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Palladium-Catalyzed Intermolecular C3 Alkenylation of Indoles Using Oxygen as the Oxidant

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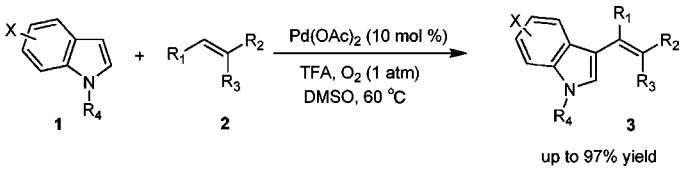
ABSTRACT



A general and efficient palladium-catalyzed intermolecular direct C3 alkenylation of indoles using oxygen as the oxidant has been developed. The reaction is of complete regio- and stereoselectivity. All products are *E*-isomers at the C3-position, and no *Z*-isomers or 2-substituted product can be detected.

3-Vinylindoles, as versatile building blocks, can be utilized in the synthesis of a number of biologically significant compounds such as indole alkaloids, carbazoles, and carbolines.[1−3] More recently, some of 3-vinylindole compounds have been reported to display interesting biological activities, such as anticancer agents,[4] antiviral agents,[5] and antibacterial agents.[6] In the past decades, much attention has been paid to the preparation of 3-vinylindoles. Undoubtedly, an efficient catalytic intermolecular direct alkenylation of indoles with alkenes by regioselective C−H functionalization can provide an atom- and step-economical method for the construction of 3-vinylindoles.[7]

Despite considerable efforts, to date, the intermolecular direct C3 alkenylation of indoles with alkenes has been limitied.[8,9] In 2005, Gaunt and co-workers realized

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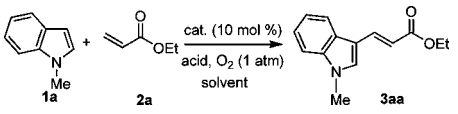
palladium(II)-catalyzed direct and solvent-controlled regioselective alkenylation of indoles using $Cu(OAc)_2$ (1.8 equiv) as oxidant.[10] Then Djakovitch and Rouge described a heterobimetallic [Pd/Cu]-catalyzed C3-alkenylation of *N*-unprotected indoles with acrylate in the presence of bubbling air in 2007.[11] Recently Jiao et al. reported organocatalytic direct C3-alkenylation of indoles with α,β-unsatured aldehydes using DDQ (1.3 equiv) as oxidant.[12] Despite these important advances, some challenging issues still remained; for example, (1) large excess of oxidants was used to regenerate the catalyst;[10] (2) stiochiometric amounts of the reduced external oxidant (such as $Cu(OAc)_2$,[10] DDQ[12]) were produced as waste; and (3) substrate scope was limited and some cases were of poor selectivity.[11] Herein, we disclose a general, efficient and structurally versatile palladium(II)-catalyzed intermolecular C3 alkenylation of indoles with alkenes under an O_2 atmosphere, characterized by complete regio- and stereoselectivity. Compared with $Cu(OAc)_2$ and DDQ, oxygen is an ideal oxidant and offers attractive industrial prospects in terms of green and sustainable chemistry while producing no reduced waste.[13]

Table 1. Optimization of Reaction Conditions[a]



enty	cat	acid (equiv)	temp (°C)	time (h)	yield (%)[g]
1[b]	$Pd(OAc)_2$		rt	45	<10
2	$Pd(OAc)_2$	TFA (1)	rt	45	45
3	$Pd(OAc)_2$	TFA (5)	rt	45	69
4	$Pd(OAc)_2$	TFA (8)	rt	30	87
5	$Pd(OAc)_2$	TFA (10)	rt	30	86
6[c]	$Pd(OAc)_2$	TFA (8)	rt	30	≤70
7	$Pd(OAc)_2$	TFA (8)	60	3.5	85
8	$Pd(OAc)_2$	TFA (8)	90	2	65
9	$Pd(OAc)_2$	TFA (8)	120	0.5	40
10	$Pd(TFA)_2$	TFA (8)	60	4.5	72
11[b]	$Pd(TFA)_2$		60	24	45[d]
12	$PdCl_2$	TFA (8)	60	3.5	45
13	$Pd(OH)_2$	TFA (8)	60	3.5	60
14	$Pd(PPh_3)_2Cl_2$	TFA (8)	60	3.5	nd
15[e]	$Pd(OAc)_2$	acids (8)	60	3.5	≤45
16[f]	$Pd(OAc)_2$	TFA (8)	60	4.5	75

