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Palladium-catalyzed oxidative annulation of *in situ* generated enones to pyrroles: a concise route to functionalized indoles†

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Palladium(II)-catalyzed, copper(II)-mediated indole synthesis was achieved from the reactions of *N*-substituted simple pyrroles with enones generated *in situ* from 3-chloropropiophenones. A benzene ring was thus constructed onto a pyrrole backbone, affording substituted indole derivatives. A domino dehydrochlorination/C–H olefination /Diels–Alder cycloaddition/dehydrogenative aromatization sequence was established as the reaction pathway. The present methodology provides a concise route to highly functionalized indole derivatives.

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Indoles are very important structural motifs in many organic compounds.^{1,2} Although Fischer indoles were first reported in 1883,³ the recently known indole syntheses are predominantly directed towards construction of a pyrrole ring onto a prefunctionalized benzene precursor.⁴ However, the alternative method which uses a pyrrole ring as the “template”-like structure to establish a benzene ring onto it is much less common.⁵ In this aspect, anionic benzannulation of *N*-methylpyrroles with alkenes or alkynes was employed to form functionalized indoles.⁶ Intramolecular cyclization of vinylpyrroles^{7a} and alkynylated pyrroles^{7b} occurred to give multi-substituted indoles under various conditions, respectively. Diels–Alder reactions of 2-vinylpyrroles with maleimides,^{8a} and 2- or 3-nitropyrroles with dienes,^{8b} were realized for the same purpose. Lewis acid-catalyzed pyrrolyl-supported enynals with enols or enol ethers,^{9a} and ruthenium(0)-mediated annulation of pyrroles with propargyl alcohols^{9b} yielded indoles under relatively harsh conditions. Palladium-catalyzed oxidative decarboxylative annulation of *N*-methylpyrrole-2-carboxylic acid with alkynes generated indoles as reaction intermediates.¹⁰ Substituted indoles were also obtained from one-pot, two-step reactions of pyrroles with β -nitroacrylates.¹¹ Benzannulation of pyrroles with rhodium enalcarbenoids formed substituted

indoles.¹² Because establishment of an indole core is often encountered in the synthesis of functionalized molecules,⁴ concise and direct indole synthesis from relatively simple pyrroles has been strongly desired.

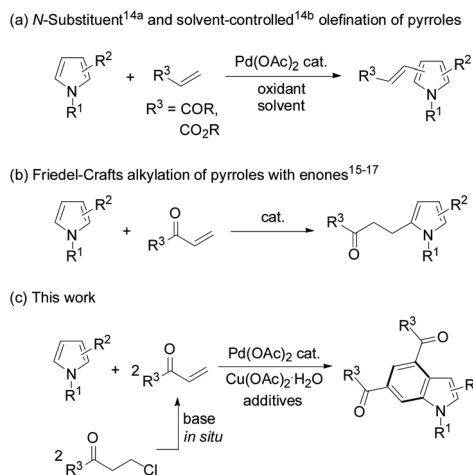
As transition-metal-catalyzed C–H activation has recently become a promising straightforward route to construct carbon–carbon and carbon–heteroatom bonds, oxidative cross-coupling of a pyrrole with two olefin molecules to form a benzene ring seems to be a potential route to access indole derivatives. However, in contrast to other *N*-heterocycles which can be used as coupling partners for carbon–carbon bond formation,¹³ direct oxidative cross-coupling of pyrroles with olefins has seldom been documented due to the poor regioselectivity, polyolefination, and significant polymerization of the pyrrole substrates under oxidative conditions. In 2006, Gaunt *et al.* reported palladium-catalyzed olefination of simple pyrroles by acrylates through *N*-protecting groups differentiating in steric and electronic properties,^{14a} and later Yao's lab achieved palladium-catalyzed solvent-controlled switchable olefination of 3,4-disubstituted pyrroles with electron-deficient olefins^{14b} (Scheme 1a). Under acid,¹⁵ iodine,¹⁶ or organocatalysis¹⁷ conditions pyrrole substrates usually underwent Friedel–Crafts alkylation with α,β -unsaturated ketones (enones) (Scheme 1b). Intrigued by the advantages of using *in situ* generated enones as olefin sources for carbon–carbon bond formation,^{18–21} we reasonably envisioned the oxidative annulation reactions of β -chloroalkyl ketones to pyrroles. Herein, we report direct synthesis of indoles from pyrroles and 3-chloropropiophenones in a one-shot style (Scheme 1c).

