C–H Alkenylation

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Palladium(II)-Catalyzed Regioselective Direct C2 Alkenylation of Indoles and Pyrroles Assisted by the *N*-(2-Pyridyl)sulfonyl Protecting Group**

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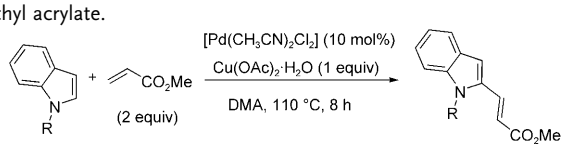
Driven by its synthetic power and environmental friendliness, C–C bond-forming reactions through catalytic activation of C_{sp^2}–H bonds constitutes a hot area of research.[1] Since the pioneering work by Murai et al.[2] and Fujiwara and co-workers,[3] remarkable progress has been made in this field, with palladium occupying a prevalent position.[4] Most of these procedures rely on the use of a coordinating functionality that aids in the transition metal mediated functionalization of a proximal C–H bond. However, from a synthetic viewpoint, the practicality of the directing groups can be compromised when the target molecule does not contain such functionality. Therefore, the discovery of efficient and removable directing groups is in high demand.[5]

Owing to the prevalence of the indole unit in pharmaceuticals and bioactive natural products, its regioselective C–H functionalization represents an important challenge in this area. In contrast to the much more developed C–H arylation reactions,[6] direct alkenylations have received much less attention.[7–10] A particularly challenging transformation is the intermolecular direct alkenylation at the C2-position, for which only three protocols have been reported.[7] Ricci and co-workers reported the palladium(II)-catalyzed regiocontrolled C2 alkenylation of indole directed by a nonremovable *N*-2-pyridylmethyl group.[7a] Gaunt and co-workers described a practical method for the palladium(II)-catalyzed alkenylation of indoles (without an N-protecting group) in which the regioselectivity can be switched from C3 to C2 by varying the nature of the solvent and additives.[7b] However, decreased reaction yield was found in C2 alkenylation. Miura, Satoh et al. disclosed the palladium(II)-catalyzed C–H alkenylation/decarboxylation of indole-3-carboxylic acids to afford exclusively 2-alkenyl indoles, where the carboxyl group blocks the C3-position and acts as a removable directing group.[7c] Despite these important advances there is room for innovation, both in increasing the efficiency of the reaction and in improving the current limited scope with regard to both the alkene component and directing group. To date, only monosubstituted electrophilic alkenes (mainly acrylates) have been applied in the C2 alkenylation of indoles, except for one isolated example of coupling with styrene.[7c] We disclose herein a highly efficient and structurally versatile palladium(II)-catalyzed C2 alkenylation of indoles and pyrroles employing the easily installed and removed *N*-(2-pyridyl)sulfonyl directing group.[11]

Given the electrophilic nature of the palladium(II) center, our first challenge was to find an N-protecting group for the C2 functionalization of indole instead of the more nucleophilic C3-position. A set of potential directing groups were examined in the reaction of derivatives **2**–**7** with methyl acrylate under $[Pd(CH_3CN)_2Cl_2]$ catalysis (10 mol%) using $Cu(OAc)_2{\cdot}H_2O$ (1 equiv) as an oxidant in DMA at 110°C (Table 1).[12] Not unexpectedly, under such conditions the indole **1** cleanly underwent C3 alkenylation with complete regiocontrol (Table 1, entry 1).[7b,c,9] In contrast, the Boc-protected derivative **2** led to a 68:32 mixture of C2/C3 alkenylation products, in very low conversion (Table 1, entry 2). Both C2 regioselectivity and conversion were enhanced by switching to a Ts group (Table 1, entry 3) or a *p*-Ns group (Table 1, entry 4), albeit at an unpractical level. *N*-Heteroarylsulfonyl groups strongly influenced the reactivity and regiocontrol. For example, the *N*-(2-thienyl)sulfonyl group in **5** led to low conversion and no regiocontrol

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



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

[a] Determined by ^{1}H NMR methods from the reaction mixture. [b] Conversion yield (^{1}H NMR) of C2-alkenylation product. In parenthesis, yield of product isolated after chromatography (regioisomeric mixtures could not be separated). [c] In the C3–H alkenylation product. Boc = *tert*-butoxycarbonyl, Ts = *para*-toluenesulfonyl, *p*-Ns = *para*-nitrobenzenesulfonyl.

