Oxidative Heck Reaction

Palladium-Catalyzed Intermolecular Alkenylation of Indoles by Solvent-Controlled Regioselective C–H Functionalization**

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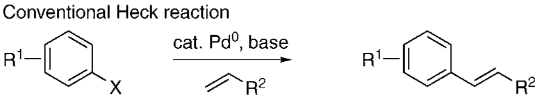
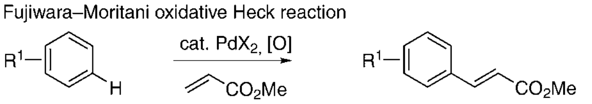
Over the past three decades the Heck reaction has become one of the most fundamental metal-catalyzed C–C bond-forming processes for the synthesis of complex molecules.[1] It has had a huge impact on organic synthesis despite the disadvantage that the overall coupling of the two fragments requires two discrete activation steps: 1) the formation of an aryl or vinyl halide and 2) the palladium(0)-catalyzed union of the reaction partners [Eq. (1)]. A direct oxidative Heck reaction would bypass the need for preactivated reaction partners and lead to a more efficient process. To this end, Fujiwara, Moritani et al. developed an efficient coupling of arenes and activated alkenes through an oxidative palladium(II)-catalyzed process, and this transformation has found widespread use in synthesis [Eq. (2)].[2]



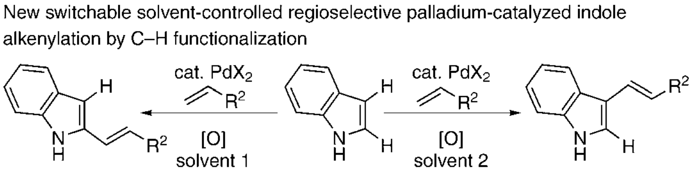
(1)



(2)

We are interested in the development of catalytic processes that exploit selective and controllable C–H functionalization[3] to elaborate simple aromatic compounds to useful products. The catalytic functionalization of aromatic heterocycles is an important transformation, and methods for the synthesis and elaboration of indoles in particular have received significant attention.[4] The indole motif is a ubiquitous feature of alkaloid and peptide natural products and represents an important structural element for the pharmaceutical industry. As a result, many useful and practical processes exist for the modification of the indole structure, and, as previously mentioned, metal-catalyzed coupling reactions are of particular utility, although these methods often require a prefunctionalized indole unit for each elaboration.[4,5] Surprisingly, the development of an oxidative C3 alkenylation of free (NH) indoles has received little attention,[6] and to the best of our knowledge there is no example of an intermolecular oxidative C2 alkenylation of a free (NH) indole.[7] Nor is there a method to select between the two positions of the important fundamental motif. Herein we describe a general direct oxidative Heck reaction that exploits a novel, selective, solvent-controlled, palladium-catalyzed C–H functionalization of free (NH) indoles and leads to the elaboration of the heteroaromatic core at either the 2- or the 3-position [Eq. (3)].

The natural reactivity of indole suggested that palladation and Heck coupling would take place preferentially at the 3-



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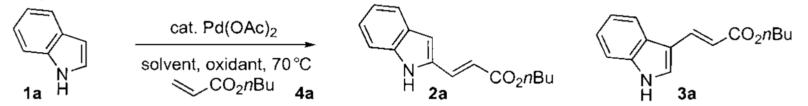
position.[6] However, we speculated that it might be possible to control the selectivity of the reaction by the use of different solvents and additives. Fundamental to this hypothesis was the knowledge that the migration of groups from the 3- to the 2-position of indole has been observed in the alkylation of 3-substituted indoles (Scheme 1).[8] By analogy, we anticipated that a migration of the C3–PdX bond to the 2-position would enable a complementary C–H functionalization process.

