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Pd-^{t}BuONO Cocatalyzed Aerobic Indole Synthesis

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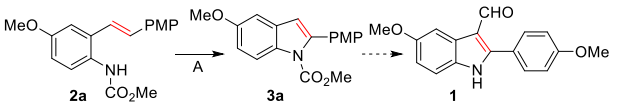
Abstract. A Pd-^{t}BuONO co-catalyzed scalable and practical synthesis of indoles with molecular oxygen as terminal oxidant is developed. Either terminal or internal 2-vinylanilines could be smoothly converted to desired indoles under one general condition. This method has been evaluated in the large scale synthesis of indomethacin and a potential *anti*-breast cancer drug candidate **1**.
Keywords: palladium, tert-butyl nitrite, aerobic, indoles, paharmerceuticals

C4-C7 Substituted indoles are among one of the most important heterocycles due to numerous biologically active natural products as well as medicinal agents based on the benzopyrrole skeleton[1] and hence starting with the seminal studies by Fischer,[2] a huge number of routes to prepare this class of compounds have been developed.[3-8] Of the palladium-catalyzed indole synthesis, Hegedus indole synthesis is one of the most powerful methods, normally using benzoquinone (BQ) as oxidant. Recently, several modifications using molecular oxygen as terminal oxidant have been reported, however, only limited scope has been achieved for each method. The drug candidate **1** is a potential *anti*-breast cancer medicine, which is synthesized from indole intermediate **3a** (Scheme 1). Four representative methods using palladium as catalyst have been evaluated in the construction of **3a** from **2a**. Unfortunately, none method could afford more than 20% of yield, even if ^{t}BuOH was used as solvent. The conditions with BQ as oxidation gave no conversion of starting material. Hence new methods should be explored for such purpose.

The *aza*-Wacker oxidation[9] of substituted alkenes could prepare the corresponding C2 and C4 to C7 substituted indoles and seems to be a straightforward and practical method thus has attracted comprehensive attention, whereas only a few examples have been reported to access all C4 to C7 substituted indoles in one general procedure. Besides, the substrate scope is often limited. On the basis of our previous work on Pd-^{t}BuONO co-catalyzed aerobic oxygenations of alkenes,[10a-c] we envisioned that a general synthetically practical approach from 2-vinylanilines *via* Pd-^{t}BuONO-O_2 system would be suitable for the C4 to C7 substituted indole synthesis.



ref.	condition A	**3a**(%)	**2a**(% recovered)
6a-b	$Pd(CH_3CN)_2Cl_2$, BQ, LiCl, THF, 100 °C, 28 h	0 (7)[a]	99 (88)[a]
4g	$Pd(OAc)_2$, O_2, DMSO, 80 °C, 72 h	16 (6)[a]	53 (86)[a]
5c	$Pd(OAc)_2$, O_2, pyridine, 80 °C, 17 h	20 (17)[a]	61 (69)[a]
4h	$Pd(OAc)_2$, PPh_3, O_2, 80 °C, 24 h	5 (3)[a]	83 (91)[a]

[a] The numbers in parentheses refer to yields obatained using ^{t}BuOH as solvent.

Scheme 1.

Reaction conditions were investigated in the conversion of **4a** to indole **5a** (Table 1). Pd-salts were screened and $Pd(PhCN)_2Cl_2$ afforded **5a** in 77% of yield (entry 6). The reaction under argon atmosphere gave only 17% of **5a**, indicating oxygen is a necessary terminal oxidant and TBN itself can work as oxidant (entry 8). The reaction in EtOH gave a little lower yield (entry 10) whereas the reactions in other solvents such as dioxane, toluene and DMF were not efficient (entries 11-13). Reaction at 80 °C gave same results as that at 70 °C (entries 6-7). Consequently, the reaction conditions demonstrated in entry 7 was chosen as the standard conditions for further investigation of the scope of substituted indoles.