Initially, the reaction of *N*-methyl-2-phenylpyrrole (**1a**) with 3-chloropropiophenone (**2a**) was conducted to screen the reaction conditions (Table 1). In the presence of 10 mol% Pd(OAc)₂ as the catalyst, Cu(OAc)₂·H₂O (6.0 equiv.) as the oxidant, and

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Scheme 1 Direct reactions of pyrroles with electron-deficient olefins.

NaOAc (4 equiv.) as the base, the target product **3a** was obtained in 41% yield from the reaction in DMSO at 100 °C (Table 1, entry 1). Among the screened solvents, *i.e.*, DMSO, DMF, toluene, THF, and dioxane, a mixture of DMF/DMSO (*v/v*, 9/1) effected the reaction best (Table 1, entry 3). Cu(OAc)₂, AgOAc, Ag₂CO₃, benzoquinone, *t*BuOO*t*Bu, and dioxygen were used to promote the reaction, and only Cu(OAc)₂·H₂O was found to be the most efficient oxidant (Table 1, entries 1–4). The reaction hardly occurred without an oxidant, and the air atmosphere facilitated the reaction (Table 1, entries 5 and 6). A combination of additives tetra-butyl ammonium bromide (TBAB) and pivalic acid (PivOH) enhanced the yield of **3a** to 70% (Table 1, entries 7–9). With a lower loading of the oxidant

(4 equiv.) at a higher temperature (130 °C) the target product was also obtained in a decent yield (68%), while varying the temperature around 130 °C was detrimental to the reaction efficiency (Table 1, entries 10–13). Various palladium sources and bases were also investigated, and Pd(OAc)₂ and NaOAc were shown to be the most efficient catalyst and base for the desired reaction, respectively (see the ESI†). To ease the work-up procedure by using a less amount of oxidant, the conditions for entry 12 were considered as those suitable for the desired reaction (Table 1).