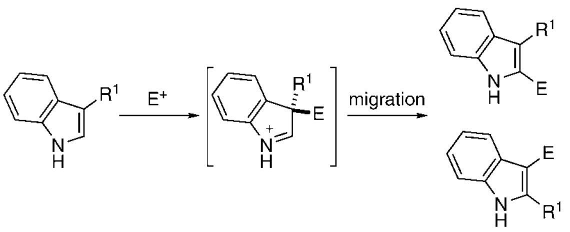
We began by screening the reaction between indole (**1a**, R^1 = H) and *n*-butyl acrylate (**4a**) in the presence of $Pd(OAc)_2$ as a catalyst with a variety of solvents and $Cu(OAc)_2$ as the oxidant.[9] Reactions in polar solvents gave exclusively the C3-functionalized indoles **3a** (Table 1, entries 1–2), except when 1,4-dioxane was used (Table 1, entry 3), in which case no reaction was observed, perhaps because of the insolubility of $Cu(OAc)_2$ in this solvent. The use of *tert*-butyl benzoyl peroxide (*t*BuOOBz) as the soluble reoxidizing agent, however, led to a reaction in 1,4-dioxane, but with a surprising reversal of selectivity to produce a 2:1 mixture of the C2- and C3-substituted indoles **2a** and **3a**, respectively (Table 1, entry 4). Careful monitoring of the reaction showed that **3a** predominated at the beginning of the reaction with **2a** only starting to form as the reaction proceeded. Benzoic acid is produced as a result of the reoxidation of Pd^0 by *t*BuOOBz, and it was believed that the increasing concentration of acid may be responsible for the switch in selectivity as the reaction progresses. This hypothesis was supported by the result of the reaction in DMF/AcOH, which led to a 1:1 mixture of isomers (Table 1, entry 5), whereas only **3a** was formed in DMF alone. To our delight, the use of AcOH as a cosolvent with 1,4-dioxane led to a 7:1 ratio of **2a**:**3a** (Table 1, entry 6) and demonstrated that the regioselectivity of palladium-catalyzed indole alkenylation could be controlled.

Table 1: Optimization studies for indole functionalization.[a]



Entry	Catalyst loading [%]	Oxidant (equiv)	Solvent (*v*/*v*)	Yield of **2**+**3** [%][b]	**3a**/**2a**
1	10	$Cu(OAc)_2$ (1.8)	DMF	54	>95:5
2	10	$Cu(OAc)_2$ (1.8)	DMSO	66	>95:5
3	10	$Cu(OAc)_2$ (1.8)	1,4-dioxane	n.r.	–
4	10	*t*BuOOBz (0.9)	1,4-dioxane	48	1:2
5	10	$Cu(OAc)_2$ (1.8)	DMF/AcOH (3:1)	54	1:1
6	20	*t*BuOOBz (0.9)	1,4-dioxane/AcOH (3:1)	58	1:7
7	10	$Cu(OAc)_2$ (1.8)	DMF/DMSO (10:1)	79	>95:5
8	10	*t*BuOOBz (0.9)	MeCN/AcOH (3:1)	65	>95:5
9	10	*t*BuOOBz (0.9)	1,4-dioxane/AcOH/DMSO (3:1:0.4)	66	>95:5

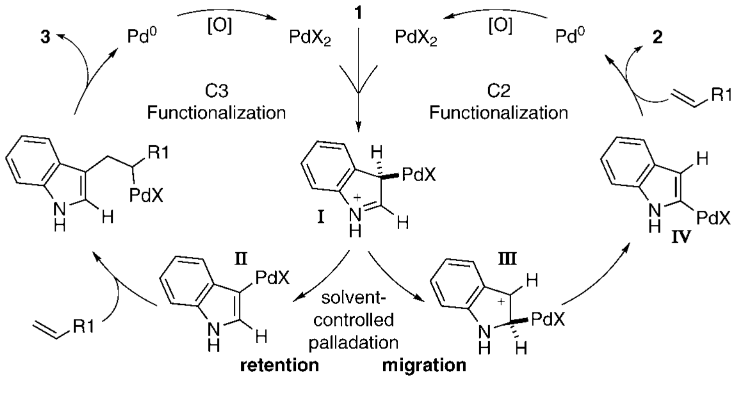
[a] For all reactions the mixture (0.4 M) was stirred for 18 h. [b] Yields after isolation and purification by flash silica-gel chromatography. n.r. = no reaction. Bz = benzoyl, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide.