First, indoles without C2 or C3 substituents were investigated. Indoles **5d** to **5h** bearing C4 to C7 fluoro- or chloro-substituent could be readily obtained. C2-C3 unsubstituted indoles with C6-C7 dialkoxyl (**5i-j**), C5-aryl (**5k**), and C5-methoxyl (**5l**) groups were all synthesized in good yields. Benzo(dipyrrole) **5m** could also be prepared. C3-phenyl and methyl indoles **5o** and **5p** were not obtained, whereas such C3-substituted indoles could be easily prepared from corresponding indoles precursors *via* Friedel-Crafts reaction. 5-Br indole **5q** is not available due to the quick formation of Pd-black. Indoles **5r** and **5t** bearing NO_2 or 2-furyl groups are all obtained in moderate yields. Indole **5s**

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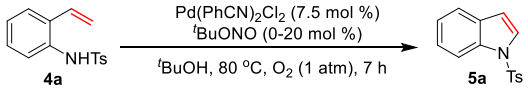
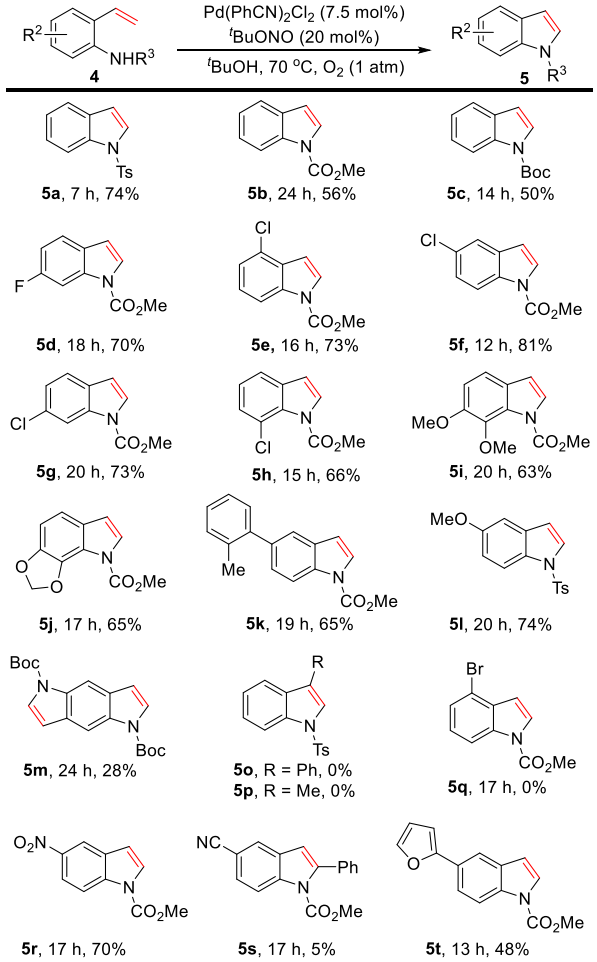
with 5-CN is afforded in low yield due to the low solubility.

Table 1. Reaction conditions.[a]



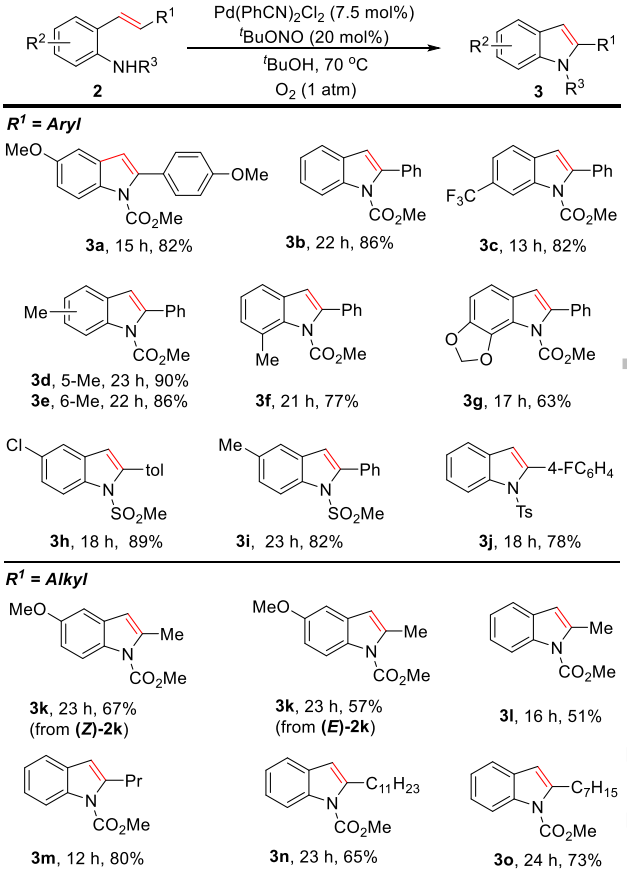
No	[Pd][%]	^{t}BuONO	solvent	**5a**[%][b]
1	none	none	^{t}BuOH	0
2[c]	Pd-Cu-NO_2	20%	^{t}BuOH	38
3	$Pd(OAc)_2$	20%	^{t}BuOH	9
4	$PdCl_2$	20%	^{t}BuOH	4
5	$Pd(MeCN)_2Cl_2$	20%	^{t}BuOH	42
6	$Pd(PhCN)_2Cl_2$	20%	^{t}BuOH	77
7[d]	$Pd(PhCN)_2Cl_2$	20%	^{t}BuOH	77
8[e]	$Pd(PhCN)_2Cl_2$	20%	^{t}BuOH	17
9	$Pd(PhCN)_2Cl_2$	none	^{t}BuOH	trace
10	$Pd(PhCN)_2Cl_2$	20%	EtOH	62
11	$Pd(PhCN)_2Cl_2$	20%	dioxane	27
12	$Pd(PhCN)_2Cl_2$	20%	toluene	24
13	$Pd(PhCN)_2Cl_2$	20%	DMF	9

