are normally formed selectively.[20] In contrast, to the best of our knowledge, only three protocols have been reported so far for direct C–H alkenylation at the C2 position of C2/C3-unsubstituted indoles (Scheme 1, left).[21–23] Gaunt et al. have described a practical method for the Pd^{II}-catalysed alkenylation of NH indoles in which the regioselectivity can be switched from C3 to C2 by varying the nature of the solvent and the additives.[21a] Ricci et al. reported Pd^{II}-catalysed, regiocontrolled C2 alkenylation of indole directed by a non-removable *N*-2-pyridylmethyl group.[21b] Recently, Miura, Satoh et al. disclosed the Pd^{II}-catalysed C–H alkenylation–decarboxylation of indole-3-carboxylic acids to afford selectively 2-alkenyl indoles, in which the carboxyl group blocks the C3 position and acts as a removable directing group.[21c] Despite these outstanding advances, there is plenty of room for improvement, both by increasing the efficiency of the reaction and enlarging the currently limited scope with regard to the alkene component and the directing group. For instance, to date, only monosubstituted electrophilic alkenes (mainly acrylates and acrylamides) have been utilised in the C2–H alkenylation of indoles, except for an isolated example that involved coupling with styrene.[21c] Furthermore, this limited alkene versatility is a common trend in many metal-catalysed C–H alkenylation reactions of other aromatic and heteroaromatic compounds.[1,23]

Herein, we describe in detail an efficient and structurally versatile Pd-catalysed C2–H alkenylation of indoles and pyrroles, as well as an efficient intermolecular, dehydrogenative homocoupling of indoles to give 2,2′-biindoles. Some mechanistic studies based upon intermolecular competition experiments and kinetic isotope effects have also been undertaken. For both types of transformation, the presence of a *N*-(2-pyridyl)sulfonyl[24] directing group proved to be crucial to ensuring high reactivity and complete regiocontrol.[25]

Results and Discussion

As mentioned, the normal reactivity (non-directed pathway) of 2,3-unsubstituted indoles in oxidative Heck reactions with activated olefins (e.g., methyl acrylate) favours the formation of the 3-alkenylated product.[20,21b,26] Our first aim was to find a removable N-protecting group that allows functionalisation of the C2–H position of the indole unit over the more nucleophilic C3–H position. A set of potential directing groups were examined for the reactions of indole (**1**) and derivatives **2–10** with methyl acrylate under [$Pd(CH_3CN)_2Cl_2$] catalysis (10 mol%) with $Cu(OAc)_2{\cdot}H_2O$ (1 equiv) as the reoxidant in dimethylacetamide (DMA) at 110 °C (Table 1).[27] As expected under such conditions, the free indole (**1**) underwent clean C3 alkenylation with complete regioselectivity (75% conversion, Table 1, entry 1). In contrast, the *N*-*tert*-butoxycarbonyl derivative (*N*-Boc) **2** led to a 68:32 mixture of C2/C3 alkenylation products, albeit in very low conversion (Table 1, entry 2). Both C2 regioselectivity and conversion were enhanced by switching to a *N*-tosyl (*N*-Ts) or *N*-nosyl (*N*-Ns) group (Table 1, entries 3 and 4, respectively), albeit at an impractical yield. *N*-Heteroarylsulfonyl groups had a strong influence both reactivity and regioselectivity. For example, *N*-(2-thienyl)sulfonyl indole (**5**) led to low conversion (18%) and no regioselectivity (C2/C3 = 50:50, Table 1, entry 5), whereas *N*-(8-quinolyl)sulfonyl indole (**6**) showed improved reactivity, yet modest regioselectivity (Table 1, entry 6). Pleasingly, *N*-(2-pyridyl)sulfonyl

Table 1. Effect of N-substitution on the C2 alkenylation of indole with methyl acrylate.



	R	Product	C2/C3[a]	Yield [%][b]
1	H (**1**)	**11**[c]	<2:>98	75 (66)[d]
2	Boc (**2**)	**12**	68:32	10
3	Ts (**3**)	**13**	87:13	45 (30)[d]
4	*p*-Ns (**4**)	**14**	85:15	28
5	(2-thienyl)SO_2– (**5**)	**15**	50:50	18
6	(8-quinolyl)SO_2– (**6**)	**16**	79:21	70 (50)[d]
7	(2-pyridyl)SO_2– (**7**)	**17**	>98:<2	100 (75)[d]
8	(3-pyridyl)SO_2– (**8**)	**18**	76:24	27
9	(2-pyrimidinyl)SO_2– (**9**)	–	–[e]	–[e]
10	(2-pyridyl)S– (**10**)	–	–[f]	–[f]

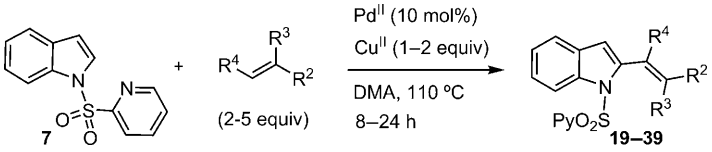
[a] Determined by ^{1}H NMR spectroscopy of the reaction mixture. [b] Conversion yield (from the ^{1}H NMR spectra) [c] C3–H alkenylation product. [d] In parentheses, isolated yield after chromatography (regioisomeric mixtures could not be separated). [e] The starting material was recovered. [f] Complex mixture.

indole (**7**) provided complete conversion and C2 regioselectivity, affording **17** in 75% isolated yield (Table 1, entry 7). The low conversion (27%) and poor regioselectivity (C2/C3 = 76:24, Table 1, entry 8) displayed by the *N*-(3-pyridyl)sulfonyl indole **8**, an isomer of **7**, highlights the key role of the (2-pyridyl)sulfonyl moiety as a directing group in C2–H activation. Surprisingly, *N*-(2-pyrimidinyl)sulfonyl indole **9** proved to be totally unreactive (Table 1, entry 9) and *N*-(2-pyridyl)sulfenyl indole (**10**) led to a complex mixture of products, likely due to the instability of the N–S bond under the harsh reaction conditions. These results provide evidence of the clear superiority of the *N*-(2-pyridyl)sulfonyl group as both an activating and regiocontrolling auxiliary.