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), catalyst (0.1 mmol), O_2 (1 atm) and acid in DMSO (5 mL) at the specified temperature. [b] No acid. [c] Solvents: EtOAc, DMF, THF, *n*-hexane, toluene, acetone, CH_3CN, dioxane, Et_2O, CH_2Cl_2, $CHCl_3$, CH_3NO_2, EtOH. [d] The conversion was 81%. [e] Acids: HCO_2H, AcOH, $PhCO_2H$, tartaric acid, *p*-toluenesulfonic, salicylic acid, boric acid, oxalic acid, maleic acid, fumaric acid. [f] Using air as oxidant. [g] Isolated yield.

Initially, we investigated the reaction of *N*-methyl indole (**1a**) and ethyl acrylate (**2a**) with 10 mol % $Pd(OAc)_2$ as the catalyst and oxygen as the oxidant in DMSO (Table 1). The reaction was found to proceed in low conversion (< 10%) (entry 1). Considering that trifluoroacetic acid (TFA) and $Pd(OAc)_2$ can facilitate the generation of more electropositive $[Pd(II)O_2CCF_3]^+$ species, which, compared with $[PdOAc]^+$, is easier to form σ-indole-Pd complexes through electophilic substitution of C−H bonds at indole 3-position,[14] 1 equiv of TFA was added to the reaction system. To our delight, the reaction gave the alkenylation product with complete C3 regioselectivity and *E* stereoselectivity, and the yield improved remarkably to 45% (entry 2). Next, the amount of TFA was investigated, and the best result was gotten when 8 equiv of TFA was used (entries 3−5). After careful solvent screening, DMSO proved to be the best solvent (entry 6). Temperature dramatically affected the reaction rate; the reaction was done within 3.5 h at 60 °C, and higher temperature led to a significant drop in the yield due to the decomposition of starting material and product (entries 7−9). $Pd(TFA)_2$ (TFA = trifluoroacetate) turned out to be an acceptable catalyst for the reaction. Nevertheless, in the absence of trifluoroacetic acid, the reaction would proceed incompletely (entries 10−11). By using other palladium source and acids, the same reaction proceeded but less efficiently (entries 12−15). It is noteworthy that the reaction rate and the yield was obviously dropped when air was used as oxidant instead of oxygen (entry 16). Accordingly, the reaction conditions were optimized as follows: $Pd(OAc)_2$ (10 mol %), TFA (8 equiv) under an oxygen atmosphere in DMSO at 60 °C.

With the optimal reaction condition in hand, we moved on to explore the scope of the alkenylation reaction. First, we studied the effect of electronic and structural variations on the alkene (Table 2). The present reaction tolerated a variety of alkenes. Monosubstituted alkenes, not only electrophilic alkenes but also the more challenging nonactivated styrene, reacted with **1a** to give the corresponding alkenylation products with complete regio- and stereoselectivity in good yields (53−83%) (entries 1−4).