[a] Conditions: **4a** (1.0 mmol), ^{t}BuONO (0.25 mmol), solvent, [Pd] (7.5 mol%), O_2 (1 atm), 7 h. [b] Determined by ^{1}H NMR. [c] With $Pd(PhCN)_2Cl_2$ (10 mol%), $CuCl_2$ (10 mol %), $NaNO_2$ (5 mol %). [d] At 70 °C. [e] Under argon.



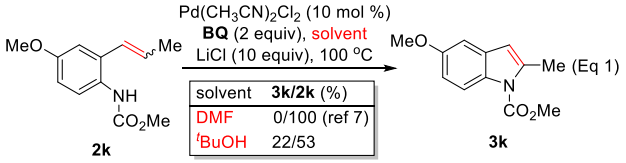
Scheme 2. Scope of terminal alkenes. Conditions: **4** (0.25 mmol), ^{t}BuOH (2 mL).

Besides the C2-unsubstituted indoles, the indoles bearing either C2-aryls (Scheme 3, **3a**-**3j**) or C2-alkyls (**3k**-**3o**) could all be prepared by this method with up to 90% of isolated yields. Indoles **3a** and **3k** are key intermediates for the synthesis of a potential *anti*-breast cancer drug candidate **1** and indomethacin.



Scheme 3. Conditions: **2** (0.25 mmol), ^{t}BuOH (2 mL).

By this method, either *E*/*Z*-isomer of **2k** could be converted to **3k** in 67% or 57% of yield, whereas the previous method with BQ as oxidant failed (Eq 1).[7] The Pd-BQ system with ^{t}BuOH as solvent afforded **3k** in 22% of yield.



solvent	**3k**/**2k** (%)
DMF	0/100 (ref 7)
^{t}BuOH	22/53

Indometacin **8** is a nonsteroidal *anti*-inflammatory drug. By using present method, 4.5 grams of indomethacin was synthesized from **2k** via 4 steps in overall 46% of yield (Scheme 4, top). Compound **1** is a potential *anti*-breast cancer drug candidate, which was prepared by this method in 3 step in 68% of yield in 13 gram-scale (Scheme 4, bottom).

As a complement to the above synthesis of C2 and C4 to C7 substituted indoles, a divergent synthesis of such indoles from C4 to C7 chloroindoles **5e**-**5h** is an alternative general strategy. Besides arylation, a wide range of substituents can be introduced by well-established cross coupling reactions (Scheme 5). For