With a regioselective C2–H alkenylation protocol in hand, we studied the effect of electronic and structural variations to the alkene (Table 2). A variety of monosubstituted alkenes, not only the typical electrophilic alkenes (Table 2, entries 1–4), but also the more challenging simple, non-conjugated alkenes, such as 1-octene and *tert*-butylethylene, successfully participated in the reaction, albeit with a lower reactivity. The former led to indole product **23**, in which the alkene is not conjugated with the indole, as the single product with 55% conversion (40% isolated yield, Table 2, entry 5), whereas the latter afforded the conjugated product in 57% yield (Table 2, entry 6). Gratifyingly, styrene derivatives (Table 2, entries 7–11) coupled efficiently with indole **7** to give the corresponding alkenylation products with excellent regioselectivity, *E* stereoselectivity and in synthetically useful yields (typically 70–85%). The reaction reached full conversion with both electron-rich and electron-poor substituents. Interestingly, this protocol can also be applied to 1,3-dienes, a class of olefins scarcely employed in C–H alkenylations.[6a,c,28] The coupling reactions of **7** with methyl 2,4-pentadienoate and 1-phenyl-1,3-butadiene (Table 2, entries 12 and 13, respectively) proceeded at the terminal double bond to give 2-dienyl indoles **30** and **31** in good yields (65–68%). Alkenes with more substituents are also suitable; good results were obtained with 1,1-disubstituted alkenes, such as methyl methacrylate, methyl α-phenylacrylate, α-ethylacrolein and α-methylstyrene, providing the corresponding double-bond-isomerised products **32**, **33**,[29] **34** and **35** in 70–72% yield (Table 2, entries 14–17).

Particularly remarkable is the participation of 1,2-disubstituted alkenes in this reaction, given the small number of precedents and lower reactivity of this kind of olefin in oxidative alkenylation (Fujiwara–Moritani) reactions.[23b,e,30] Under the standard reaction conditions, (*E*)-methyl crotonate and (*E*)-propenylbenzene underwent a smooth reaction with **7** to provide the corresponding trisubstituted alkene products **36**[29] (60% yield, Table 2, entry 18) and **37**+**38** (68% yield), in the latter case as a 40:60 mixture of double-bond-isomerised products (Table 2, entry 19). The more challenging methyl (*E*,*E*)-hexa-2,4-dienoate reacted at the distal double bond to

Table 2. Olefin scope in the C2–H alkenylation of indole **7**.[a]



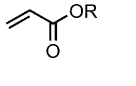
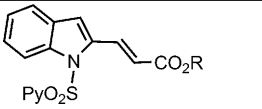
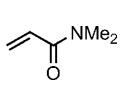
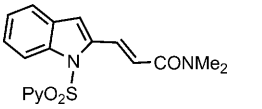
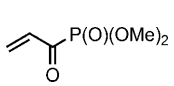
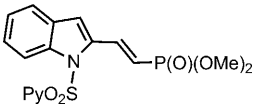
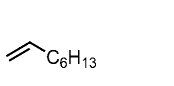
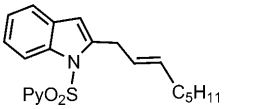
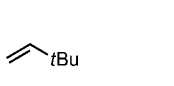
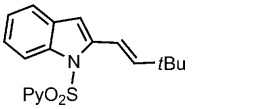
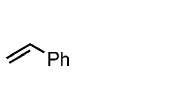
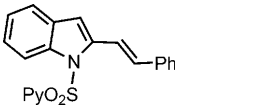
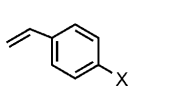
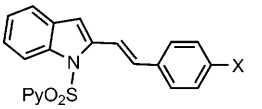
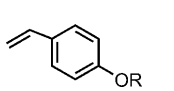
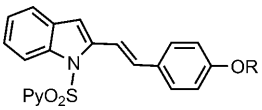
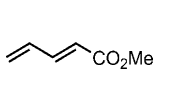
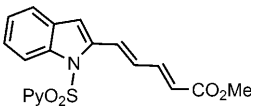
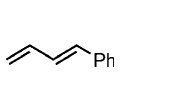
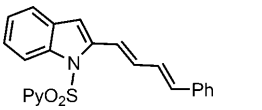
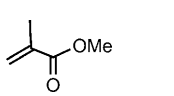
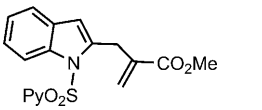
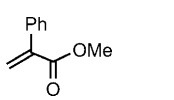
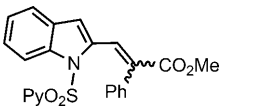
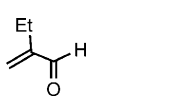
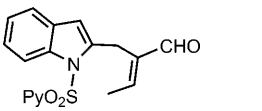
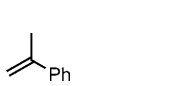
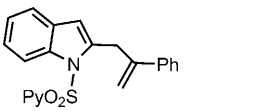
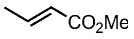
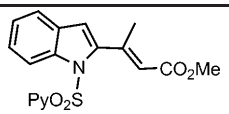
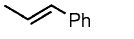
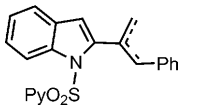
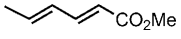
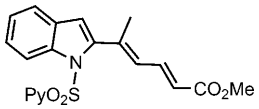
	Alkene	Product		Yield [%][b]
1 2			**19**, R = *n*Bu **20**, R = *t*Bu	72 78
3			**21**	45 (83)[c]
4			**22**	62
5			**23**	40 (56)[c]
6			**24**	57
7			**25**	85
8 9			**26**, X = F **27**, X = Br	68 74
10 11			**28**, R = Ac **29**, R = Me	75 80
12			**30**	68
13			**31**	65
14			**32**[d]	72
15			(*E*/*Z*)-**33**[e]	69
16			**34**[d,f]	70
17			**35**[d]	71