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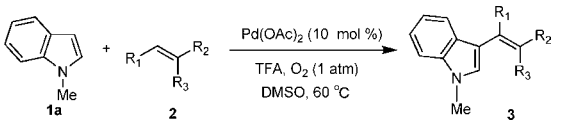
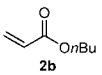
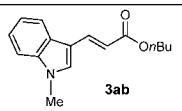
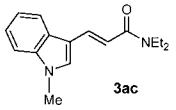
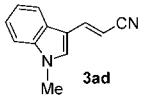
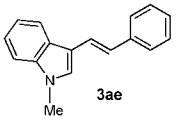
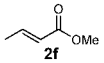
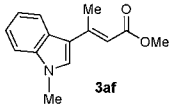
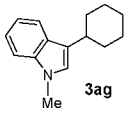
Table 2. Alkenylation of *N*-Methyl Indole with Alkenes[a]



enty	alkene	product	time (h)	yield (%)[b]
1	 2b	 3ab	3.5	83
2	 2c	 3ac	10	80
3	 2d	 3ad	5	69
4	 2e	 3ae	10	53
5	 2f	 3af	17	75
6	 2g	 3ag	17	60[c]

[a] Reaction conditions: **1a** (1 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (0.1 mmol), O_2 (1 atm) and TFA (8 mmol) in DMSO (5 mL) at 60 °C. [b] Isolated yield. [c] After hydrogenation.

Particularly noticeable is the performance of 1,2-disubstituted alkenes in the reaction in view of the small number of precedents and lower reactivity of this kind of olefin in oxidative alkenylation (Fujiwara−Moritani) reactions.[15] Under these reaction conditions, (*E*)-methyl crotonate and cyclohexene underwent a smooth reaction with **1a** to afford the corresponding trisubstituted alkene products **3af** (75% yield) and **3ag** (60% yield, the desired product was unstable and it was hydrogenated prior to isolation) (entries 5−6).

Then we examined the alkenylation of *N*-unprotected indoles with alkenes. Gratifyingly, indole is suitable substrate for this process (Table 3). The reaction of indole with a variey of electron-deficient and nonactivated monosubstituted alkenes proceeded efficiently to produce the corresponding C3 alkenylation products with complete selectivity in moderate to excellent yields (55−97%) (entries 1−6). Indole phosphonate **3bi** could also be generated from vinyl phosphonate **2i** in moderate yield (entry 7). Pleasingly, alkenes with more substituents, such as 1,1- or

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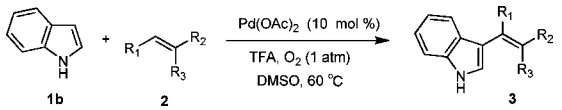
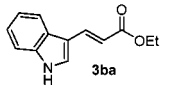
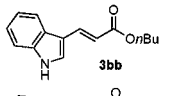
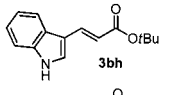
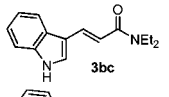
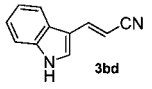
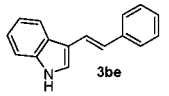
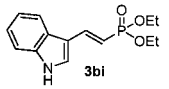
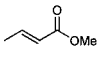
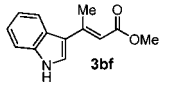
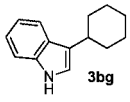
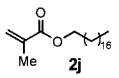
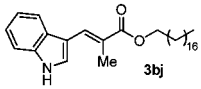
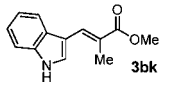
Table 3. Alkenylation of Indole with Alkenes[a]



enty	alkene	product	time (h)	yield (%)[b]
1	 2a	 3ba	1.5	97
2	 2b	 3bb	2	92
3	 2h	 3bh	2	94
4	 2c	 3bc	3.5	82
5	 2d	 3bd	4	75
6	 2e	 3be	8	55
7	 2i	 3bi	14	45[c]
8	 2f	 3bf	14	70
9	 2g	 3bg	14	70[d]
10	 2j	 3bj	8	78
11	 2k	 3bk	2.5	85

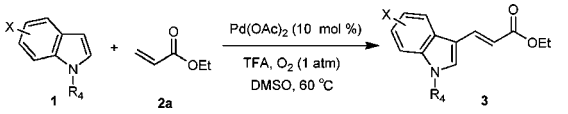
[a] Reaction conditions: **1b** (1 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (0.1 mmol), O_2 (1 atm) and TFA (8 mmol) in DMSO (5 mL) at 60 °C. [b] Isolated yield. [c] 3 mmol **2i** for 1 mmol **1b**. [d] After hydrogenation.