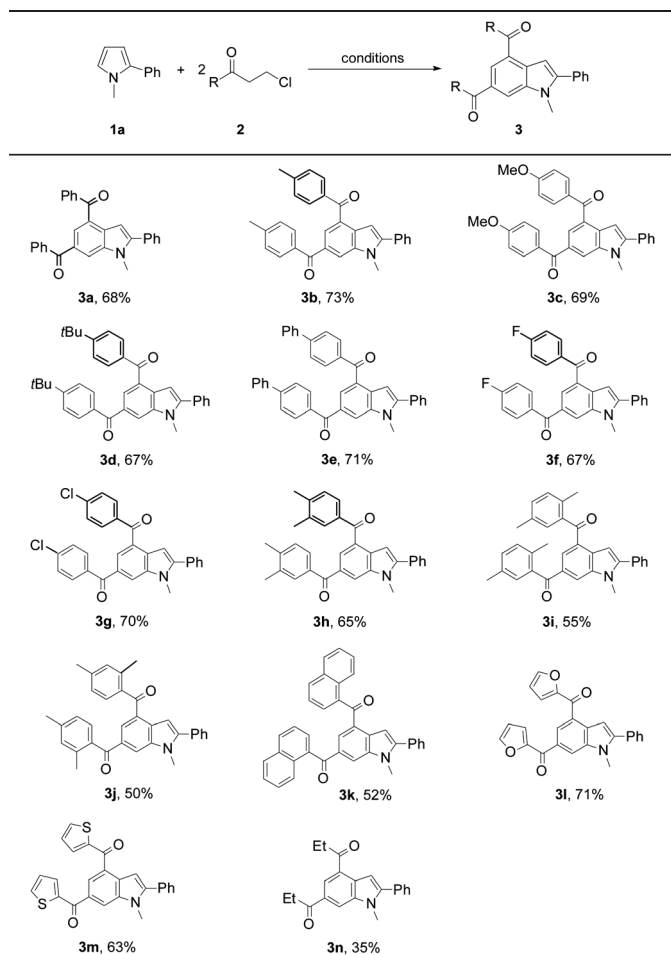
Next, the scope of 3-chloroalkyl ketones **2** was explored to probe into the protocol generality (Table 2). Pyrrole **1a** reacted with 3-chloroalkyl aryl ketones bearing a substituent on the aryl moiety proceeded to form the target products **3a–3g** in 67–73% yields, revealing no obvious electronic impact from the substituents. Increasing the steric hindrance of the aryl moiety in **2** by introducing two methyls led to the corresponding products **3h–3j** (50–65%), which is attributed to the steric effect of the *ortho*-methyl on the aryl moiety of **2**. The presence of bulky 1-naphthyl deteriorated the yield of **3k** (52%). Heteroaryl 3-chloropropionones also underwent the reactions to afford indoles **3l** (71%) and **3m** (63%), respectively. In contrast to 3-chloroalkyl aryl ketones, 5-chloropentan-3-one exhibited a low reactivity to **1a**, and its reaction with **1a** only gave **3n** in 35% yield.

The substrate scope was further investigated by reacting **2a** with a variety of pyrrole substrates **1** (Table 3). The steric hindrance from the *N*-R moieties (R = Et, allyl, Bn, and Me) differentiated the reactivity of these 2-phenylpyrroles, leading to the target indole products **4a–4d** (50–68%). A methyl substituent on the aryl group of *N*-methyl-2-arylpyrroles did not obviously affect the reaction efficiency and **4d–4f** were obtained in

Table 1 Screening of conditions for the reaction of *N*-methyl-2-phenylpyrrole (**1a**) with 3-chloropropiophenone (**2a**)^a