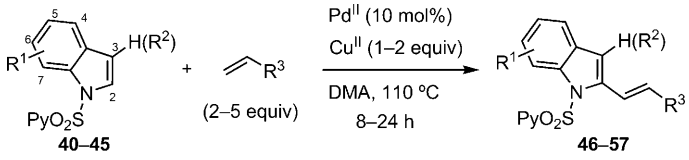
Table 2. (Continued)

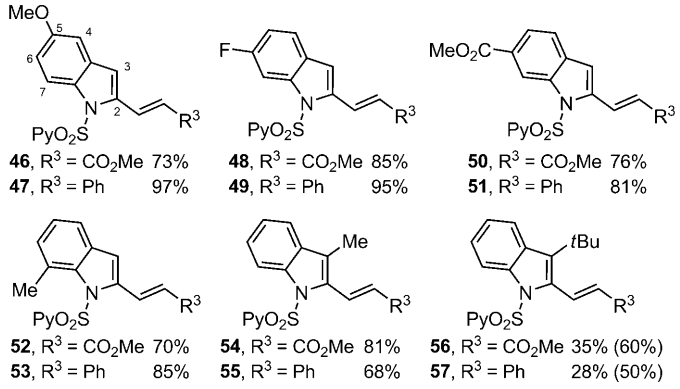
	Alkene	Product		Yield [%][b]
18			**36**[f]	60
19			**37**+**38**[d] (40:60)	68
20			**39**[f]	60

[a] Reaction conditions: **7** (0.1 mmol), alkene (2–5 equiv), [Pd(CH_3CN)$_2$Cl$_2$] (10 mol%), Cu(OAc)$_2$·H_2O (1–2 equiv), DMA, 110 °C, 8–24 h. [b] Isolated yield. [c] Yield based upon recovered indole **7**. [d] Double bond isomer of the alkenylation product. [e] As a 2.7:1 mixture of *E*/*Z* diastereomers that was efficiently separated by flash column chromatography. [f] Obtained as a single diastereomer (see the Supporting Information for structure determination).

give, in an acceptable yield, dienyl indole **39**[29] with complete stereoselectivity (Table 2, entry 20).

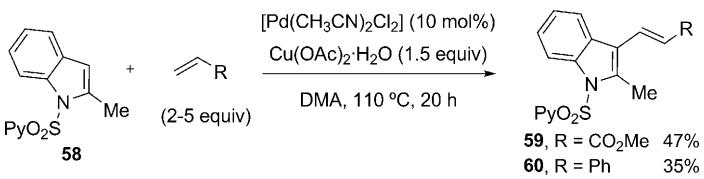
The applicable range of indole counterparts (substrates **40–45)** was explored with methyl acrylate and styrene as model olefins (Scheme 2). Electron-withdrawing or electron-donating groups at C5, C6 or C7 of the indole core did not have a significant impact upon the reactivity (products **46–53**, 70–97% yield). The reaction even tolerated substitution at C3, as demonstrated for the case of 3-methyl indole (**54** and **55**, 81 and 68% yield). Even the highly sterically demanding 3-*tert*-butyl-substituted indole proved to be a suitable substrate. Although in this case the conversions were incomplete (35–44% conversions), the corresponding olefination products **56** and **57** were formed cleanly and isolated in moderate yields (28–35% yields, 50–60% based on converted products). These results are remarkable given the difficulty in obtaining 2,3-disubstituted indoles, either by intermolecular C2–H functionalisation of 3-substituted indoles[31] or by C3–H functionalisation of 2-substituted indoles,[31a,32] due to the high sensitivity of the metal-catalysed reaction to steric effects.





Scheme 2. Structural variation of the indole. Conditions: indole **40–45** (0.1 mmol), [Pd(CH_3CN)$_2$Cl$_2$] (10 mol%), Cu(OAc)$_2$·H_2O (1–2 equiv). In parentheses, yield based upon recovered starting material **45**. Py = pyridyl

As shown in Scheme 3, blocking the reactive C2 position with a methyl group results in the formation of the C3 alkenylation product, albeit in much lower yield (**59** and **60**, 35–47%). In all cases studied, no C7–H activation product was identified.[33]



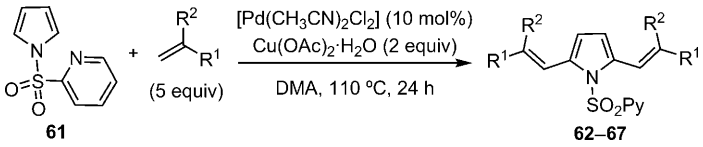
Scheme 3. C3 alkenylation of 2-methyl-substituted indole **58**.