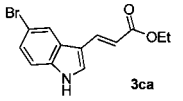
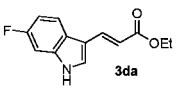
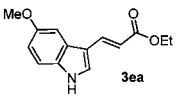
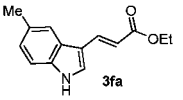
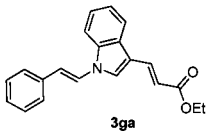
1,2-disubstituted alkenes, successfully coupled with indole to give the corresponding C3 alkenylation products in good yield (70−85%) (entries 8−11).

Finally, we undertook a study of the influence of the substitution pattern of the indole ring by using ethyl acrylate as model olefin (Table 4). Indoles possessing either electron-withdrawing groups or electron-donating groups were smoothly reacted and provided C3 alkenylation products **3** in good to excellent yields (65−90%), albeit 1-styrylindole (**1g**) proved to be less reactive than other substituted indoles. Some functional substituents such as Br, F and MeO were compatible under these conditions, which could be further transformed into other functionalities.

A plausible mechanism for the reaction is shown in Scheme 1. $Pd(OAc)_2$ is treated with TFA to get active

Table 4. Alkenylation of Indoles with Ethyl Acrylate[a]



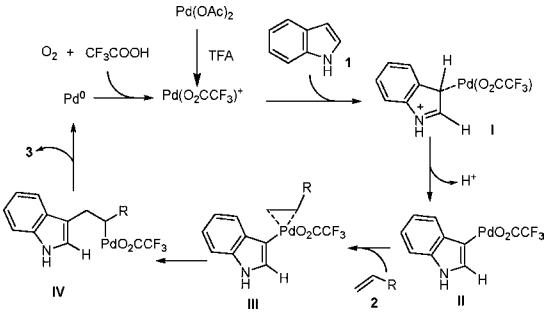
enty	alkene	product	time (h)	yield (%)[b]
1	X = 5-Br R_4 = H **1c**	 **3ca**	14	80
2	X = 6-F R_4 = H **1d**	 **3da**	2.5	87
3	X = 5-MeO R_4 = H **1e**	 **3ea**	3	85
4	X = 5-Me R_4 = H **1f**	 **3fa**	4	90
5	X = H R_4 = Ph-C=C- **1g**	 **3ga**	48	65

[a] Reaction conditions: **1a** (1 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (0.1 mmol), O_2 (1 atm) and TFA (8 mmol) in DMSO (5 mL) at 60 °C. [b] Isolated yield.

$Pd(O_2CCF_3)^+$,[14,16] which affords the C3-palladated species **II** through electrophilic addition of indole and following rearomatization. Then coordination of alkene and insertion of C=C bond results in the palladium(II) complex **IV**. Indole/alkene adduct would be released from **IV** upon syn β−H elimination, and the Pd^0 can be reoxidized to $Pd(O_2CCF_3)^+$ by O_2 in the presence of TFA to complete the catalytic cycle.[10,11]

(16) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992–1995.

Scheme 1. Plausible Mechanism for the Transformation



In summary, we have developed a general, simple and efficient method for the intermolecular direct C3 alkenylation of indoles using palladium(II) as catalyst and oxygen as the oxidant. The reaction can proceed well without Cu(II) and shows complete regio- and stereoselectivity. All products are *E*-isomers at the C3-position, and no *Z*-isomers or 2-substituted product can be detected by analyzing the reaction mixtures. The method should have many applications in organic and medical chemistry. Detailed mechanistic investigations and application to other types of heteroaromatic compounds are currently underway.

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Supporting Information Available. Detailed experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.