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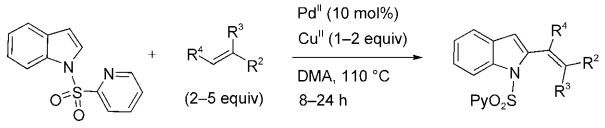
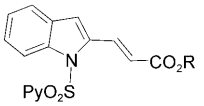
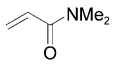
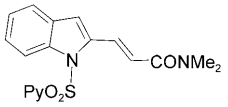
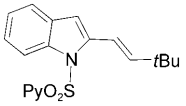
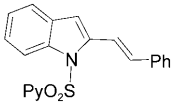
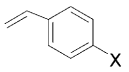
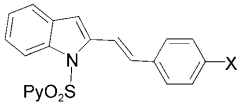
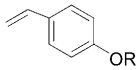
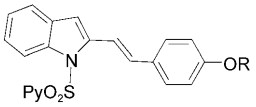
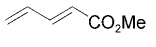
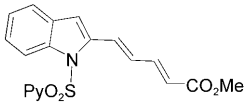
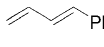
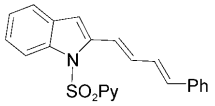
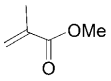
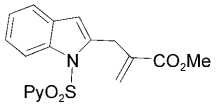
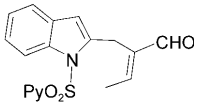
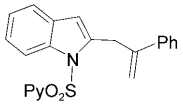
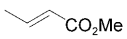
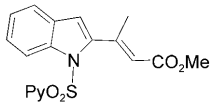
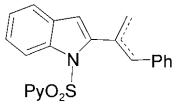
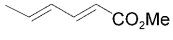
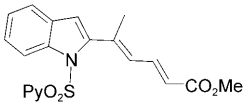
Table 2: Olefin scope in the C2 alkenylation of indole **7**.[a]



Entry	Alkene	Product		Yield [%][b]
1			**17**: R = *n*Bu	72
2			**18**: R = *t*Bu	78
3			**19**	45 (83)[c]
4			**20**	57
5			**21**	85
6			**22**: X = F	68
7			**23**: X = Br	74
8			**24**: R = Ac	75
9			**25**: R = Me	80
10			**26**	68
11			**27**	65
12			**28**[e]	72
13			**29**[d,e]	70
14			**30**[e]	71
15			**31**[d]	60
16			**32** + **33**[e] (40:60)	68
17			**34**[d]	60

[a] Reaction conditions: **7** (0.1 mmol), alkene (2–5 equiv), [Pd(CH$_3$CN)$_2$Cl$_2$] (10 mol%), Cu(OAc)$_2$·H$_2$O (1–2 equiv), DMA, 110°C, 8–24 h. [b] Yield of product isolated after chromatography. [c] Yield in parentheses based on recovered indole **7**. [d] Obtained as a single diastereomer (see the Supporting Information for structure determination). [e] Compounds are the double bond isomers of the alkenylation product. DMA = dimethylacetamide.

(Table 1, entry 5), whereas the 8-quinolylsulfonylindole (**6**) showed improved reactivity, yet modest regioselectivity (Table 1, entry 6). Pleasingly, *N*-(2-pyridyl)sulfonylindole (**7**) provided complete conversion and C2 regiocontrol affording **15** in 75% yield upon isolation (Table 1, entry 7). The low conversion and poor regiocontrol (Table 1, entry 8) displayed by 3-pyridylsulfonylindole (**8**), an isomer of **7**, highlights the key role of the 2-pyridylsulfonyl group as directing group in the C2 alkenylation, which likely occurs through stabilization of a cyclopalladated intermediate.[13,14]

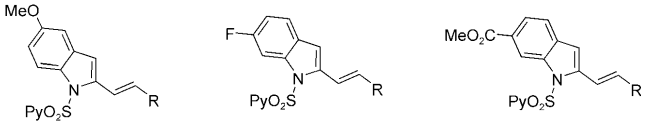
We next studied the effect of electronic and structural variations on the alkene (Table 2). A variety of monosubstituted alkenes, not only electrophilic alkenes (Table 2, entries 1–3) but also the more challenging non-activated *tert*-butylethylene (Table 2, entry 4) and styrene derivatives (Table 2, entries 5–9), coupled efficiently with the indole **7** to give the corresponding alkenylation products with excellent regiocontrol and *E* stereoselectivity in synthetically useful yields (typically 70–85%). The electronic nature of the substituents on the phenyl ring of the styrene-type substrates has no significant effect on the reactivity.