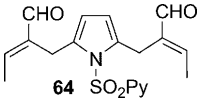
In view of these results, we decided to test the versatility of the *N*-(2-pyridyl)sulfonyl moiety as a directing group in the alkenylation of other important nitrogen heterocycles, such as pyrroles, which rival indoles in biological significance and as valuable synthetic intermediates.[34] However, pyrroles have received much less attention than indoles in direct C–H alkenylation reactions. In this field, Gaunt et al. have reported an elegant and efficient protocol for the direct alkenylation of pyrroles with electron-deficient alkenes, in which the regioselectivity at C2 or C3 can be controlled by tuning the steric or electronic properties of the N-protecting group.[30]

Table 3 shows the feasibility of the C2 alkenylation of pyrroles assisted by the *N*-(2-pyridyl)sulfonyl group.[35] First, we confirmed again the key role exerted by the 2-pyridylsulfonyl group: a very low reactivity (<10% conversion) was observed in the reaction of the *N*-tosyl pyrrole with methyl acrylate under the conditions used in Table 3. In sharp contrast, 2-pyridylsulfonyl pyrrole **61** produced the corresponding products of double alkenylation cleanly at C2 and C5 (**62–67**) in acceptable to good yields. No C3 alkenylation products were detected. Electronically varied olefins, including acrylates (Table 3, entries 1 and 2), α-ethylacrolein (Table 3, entry 3), styrenes (Table 3, entries 4 and 5) and a non-activated olefin, 3,3-dimethyl-1-butene (Table 3, entry 6) were suitable olefin substrates.

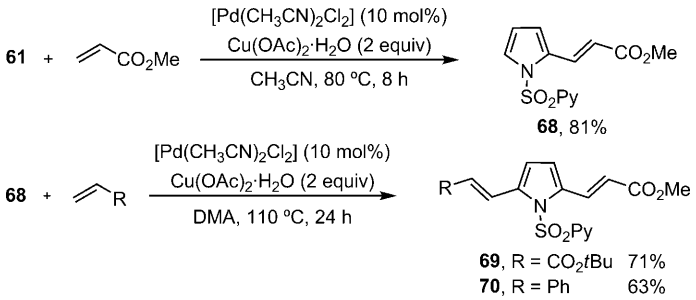
It is interesting to note that the selective C2 monoalkenylation of **61** with methyl acrylate was efficiently achieved under milder reaction conditions (CH_3CN, 80 °C, 8 h), to give the corresponding pyrrole **68** in 81% yield (Scheme 4). This compound opened up access to unsymmetrical 2,5-disubstituted pyrroles through subsequent C5 alkenylation

Table 3. Direct C–H alkenylation of *N*-(2-pyridyl)sulfonyl pyrrole (**61**).



	R^1	R^2	Product	Yield [%][a]
1	CO_2nBu	H	**62**	80
2	CO_2tBu	H	**63**	79
3	CHO	Et	 **64**	65
4	Ph	H	**65**	55 (82)[b]
5	4-FC_6H_4	H	**66**	69
6	tBu	H	**67**	62

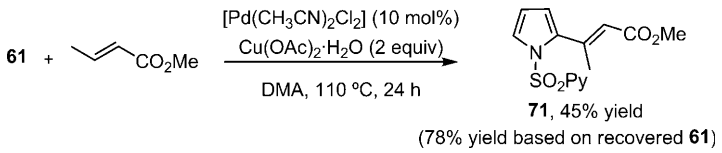
[a] Isolated yield after chromatography. [b] In parentheses, yield based upon recovered pyrrole 59.



Scheme 4. Regioselective sequential C2/C5 double alkenylation.

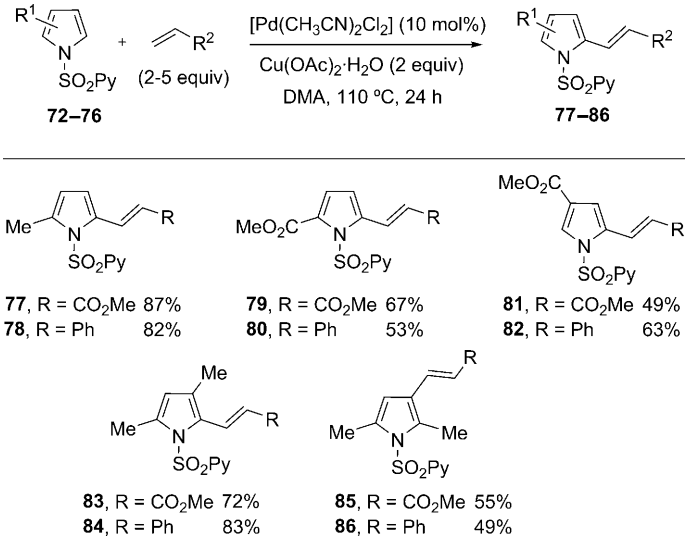
with a different olefin, such as *tert*-butyl acrylate (product **69**, 71% yield), or styrene (**70**, 63% yield, Scheme 4). Disappointingly, these conditions for selective monoalkenylation at C2 could not be extended to other olefins. For example, the reaction of **61** with *tert*-butyl acrylate afforded a 38:10:52 mixture of the monoalkenylation product, dialkenylated **63** and starting material **61**, whereas the reaction of **61** with styrene led to a 50:50 mixture of the corresponding dialkenylation product **65** along with the pyrrole starting material **61**.