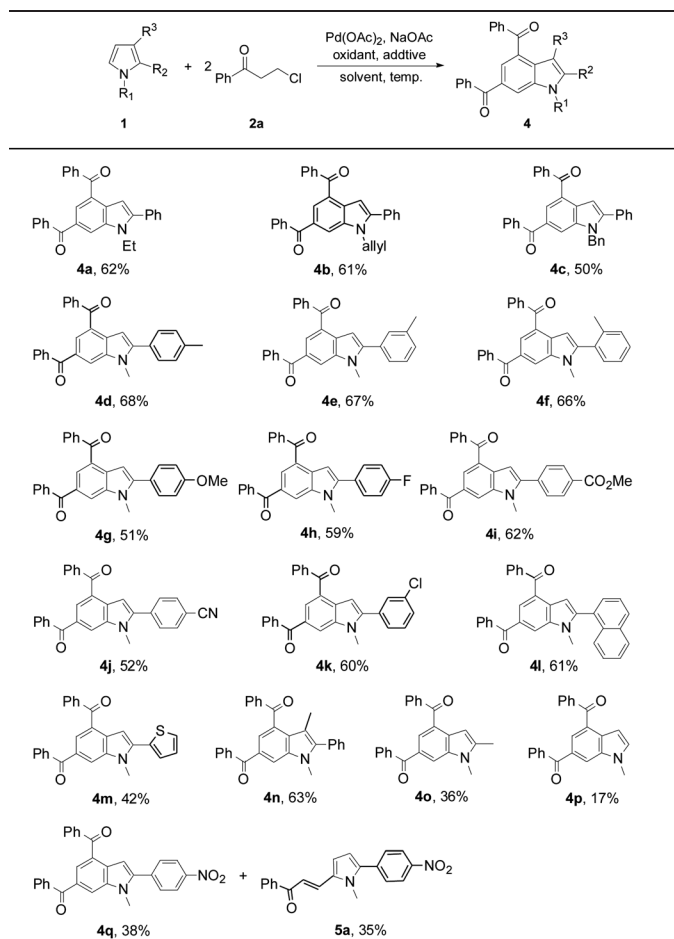
Entry	Oxidant	Solvent	Additive (equiv.)	Temp (°C)	Yield ^b (%)
1	Cu(OAc) ₂ ·H ₂ O	DMSO		100	41
2	Cu(OAc) ₂ ·H ₂ O	DMF		100	42
3	Cu(OAc) ₂ ·H ₂ O	DMF/DMSO ^c		100	64
4	Cu(OAc) ₂	DMF/DMSO ^c		100	61
5 ^d		DMF/DMSO ^c		100	<1
6	Air	DMF/DMSO ^c		100	13
7	Cu(OAc) ₂ ·H ₂ O	DMF/DMSO ^c	TBAB (0.5)	100	65
8	Cu(OAc) ₂ ·H ₂ O	DMF/DMSO ^c	PivOH (1.0)	100	66
9	Cu(OAc) ₂ ·H ₂ O	DMF/DMSO ^c	TBAB/PivOH ^f	100	70
10 ^e	Cu(OAc) ₂ ·H ₂ O	DMF/DMSO ^c	TBAB/PivOH ^f	100	60
11 ^e	Cu(OAc) ₂ ·H ₂ O	DMF/DMSO ^c	TBAB/PivOH ^f	80	48
12 ^e	Cu(OAc) ₂ ·H ₂ O	DMF/DMSO ^c	TBAB/PivOH ^f	130	68
13 ^e	Cu(OAc) ₂ ·H ₂ O	DMF/DMSO ^c	TBAB/PivOH ^f	140	52

^a Conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), catalyst (0.02 mmol), base (0.8 mmol), oxidant (1.2 mmol), solvent (2.5 mL), air, 24 h. ^b Isolated yields based on **1a**. ^c DMF/DMSO (*v:v* = 9:1). ^d Under 0.1 MPa N₂ atmosphere. ^e Cu(OAc)₂·H₂O (0.8 mmol). ^f TBAB (0.1 mmol) and PivOH (0.2 mmol).

Table 2 Scope of 3-chloroalkyl ketones^{a,b}

^a Conditions: **1a** (0.2 mmol), **2** (0.8 mmol), Pd(OAc)₂ (0.02 mmol), NaOAc (0.8 mmol), Cu(OAc)₂·H₂O (0.8 mmol), TBAB (0.1 mmol), PivOH (0.2 mmol), DMF/DMSO (2.5 mL, v/v = 9:1), air, 130 °C, 24 h.

^b Isolated yields based on **1a**.

Table 3 Scope of pyrroles^{a,b}

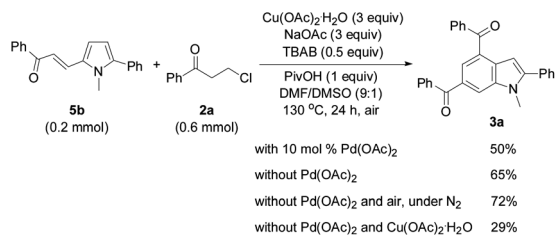
^a Conditions: **1** (0.2 mmol), **2a** (0.8 mmol), Pd(OAc)₂ (0.02 mmol), NaOAc (0.8 mmol), Cu(OAc)₂·H₂O (0.8 mmol), TBAB (0.1 mmol), PivOH (0.2 mmol), DMF/DMSO (2.5 mL, v/v = 9:1), air, 130 °C, 24 h.

^b Isolated yields based on **1**.