Scheme 1. Electrophilic attack on indoles.

Further optimization showed that the use of DMSO as a cosolvent with DMF improved the yield of **3a** (Table 1, entry 7), thus suggesting that DMSO may prevent the precipitation of Pd^0 in the reaction mixture prior to reoxidation.[10a] Although no further improvements to the C2 functionalization reaction were made,[11] we found that the use of MeCN/AcOH switched the selectivity back in favor of the 3-position (Table 1, entry 8), as did the addition of DMSO to the reaction in 1,4-dioxane/AcOH (Table 1, entry 9).[10b] It is remarkable that the addition of a polar coordinating cosolvent seems to promote a total switch in the selectivity of the reaction, and investigations into the nature of this selectivity are ongoing.

Although at this stage we can not be certain of the mechanism of this process, we propose plausible pathways for the two reactions in Scheme 2. Palladation at C3 is thought to occur via intermediate **I**, and following rearomatization to **II** a Heck-type reaction forms the C3-functionalized indole **3**. Under neutral conditions, the acetate ion formed from the attack of indole on $Pd(OAc)_2$ will readily remove a proton from **I** to form the C3-palladated species **II**. In contrast, under acidic reaction conditions we propose that this deprotonation would be slowed, which could allow a migration of the C3–PdX bond in **I** to the highly activated 2-position of the iminium intermediate to give intermediate **III** and ultimately **IV**.[12] The effect of the cosolvent, as well as the presence of

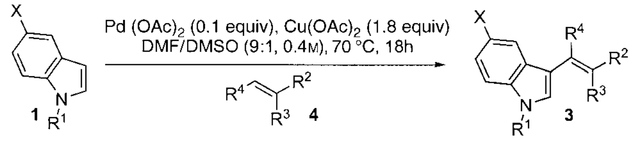


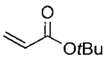
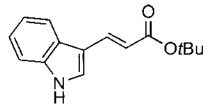
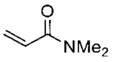
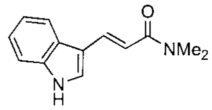
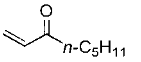
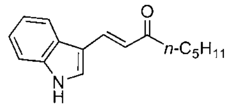
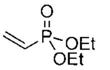
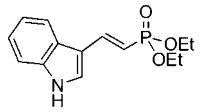
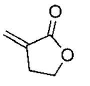
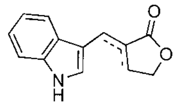
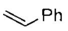
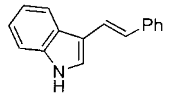
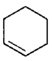
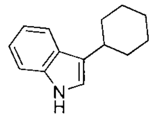
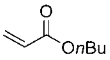
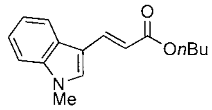
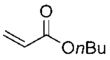
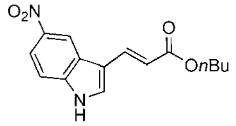
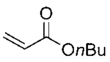
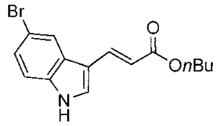
Scheme 2. Proposed mechanism of C–H functionalization.

AcOH, is also important since the results in Table 1 suggest that strongly coordinating solvents (DMSO, MeCN) override any effect that the presence of acid may have, thus leading to C3 selectivity. However, with weakly coordinating 1,4-dioxane as a solvent the proposed migration still appears to be facile, even without the addition of acid, thus leading to the C2-functionalized indole **2** as the major isomer. It is also possible that the C3 palladation is reversible, and that the intermediate derived from C2 palladation is ultimately formed prior to coupling. In this case the C2-palladated species must be thermodynamically more stable and the rate of insertion into the alkene slow. Mechanistic investigations are currently underway, and these results will be reported in due course.