As a final example of the alkene counterpart, we studied the reaction with a challenging 1,2-disubstituted alkene, (*E*)-methyl crotonate (Scheme 5). Interestingly, although the reactivity was much lower (50% conversion after 24 h), the monoalkenylation product **71** could be isolated in moderate yield with only the *E* stereoisomer formed (45% isolated yield).



Scheme 5. C2 alkenylation of pyrrole **61** with (*E*)-methyl crotonate.

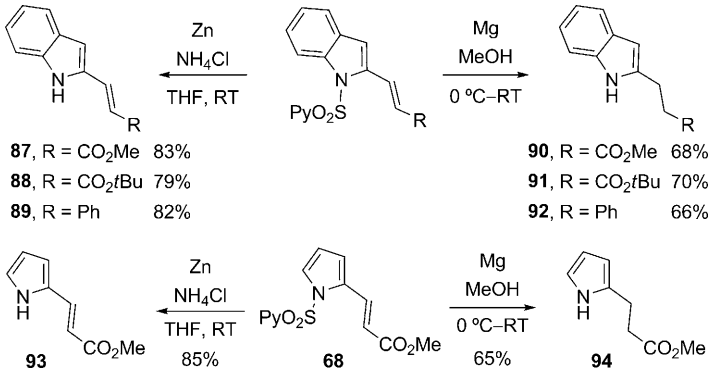
Finally, we undertook a study of the influence of the substitution pattern of the pyrrole ring (substrates **72–76**) by using methyl acrylate and styrene as model olefins (Scheme 6). For the α-substituted pyrroles **72** and **73**, acceptable to good yields were obtained of the expected C2 alkenylated pyrroles **77–80** (53–87% yield), albeit the electronically poorer pyrrole **73** (products **79** and **80**) proved to be less reactive than the methyl-substituted pyrrole **72** (products **77** and **78**). On the other hand, the procedure also tolerated the presence of substitution at the β position. Thus, pyrroles **81–84** were isolated in satisfactory yields (49–83%) from the β-substituted pyrroles **74** and **75**. In the case of ester-substituted pyrrole **74**, only C2 alkenylation at the electronically more reactive, least hindered α position was observed (formation of the 2,4-disubstitued pyrroles **81** and **82**). As a last example of pyrrole substitution, 2,5-dimethyl pyrrole **76**, which has both "C2 positions" blocked, reacted at C3, albeit with much lower reactivity (products **85** and **86**). This behaviour parallels that previously observed for 2-methyl-substituted indole **58** (see Scheme 3).



Scheme 6. Structural variations at the pyrrole.

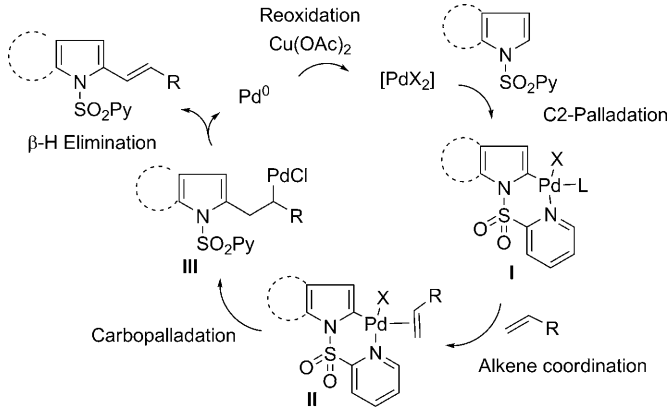
The simple reductive removal of the 2-pyridylsulfonyl group to generate the free NH indoles allowed us to realise the full synthetic utility of this method (Scheme 7). Interestingly, the sulfonyl cleavage can be directed to the selective formation of either C2-alkenyl or C2-alkyl indoles (products **87–89** and **90–92**, respectively),[36] depending upon the reducing agent used (Zn or Mg, respectively). This deprotection can also be applied to pyrrole derivatives with comparable efficiency, as exemplified by the transformation of **68** into the known derivatives **93** and **94**.[36]

The significant activation brought about by the 2-pyridylsulfonyl group suggests an auxiliary-controlled, direct cyclopalladation at the C2 of indole (or pyrrole), facilitated by coordination of palladium(II) to the nitrogen in the 2-pyri-



Scheme 7. Deprotection of 2-alkenyl-*N*-(2-pyridyl)sulfonyl indoles and pyrroles.

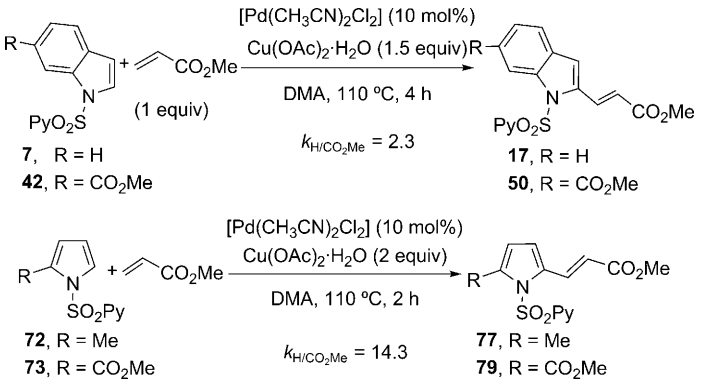
dylsulfonyl group to form a six-membered ring, producing palladacycle **I**[37] (Scheme 8). Coordination of the olefin (intermediate **II**) followed by 1,2-migratory insertion would



Scheme 8. Proposed simplified catalytic cycle for the selective C2 alkenylation reaction.