This protocol can be also applied to 1,3-dienes, a type of olefin which is rarely employed in C–H alkenylations.[5i,15] The coupling of **7** with methyl-2,4-pentadienoate (Table 2, entry 10) and 1-phenyl-1,3-butadiene (Table 2, entry 11) proceeded at the terminal double bond to give the 2-dienyl indoles **26** and **27**, respectively, in good yields. Alkenes with higher substitution are also suitable. Good results were obtained with 1,1-disubstituted alkenes, such as methyl methacrylate, α-ethylacrolein, or α-methylstyrene, providing the corresponding double bond isomerized alkenylation products **28**, **29**, and **30**, respectively, (Table 2, entries 12–14). Particularly remarkable is the participation of 1,2-disubstituted alkenes, given the

few precedents and lower reactivity of this kind of olefins in oxidative alkenylation (Fujiwara–Moritani) reactions.[10a,16] Under the standard reaction conditions, (*E*)-methyl crotonate and (*E*)-propenylbenzene underwent smooth reaction with indole **7** to provide the corresponding trisubstituted alkene products **31** (60% yield, Table 2, entry 15) and **32** + **33** (68% yield), respectively; in the latter case a 40:60 mixture of double bond isomerization products was present (Table 2, entry 16). The more challenging methyl-(*E*,*E*)-hexa-2,4-dienoate reacted at the distal double bond to give in acceptable yield the dienyl indole **34** with complete stereocontrol (Table 2, entry 17).

Scope at the indole counterpart was explored with methyl acrylate and styrene as model olefins (Table 3). Electron-withdrawing or electron-donating groups at C5, C6, or C7 of

Table 3: Structural variations on the indole counterpart.[a]



35: R = CO_2Me, 73%
36: R = Ph, 97%
37: R = CO_2Me, 85%
38: R = Ph, 95%
39: R = CO_2Me, 76%
40: R = Ph, 81%
41: R = CO_2Me, 70%
42: R = Ph, 85%
43: R = CO_2Me, 81%
44: R = Ph, 68%
45: R = CO_2Me, 47%
46: R = Ph, 35%

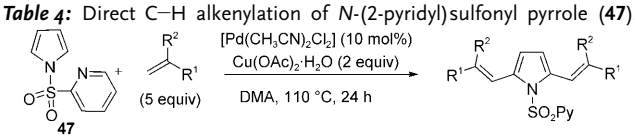
[a] Reaction conditions: *N*-SO_2Py-indole (0.1 mmol), [$Pd(CH_3CN)_2Cl_2$] (10 mol%), $Cu(OAc)_2{\cdot}H_2O$ (1–2 equiv), alkene (2–5 equiv), DMA, 110°C, 8–24 h.

the indole ring did not have a significant impact in the reactivity (products **35**–**42**). The reaction even tolerates substitution at C3, as demonstrated in the case of 3-methylindole (products **43** and **44**). This is remarkable, as the C2 functionalization of 3-substituted indoles to give 2,3-disubstituted products still remains an important challenge.[17] Blocking the reactive C2-position with a methyl group resulted in the formation of the C3-alkenylation products, albeit in much lower yields (products **45** and **46**). In all cases studied, no C7-substituted products were detected.

Encouraged by these results, we decided to test the versatility of the 2-pyridylsulfonyl group in the alkenylation of other nitrogen heterocycles. We focused our efforts on extending this methodology to pyrrole derivatives, which rival indoles in biological significance and as valuable synthetic intermediates.[18] This skeleton has received much less attention that indoles in direct C–H functionalization reactions, possibly because of its lower stability under harsh oxidative conditions. Gaunt and co-workers have reported a mild 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.[10a]

Table 4 shows the feasibility of the C2 alkenylation of pyrroles aided by the *N*-(2-pyridyl)sulfonyl group.[19] Under

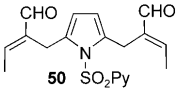
Table 4: Direct C–H alkenylation of *N*-(2-pyridyl)sulfonyl pyrrole (**47**).



47; (5 equiv); [$Pd(CH_3CN)_2Cl_2$] (10 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2 equiv), DMA, 110 °C, 24 h

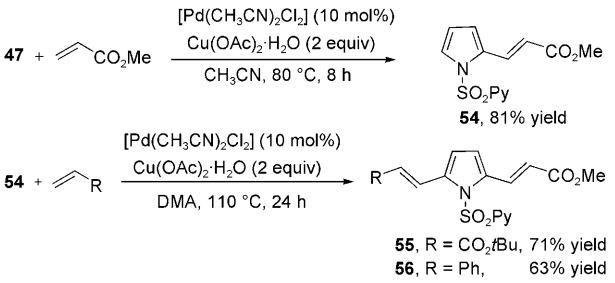
Entry	R^1	R^2	Product	Yield [%][a]
1	CO_2nBu	H	**48**	80
2	CO_2tBu	H	**49**	79
3	CHO	Et	**50**[c]	65
4	Ph	H	**51**	55 (82)[b]
5	4-FC_6H_4	H	**52**	69
6	*t*Bu	H	**53**	62

[a] Yield of product isolated after chromatography. [b] Yield in parentheses based on recovered pyrrole **47**. [c] See structure below.