Table 2 shows that a range of indoles and alkenes participate in the regioselective oxidative coupling reaction. Importantly, free (NH) indoles are suitable substrates for this process. The C3-functionalization process worked well for electron-deficient alkenes, such as **4a–d**, which reacted with **1a** to form indoles **3a–d** in good yield. Indole phosphonate **3e** could also be generated from vinyl phosphonate **4e** in good yield. The reaction of **1a** with lactone **4f** produced a mixture of alkenyl indole regioisomers **3f** (1:1) in 66% combined yield. The non-activated alkenes styrene (**4g**) and cyclohexene (**4h**) reacted with **1a** to form the corresponding indoles **3g** and **3h** (after hydrogenation) in good yield. The *N*-methyl indole derivative **1b** reacted with **4a** to form **3i** in 75% yield, and 5-nitroindole **1c** was smoothly converted into **3j** in 76% yield. Of particular note was the use of 5-bromoindole (**1d**); the highly versatile product **3k** was isolated in 75% yield with the aryl bromide moiety intact. Thus, this first general method for the direct oxidative Heck coupling at C3 of free (NH) indoles can be applied to a range of indoles and alkenes.

Table 2: Regioselective C3 functionalization of indoles.



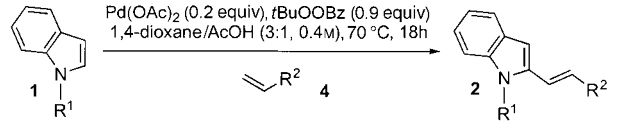
Entry	Alkene		Indole	Product[a]		Yield [%][b]
1		**4b**	X, R^1 = H **1a**		**3b**	91
2		**4c**	X, R^1 = H **1a**		**3c**	70
3		**4d**	X, R^1 = H **1a**		**3d**	68
4		**4e**[d]	X, R^1 = H **1a**		**3e**	70
5		**4f**	X, R^1 = H **1a**		**3f**	66[c]
6		**4g**[e]	X, R^1 = H **1a**		**3g**	62
7		**4h**[f]	X, R^1 = H **1a**		**3h**	62
8		**4a**	X = H, R^1 = Me **1b**		**3i**	75
9		**4a**	X = NO$_2$, R^1 = H **1c**		**3j**	76
10		**4a**	X = Br, R^1 = H **1d**		**3k**	75

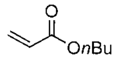
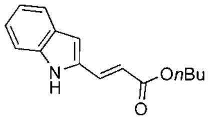
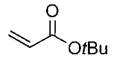
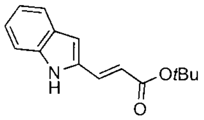
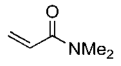
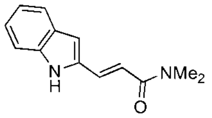
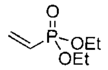
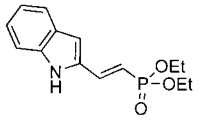
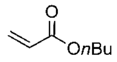
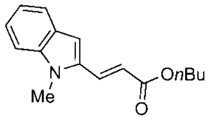
[a] Only the C3-functionalized isomer was produced. [b] Yields of products after purification. [c] A 1:1 mixture of isomers was produced. [d] **4e**: 5 equivalents. [e] **1a**: 2 equivalents, **4g**: 1 equivalent. [f] **4h**: 10 equivalents used because of its volatility; yield after hydrogenation.