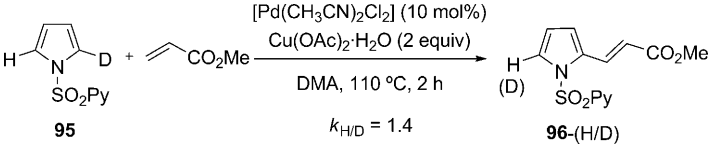
lead to alkyl–Pd intermediate **III**, which would rapidly evolve through β-hydride elimination to afford the alkenylation product. Finally, $Cu(OAc)_2$ is assumed to play the role of oxidant, converting Pd^0 into Pd^{II} in order to close the catalytic cycle. In full agreement with the *syn* character of the carbopalladation and β-hydrogen elimination steps, the alkenylation reactions with (*E*)-methyl crotonate afforded stereoselectively the trisubstituted alkenes of *E* configuration (indole **36** and pyrrole **71**).

In general terms, the key carbopalladation step may proceed through different pathways: primarily either a σ-bond metathesis (concerted metallation–deprotonation) or electrophilic aromatic-type substitution (S_EAr). To gain insight into the pathway involved in this case, some mechanistic experiments were designed. Since indoles and pyrroles are known to be very reactive in a variety of electrophilic aromatic-type substitution processes and, consequently, are very sensitive to the electronic effect of the substituents, we performed some competitive experiments between electronically varied substrates. Under the standard conditions, an equimolar mixture of unsubstituted indole **7**, the electron-deficient indole **42** and methyl acrylate was subjected to the Pd-catalysed reaction conditions for 4 h (Scheme 9). This experiment revealed that the more nucleophilic substrate **7** reacted preferentially to give the major component (**17**) of the mixture of products (**17**/**50**, $k_H/k_{CO_2Me}=2.3$). As expected from this result, a more distinct trend was observed for the pyrrole series in which the substituents are directly bonded to the reactive aromatic ring; the reaction of an equimolar mixture of 2-methyl-substituted pyrrole **72**, 2-methoxycarbonyl derivative **73** and methyl acrylate provided the alkenylation product **77** with high selectivity, arising from the reaction of the more electron-rich pyrrole **72** (**77**/**79**, $k_{Me}/k_{CO_2Me}=14.3$).[38] The strong dependence of the reactivity on the electronic character of the reactive aromatic substrate suggests the participation of an electrophilic palladation pathway in the formation of the apparently key palladacycle **I**.



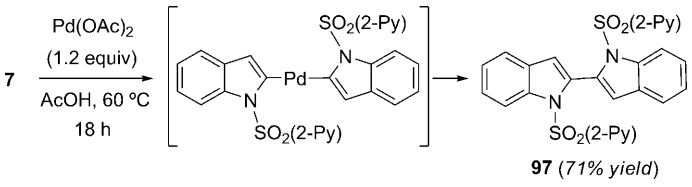
Scheme 9. Kinetic competitive experiments.

Further evidence of an electrophilic palladation mechanism was achieved by studying the kinetic isotope effect in C2 monodeuterated pyrrole derivative **95**.[39] As shown in Scheme 10, a value of 1.4 was obtained for k_H/k_D from the ^1H NMR spectrum of the reaction of monodeuterated pyrrole **95** with methyl acrylate under the normal reaction conditions (DMA, 110 °C, 2 h, 20% conversion). A similar, small kinetic isotopic effect has previously been described in some C2 arylation reactions of indoles, which is in accordance with an electrophilic palladation pathway, rather than a direct C–H activation process.[40]



Scheme 10. Intramolecular kinetic isotope effect on monodeuterated pyrrole **95**.

In an attempt to isolate a palladacycle intermediate (type **I** or related species), indole **7** was heated (60 °C) with $Pd(OAc)_2$ (1.2 equiv) in AcOH for 18 h.[41] Instead of a palladacycle, 2,2′-biindolyl **97** was formed cleanly and isolated in 71 % yield (Scheme 11). The molecular structure of compound **97** was confirmed by X-ray crystallography[42] (Figure 1). We speculate that due to the facile C2 palladation, in the absence of an alkene component, the initial palladacycle **I** evolves by forming a C2 palladated bisindolyl intermediate, which would afford **97** through reductive elimination.[43]



Scheme 11. $Pd(OAc)_2$-promoted oxidative homocoupling of indole **7** to form 2,2′-biindolyl **97**.

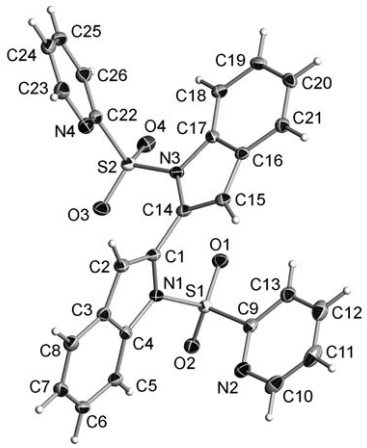
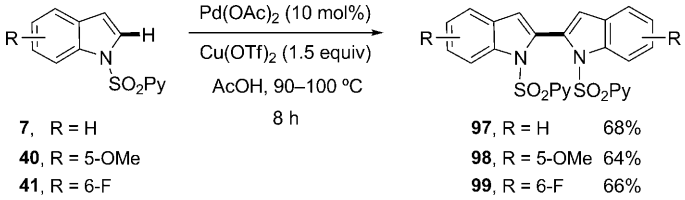


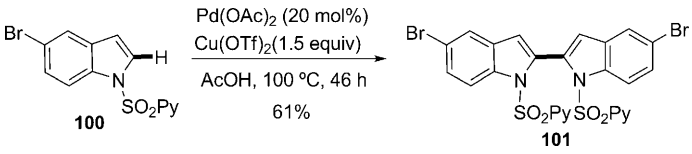
Figure 1. X-ray crystal structure of compound **97**.