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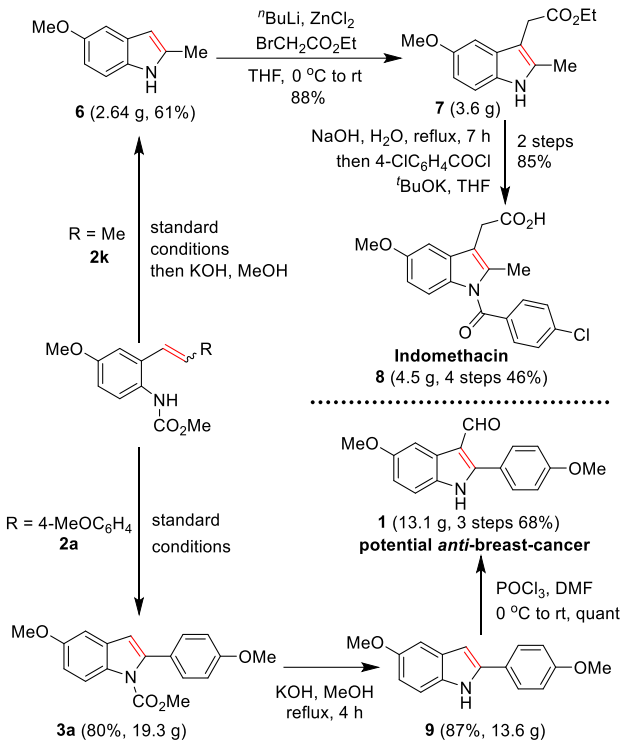
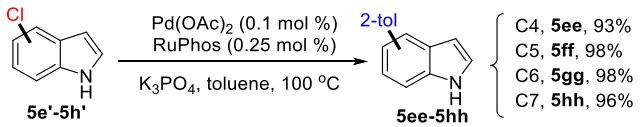
example, C4 to C7 aryl indoles **5ee-5hh** were readily synthesized from corresponding chlorides **5e-5h** in quantitative yields, whereas using the recently reported method of C5 C-H arylation, the C5 *o*-tolyl indole **5k** cannot be prepared.[8a]



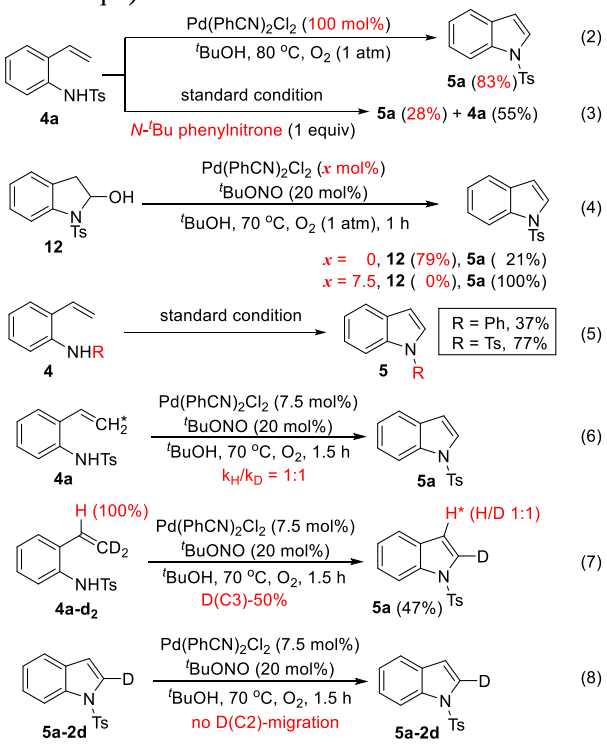
Scheme 4. Gram-scale synthesis of pharmaceuticals.



Scheme 5.

One equivalent of [Pd(II)] catalyst afforded 83% of product **5a** (Eq 2), indicating the reaction should be promoted by Pd(II) other than Pd(IV) or Pd(0). *N*-^{t}Bu phenylnitrone was added to trap NO radical[11] and it could partially inhibit the reaction (Eq 3). The possible intermediate hemiaminal **12** spontaneously formed from *anti*-Markovnikov Wacker oxidation[10a] of vinyl group of **4a** has been subjected to the reaction conditions and target product **5a** was obtained in quantitative yield (Eq 4). More nucleophilic *N*-Ph 2-vinylaniline gave much lower yield than that of *N*-Ts one, suggesting the direct *N*-atom attack might be less possible (Eq 5).

A KIE of 1 was observed (Scheme 6, Eq 6), indicating that C-H cleavage should not be the rate limiting step. Thus a direct C-H amination pathway might not be possible. The observation of 50% of deuteration at C3 position of **5a** suggests the reversible Pd-H insertion process in the reaction (Eq 7 and Eq 8).



Scheme 6.

The kinetic study reveals that the initial rate is first order dependent on Pd-cat., [^{t}BuOH], and [**4a**], whereas zeroth-order dependent on ^{t}BuONO (Figure 1). Thus palladium (II) plays the role of catalyst and either Pd, **4a** or ^{t}BuOH participate the rate determining step. Similar to previous discovery in Wacker oxidation,[10] ^{t}BuONO should act as a redox cocatalyst to regenerate Pd(II) from Pd(0).