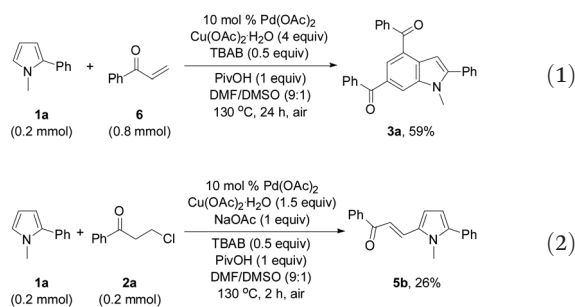
66–68% yields. However, electron-donating methoxy, and electron-withdrawing groups such as fluoro, ester, cyano, and chloro, on the aryl group deteriorated the production of **4g** (51%), and **4h–4k** (52–62%). *N*-Methyl-2-(1-naphthyl)pyrrole reacted to give **4l** (61%). The reaction also tolerated thienyl on the pyrrole ring, yielding 2-thienylindole **4m** (42%). 1,3-Dimethyl-2-phenyl-pyrrole exhibited a decent reactivity to form **4n** (63%), showing no obvious steric effect from the pyrrole backbone. However, the reaction of 1,2-dimethylpyrrole only formed **4o** in 36% yield, exhibiting a negative electronic effect from the 2-substituent of the pyrrole backbone. Owing to the multiple reactive sites in 1-methylpyrrole, the target product **4p** was only obtained in a low yield (17%). Unexpectedly, the reaction of *N*-methyl-2-(4-nitro-phenyl)pyrrole with **2a** afforded indole **4q** (38%) and the reaction intermediate 5-alkenylated pyrrole **5a** (35%). In the cases of using 2-phenyl-substituted *N*-H or *N*-Boc pyrroles, the target indole products could not be obtained. It should be noted that indole **4d** was further

structurally confirmed by X-ray crystallographic analysis (see the ESI†).

In order to investigate the reaction mechanism, controlled experiments were conducted to identify the possible reaction intermediates. We have recently established that compound **2a** can be dehydrochlorinated to form phenyl vinyl ketone (enone) **6** under basic conditions.^{21b} Thus, enone **6** (4 equiv.) was used to react with **1a** under the conditions similar to those shown in Tables 2 and 3 (eqn (1)). In this case, a base was not necessary, and **3a** was formed in 59% yield, suggesting that *in situ* generation of enone **6** from 3-chloropropiophenone is superior to direct use of the corresponding enone substrate for the synthesis of indole **3a**. To obtain the 5-alkenylated pyrrole intermediate of type **5** pyrrole **1a** was treated with **2a** in a 1:1 molar ratio by lowering both the base and oxidant loadings and shortening the reaction time to 2 h (eqn (2)). Fortunately, 5-alkenylated pyrrole **5b** was obtained in 26% yield. Then, **5b** was treated with **2a** under the controlled conditions as shown in Scheme 2. With 10 mol% Pd(OAc)₂ as the catalyst,

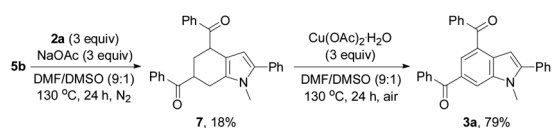
Scheme 2 Controlled reactions of **5b** with **2a**.

3a was formed in 50% isolated yield. Without $\text{Pd}(\text{OAc})_2$ the reaction occurred to form **3a** in 65% yield, and using $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as the sole mediator under a nitrogen atmosphere also led to **3a** in a decent yield (72%). The air atmosphere promoted the formation of **3a** (29%). These results have revealed that $\text{Pd}(\text{OAc})_2$ only acted as the catalyst for the oxidative alkenylation of pyrrole **1a**, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ promoted both the alkenylation of **1a** and dehydrogenative cyclization of **5b** with the *in situ* generated enone **6** to produce indole **3a**. Although the air atmosphere facilitated the formation of the target product **3a**, an additional oxidant is required to reach a satisfactory reaction efficiency.