The efficient conversion of indole **7** into 2,2′-biindolyl **97** with complete regiocontrol led us to focus on developing a catalytic variant of this dehydrogenative homocoupling of indoles (Scheme 12). The oxidative homocoupling of indoles to give 2,3′-biindoles has been reported recently,[18] but, to the best of our knowledge, the complementary homocoupling to give 2,2′-biindoles is unknown. After extensive optimisation experiments with a variety of palladium salts, oxidants and solvents, we found that the use of $Pd(OAc)_2$ (10 mol %) in the presence of $Cu(OTf)_2$ (1.5 equiv; OTf = triflate)/O_2 (1 atm) in AcOH at 90–100 °C for 8 h were the optimal conditions. In particular, the choice of $Cu(OTf)_2$ as co-oxidant[44] and AcOH as solvent[45] proved to be crucial for achieving a clean process and high conversions (68 % isolated yield of **97**). These conditions were then applied to other *N*-(2-pyridyl)sulfonyl indole derivatives. As shown in Scheme 12, the reaction tolerates electronically varied substitution patterns of the indole unit (products **98** and **99**, 64–66 % yield).



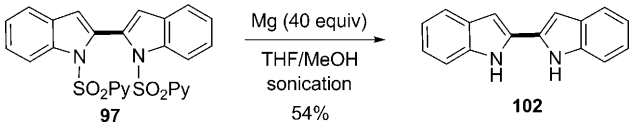
Scheme 12. Catalytic dehydrogenative intermolecular homocoupling to form 2,2′-biindoles.

Interestingly, 5-bromoindole **100** also proved to be amenable to these conditions, although it showed decreased reactivity and required higher catalyst loading (20 mol % of $Pd(OAc)_2$) and a prolonged reaction time (51 h) for complete conversion to product **101** (62 % isolated yield, Scheme 13). The bromine substitution in product **101** is synthetically valuable, offering new opportunities for selective functionalisation through standard cross-coupling strategies.



Scheme 13. Synthesis of 5,5′-dibromo-2,2′-biindolyl compound **101**.

The feasibility of the cleavage of the two *N*-(2-pyridyl)sulfonyl groups of the 2,2′-biindolyl system was demonstrated for compound **97**, for which deprotection with excess Mg turnings in MeOH led to free NH-2,2′-biindole **102** in 54 % yield (Scheme 14).



Scheme 14. Cleavage of the *N*-(2-pyridyl)sulfonyl groups in 2,2′-biindolyl systems.

Conclusion

We have demonstrated the excellent ability of the *N*-(2-pyridyl)sulfonyl group to function as a directing group for the direct C2–H functionalisation of indoles and pyrroles and its facile elimination by N–S reductive cleavage. An efficient Pd^{II}-catalysed regioselective alkenylation of indoles and pyrroles affording the corresponding products in good isolated yields (typically ≥70 %) and with complete regiocontrol for the C2 position is described. A remarkable feature of this methodology is that it displays high structural versatility with regard to both substitution of the heterocycle and the

alkene (including conjugated electron-deficient alkenes, styrenes and 1,3-dienes, as well as conjugated 1,1- and 1,2-disubstituted olefins). Two reductive desulfonylation protocols have been developed to afford either the C2-alkenylated or C2-alkylated NH products in good yield. In addition, by using the same sulfonyl directing group, we performed the catalytic, dehydrogenative, intermolecular homocoupling of indole derivatives to give 2,2′-biindolyl systems in good yields and with complete regiocontrol. Mechanistic investigations based upon reactions with isotopically labelled starting materials and competitive kinetic studies suggest an electrophilic aromatic pathway for the key palladation step. We anticipate that this, and related metal-coordinating, heteroaryl sulfur-based groups, have great potential as activating and removable scaffolds to open up new perspectives in the area. Extension of this concept to other C–H functionalisations is underway.

Experimental Section

Representative procedure for direct C–H alkenylation:

The conversion of *N*-(2-pyridyl)sulfonyl indole (7) into methyl 3-[*N*-(2-pyridylsulfonyl)indol-2-yl]acrylate (17): A screw-capped test tube was charged with **7** (25.8 mg, 0.1 mmol), $[PdCl_2(CH_3CN)_2]$ (2.6 mg, 10 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (20.0 mg, 0.1 mmol). The mixture was placed under a nitrogen atmosphere, then DMA (1 mL) and methyl acrylate (16.8 μL, 0.2 mmol) were added. This mixture was heated to 110 °C for 8 h, and was then allowed to cool to room temperature, diluted with EtOAc (10 mL) and washed with water (3×5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtAcO, 9:1) to afford **17** as a yellow solid (25.6 mg; 75%; m.p. 197–199 °C; see the Supporting Information for spectroscopic data).