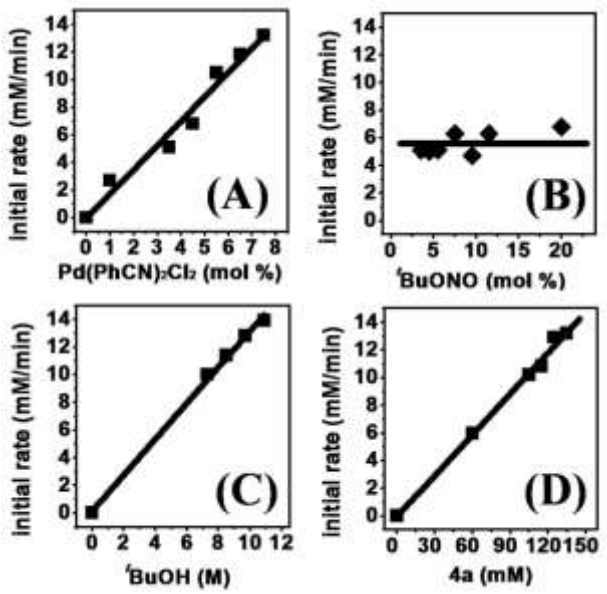
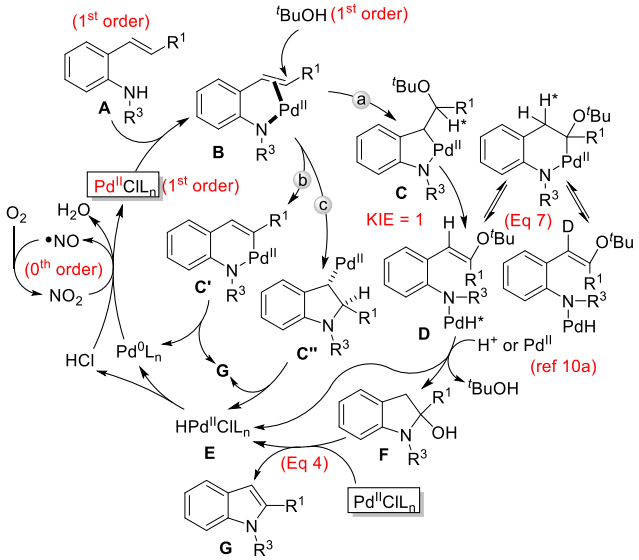


Figure 1. Kinetic study. The dependence of initial rates (A) 1st order on Pd, (B) 0th order on ^{t}BuONO, (C) 1st order on [^{t}BuOH], and (D) 1st order on starting material [**4a**].

On the basis of the experimental evidence, a plausible reaction mechanism is proposed (Scheme 7). Pathway (a) involves a regioselective Wacker oxidation followed by the spontaneous annulation to hemiaminal **F**, which can quantitatively converted to indole **G** (eq 4). The reductive elimination produces the final indole product as well as the Pd(II) species **E**, followed by the regeneration of catalytically active Pd(II) via the oxidation with molecular oxygen mediated by NO*x*. H_2O_2 is not observed and the final product of O_2 is H_2O. In pathway (b) the direct C-H activation affords the key intermediate **C'** from complex **B**, however, the KIE and kinetic study do not support it. Despite of the fact that the *aza*-Wacker process via pathway (c) cannot be ruled out by far, the slower reaction with more nucleophilic starting material (*N*-Ph instead of *N*-Ts, eq 5) as well as the first order dependence of the initial rate on [^{t}BuOH] does not support this pathway.



Scheme 7. Proposed mechanism.

In conclusion, we have developed a general and practical synthesis of functionalized indoles via an aerobic intramolecular *aza*-Wacker of 2-vinylanilines with molecular oxygen as terminal oxident which is enabled by an organic redox cocatalyst and a bulky alcohol solvent. This method has been evaluated in the large scale synthesis of indomethacin and a potential *anti*-breast cancer drug candidate **1** to demonstrate its application potential.

Experimental Section

$Pd(PhCN)_2Cl_2$ (7.2 mg, 0.019 mmol) was weighed into a 25 mL Schlenk tube and dried under high vacuum for 15 min. Under O_2 (1 atm balloon), ^{t}BuOH (2 mL), ^{t}BuONO (5.2 mg, 0.05 mmol) and a vinylaniline (0.25 mmol) were sequentially added. The resulting reaction mixture was heated and stirred at 70 °C (monitored by TLC). The reaction was quenched by the filtration through a thin silica gel pad and washed with EtOAc. The filtrate was concentrated and the residue was purified by chromatography on silica gel to afford the corresponding products.

Acknowledgements

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