We next turned our attention to the development of the corresponding catalytic C2 alkenylation. When the reactions were performed with dioxane/AcOH as the solvent (Table 1, entry 6) the regioselectivity of the oxidative process was switched in favor of reaction at the 2-position (Table 3). However, the yields were generally lower in these cases, presumably as a result of competitive oxidative decomposition of indole **1a** and the product **2** under these reaction conditions. Nevertheless, indole alkenylation occurred selectively at the C2 position with all substrates tested, in generally good yields for this type of transformation. Interestingly, the use of *N*-methylindole (**1b**) resulted in no alkenylation at either C2 or C3 under these conditions, thus highlighting a potentially crucial role of the free NH moiety in these reactions.

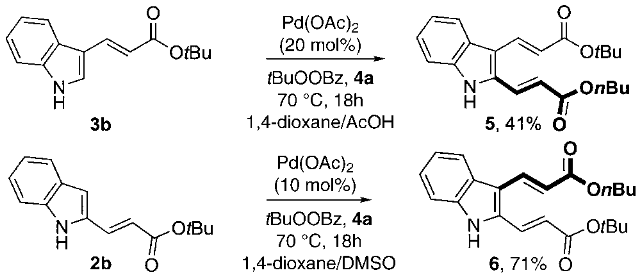
It was also possible to further derivatize the indole products through C–H functionalization (Scheme 3). Indole **3b** reacted with **4a** to form **5** in a moderate 41% yield as the

Table 3: Regioselective C2 functionalization of indoles.



Entry	Alkene		Indole	Product[a]		Yield [%][b]
1		**4a**	$R^1 = H$ **1a**		**2a**	51[c]
2		**4b**	$R^1 = H$ **1a**		**2b**	57
3		**4c**	$R^1 = H$ **1a**		**2c**	34
4		**4e**	$R^1 = H$ **1a**		**2e**	51
5		**4a**	$R^1 = Me$ **1b**		**2i**	n.r.

[a] Only the C2-functionalized isomer was produced. [b] Yields of products after purification. [c] A 7:1 mixture of **2**/**3** was produced; 51 % is the yield of isolated **2a**.



Scheme 3. Formation of bis(alkenyl)indoles.

sole product, whereas indole **2b** was converted into diene **6** in 71 % yield through reaction with **4a** in 1,4-dioxane/DMSO. This strategy thus allows the selective installation of substituents at either position in any order and provides access to highly functionalized indoles by catalytic methods.

In summary, we have developed a general method for the selective intermolecular alkenylation of indoles through a palladium-catalyzed C–H functionalization reaction. The nature of the solvent determines the regioselectivity of the reaction, so that the alkenylation can be directed to either the 2- or the 3-position of free (NH) indoles. This discovery could have important consequences for the selective elaboration of other heteroaromatic core structures. Current efforts are directed towards the improvement of the efficiency and scope of the reaction, a more detailed mechanistic investigation, and application to other types of heteroaromatic compounds.

Experimental Section

General procedure for C3 alkenylation: Palladium acetate (0.1 equiv) was added to a mixture of the alkene (2 equiv), copper(II) acetate (1.8 equiv), and the indole (1 equiv) in DMF/DMSO (9:1, 0.4 M), and the reaction mixture was stirred at 70 °C. After 18 h the reaction mixture was cooled to room temperature and partitioned between water and ethyl acetate, then filtered through a plug of celite. The layers were separated, and the organic layer was washed with aqueous saturated brine solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography afforded the C3-alkenylated indole.

General procedure for C2-alkenylation: Palladium acetate (0.2 equiv) was added to a mixture of the alkene (2 equiv), *t*BuOOBz (0.9 equiv), and the indole (1 equiv) in 1,4-dioxane/AcOH (3:1, 0.4 M), and the reaction mixture was stirred at 70 °C. After 18 h the reaction mixture was cooled to room temperature and neutralized with aqueous sodium hydrogen carbonate solution, diluted with ethyl acetate, and filtered through a plug of celite. The layers were separated, and the organic layer was washed with aqueous sodium hydrogen carbonate solution and aqueous saturated brine solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography afforded the C2-alkenylated indole.

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