Representative procedure for the dehydrogenative homocoupling to form 2,2′-biindoles:

The conversion of *N*-(2-pyridyl)sulfonyl indole (7) into *N,N′*-bis(2-pyridylsulfonyl)-2,2′-biindole (97): A screw-capped test tube was charged with **7** (51.6 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and $Cu(OTf)_2$ (108.5 mg, 0.3 mmol), followed by addtion of AcOH (2 mL). Then O_2 was bubbled into the mixture for 5 min. The mixture was then heated to 90–100 °C for 8 h, before it was allowed to cool to room temperature, diluted with CH_2Cl_2 (20 mL) and washed successively with NH_4OH (2× 10 mL), sat. aq NH_4Cl (10 mL) and sat. aq NaCl (10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was diluted with CH_2Cl_2 (10 mL) and passed through a pad of Celite with a thin layer of silica gel on top. The filtrate was concentrated to dryness to afford **97** as a light brown solid (35.1 mg; 68%; m.p. 257–259 °C; see the Supporting Information for spectroscopic data).

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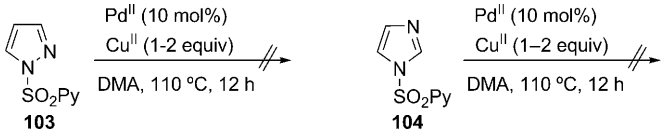
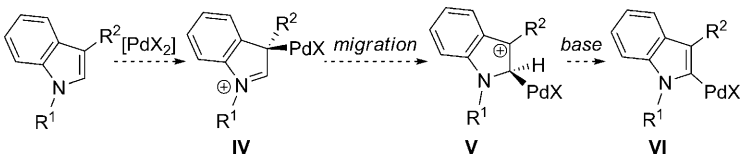
[35] No reaction was observed when we tried the alkenylation of the sulfonyl pyrazole and imidazole derivatives **103** and **104** (see image below). The lack of reactivity shown by these substrates can be ascribed to their considerably more electron-poor nature compared with indoles and pyrroles in an S_EAr mechanism and/or the presence of an additional basic N atom that could bind to Pd and inhibit catalysis.



[36] Compounds **87**–**94** are known. See the Supporting Information for details.

[37] Catalytic palladation at C2 in NH and NMe indoles has been proposed (refs. [21a] and [40a]) to occur via initial palladation at C3 to give intermediate **IV**, followed by migration of the C3−PdX bond in **IV** to the highly activated 2 position of the iminium intermediate to give **V** and ultimately **VI** by proton abstraction (see image below). Although this type of migration mechanism cannot be discarded, it seems unlikely in light of the participation of 3-*tert*-butyl indole derivative **45** in the C2 alkenylation (products **56** and **57**, Scheme 2), which would involve the initial formation of a highly sterically congested iminium intermediate of type **IV** with an electron-withdrawing N substituent ($R^1 = SO_2Py$, $R^2 = t$Bu). On the other hand, C2 palladation of indoles containing a strongly directing group with stoichiometric amounts of the palladium source have also been reported, see: a) S. Tollari, F. Demartin, S Cenini, G. Palmisano, P. Raimondi, *J. Organomet. Chem.* **1997**, *527*, 93; b) M. Nonoyama, K. Nakajima, *Polyhedron* **1998**, *18*, 533. See also reference [21b].



[38] Under the conditions previously developed for selective monoalkenylation (CH_3CN, 80 °C), only the more electron-rich substrate **72** gave olefination product **77**, while the electron-poor pyrrole **73** remained unaltered.

[39] This compound was prepared in three steps from *N*-*tert*-butoxycarbonyl-2-bromopyrrole by halogen/lithium exchange with *n*BuLi and

subsequent deuteration with CD_3OD (74%), then N-deprotection with NaOMe followed by N-sulfonylation with 2-$PySO_2Cl$/NaH (55% over the last two steps). Attempts to effect direct bromo/lithium exchange from 2-bromo-*N*-(2-pyridyl)sulfonyl pyrrole resulted in competitive deprotonation at the pyridyl ring. See the Supporting Information for experimental details.

[40] A similar kinetic isotope effect has been observed in Pd^{II}-catalysed C2–H arylation of indoles: a) B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050. For related results in other aromatic systems, see: b) J.-J. Li, R. Giri, J.-Q. Yu, *Tetrahedron* **2008**, *64*, 6979; c) S. Chuprakov, N. Chernyak, A. S. Dudnik, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 2333; for mechanistic studies supporting a concerted metallation/proton abstraction in Pd-catalysed arylations, see, for instance: d) S. Pascual, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *Tetrahedron* **2008**, *64*, 6021; e) D. García-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880; f) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848; g) Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, C. Qin, Y. Wang, *Angew. Chem.* **2007**, *119*, 5650; *Angew. Chem. Int. Ed.* **2007**, *46*, 5554; see also reference [23i].

[41] Attempts to access such palladacycles by oxidative addition to 2-bromo-*N*-(2-pyridyl)sulfonyl indole resulted in the formation of complex mixtures.

[42] CCDC-736591 [unit cell parameters: $a=8.4276(2)$, $b=11.8616(2)$, $c=12.3533(3)$ Å, $\alpha=105.9180(10)$, $\beta=106.289(2)$, $\gamma=91.296(2)°$, space group $P\bar{1}$] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[44] Other co-oxidants including $Cu(OAc)_2$, AgOAc, benzoquinone, $PhI(OAc)_2$, oxone and *t*BuOOH led to very low conversions (<10%), whereas $Ce(SO_4)_2$ provided slightly lower reactivity than $Cu(OTf)_2$.

[45] The use of AcOH proved to be essential for achieving high conversions, since other polar solvents, such as DMA, DMSO, DMF, CH_3CN or *t*BuOH, resulted in conversions lower than 20%. Propionic acid was similarly effective, but not TFA.

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