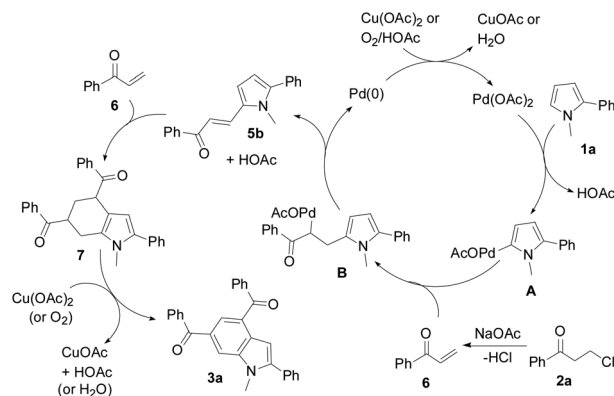


Taking the observed regioselectivity into account, we assume that **3a** is formed through the Diels–Alder reaction of intermediate **5b** with enone **6** generated *in situ* from **2a** followed by dehydrogenative aromatization. Indeed, the Diels–Alder reaction intermediate, that is, tetrahydroindole **7**, was isolated in 18% yield from the reaction of **5b** with **2a** (3 equiv.) in the presence of a NaOAc base (3 equiv.) under an inert atmosphere without the catalyst, oxidant, and additives. The dehydrogenative aromatization reaction of **7** was conducted by means of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as the oxidant, affording the target product **3a** in 79% yield (Scheme 3).

A plausible mechanism is proposed in Scheme 4. Pyrrole **1a** initially undergoes palladation at its 5-position to form a



Scheme 3 Identification of the Diels–Alder reaction intermediate.



Scheme 4 Proposed mechanism.

palladated species **A** and HOAc via C–H activation. Species **A** reacts with the *in situ* generated enone **6** from **2a** to yield an olefin insertion species **B**. Subsequent reductive elimination produces 5-alkenylated pyrrole **5b** and the $\text{Pd}(0)$ species. A Diels–Alder cycloaddition of enone **6** to **5b** forms tetrahydroindole **7**, which is subsequently oxidized to indole **3a**. Both the $\text{Cu}(\text{II})$ oxidant and air facilitate regeneration of the catalyst.

In conclusion, palladium-catalyzed oxidative annulation of 3-chloropropiophenones and their analogues to *N*-substituted simple pyrroles has been successfully achieved to synthesize functionalized indoles. The synthetic protocol features construction of a substituted benzene ring onto a pyrrole backbone through the *in situ* generated enones. A domino dehydrochlorination/C–H olefination/Diels–Alder cycloaddition/dehydrogenative aromatization sequence was established as the reaction pathway. The present protocol provides a concise route to functionalized indoles.

Experimental section

A typical procedure for the synthesis of indoles from pyrroles: synthesis of **3a**

A mixture of *N*-methyl-2-phenylpyrrole (**1a**) (32 mg, 0.2 mmol), 3-chloropropiophenone (**2a**) (133 mg, 0.8 mmol), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 0.02 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (160 mg, 0.8 mmol), TBAB (32 mg, 0.1 mmol), PivOH (20 mg, 0.2 mmol), and NaOAc (66 mg, 0.8 mmol) in 2.5 mL DMF/DMSO ($v/v = 9:1$) was stirred at 130 °C under an air atmosphere for 24 h. After being cooled to ambient temperature, 10 mL CH_2Cl_2 was added and the resultant mixture was filtered through a short pad of celite, followed by rinsing with 10 mL CH_2Cl_2 . The combined filtrate was washed with brine (10 mL) and separated. The organic phase was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60–90 °C)/ $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ (30 : 1 : 3, $v/v/v$) to afford **3a** as a yellow liquid (56 mg, 68%).

Acknowledgements

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