50 CHO, CHO, SO_2Py

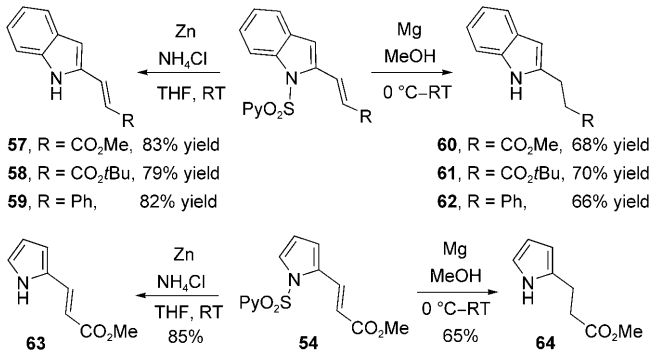
the optimized conditions, pyrrole **47** cleanly produced the corresponding products of double alkenylation at C2 and C5 (**48**–**53**) in acceptable to good yields. In all cases the C3 alkenylation product was not detected. Electronically varied olefins including acrylates (Table 4, entries 1 and 2) and α-ethylacrolein (Table 4, entry 3), styrenes (Table 4, entries 4 and 5) and a non-activated olefin such as 3,3-dimethyl-1-butene (Table 4, entry 6) are suitable olefin substrates. The selective C2 monoalkenylation of **47** with methyl acrylate was efficiently achieved under milder reaction conditions[20] (CH_3CN, 80°C, 8 h), affording pyrrole **54** in 81% yield (Scheme 1). This provides access to unsymmetrical 2,5-



Scheme 1. Regioselective sequential C2/C5 double alkenylation.

disubstituted pyrroles by subsequent C5 alkenylation with a different olefin, such as *tert*-butyl acrylate or styrene (Scheme 1; products **55** and **56**, respectively).

The easy reductive removal of the 2-pyridylsulfonyl group to generate the unprotected indoles led us to realize the full synthetic utility of this method, and it served as a chemical correlation to confirm the structure of the C2-alkenylation products[21] (Scheme 2). Interestingly, the sulfonyl removal can be directed to the selective formation of either the C2-alkenyl or the C2-alkyl indoles **57**–**59** and **60**–**62**, depending on the reducing agent used (Zn or Mg, respectively). This deprotection can also be applied to the pyrrole derivatives with comparable efficiency, as exemplified in the transformation of **54** into the known derivatives **63** and **64**.[21]



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

In summary, an efficient palladium(II)-catalyzed regioselective C2 alkenylation of indoles and pyrroles displaying high structural versatility with regard to the substitution at the alkene is described. This protocol strongly relies on the use of the *N*-(2-pyridyl)sulfonyl group as both an activating group and a readily removable protecting group. Mechanistic investigations and extension of this concept to other C–H functionalizations are underway.

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Keywords: alkenylation · C–H activation · heterocycles · palladium · sulfonyl protecting groups

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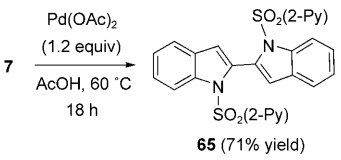
[12] See the Supporting Information for catalyst system optimization studies.

[13] In an attempt to isolate a possible palladacycle intermediate, indole **7** was heated (60 °C) with $Pd(OAc)_2$ (1.2 equiv) in AcOH for 18 hours. Instead of the palladacycle, the 2,2′-bis(indolyl) **65** was cleanly formed (71 % yield, see scheme below). Product **65** was structurally characterized by X-ray diffraction analysis (see the Supporting Information). We speculate that a C2-palladated bis(indolyl) intermediate is formed, but it rapidly evolves through reductive elimination to afford **65**. For stoichiometric $Pd(OAc)_2$-promoted intramolecular 2,2′-oxidative coupling of *N*,*N*′-carbonylindole, see: J. Bergman, N. Eklund, *Tetrahedron* **1980**, *36*, 1439.



[14] CCDC 736591 (**65**) [Unit cell parameters: a 8.4276(2) b 11.8616(2) c 12.3533(3) alpha 105.9180(10) beta 106.289(2) gamma 91.296(2) space group P-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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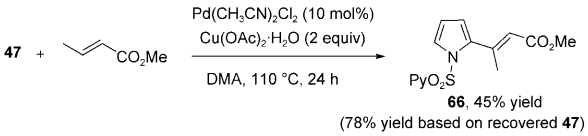
[19] The reaction of *N*-tosyl pyrrole with methyl acrylate led to less than 10% conversion of monoalkenylation product at C2 under the conditions shown in Table 4, highlighting the directing role of the 2-pyridylsulfonyl group.

[20] A 1,2-disubstituted alkene such as the (*E*)-methyl crotonate also afforded the monoalkenylation product **66** with 50% conversion [45% yield (isolated)]:



66, 45% yield
(78% yield based on recovered **47**)

[21] Compounds **57**–**59**, and **60**–**64** were known. See the Supporting Information for details.