Indoles are very important structural motifs in many organic compounds. Although Fischer indoles were first reported in 1883, the recently known indole syntheses are predominantly directed towards construction of a pyrrole ring onto a prefunctionalized benzene precursor. 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. In this aspect, anionic benzanellation of N-methylpyrroles with alkenes or alkynes was employed to form functionalized indoles. Intramolecular cyclization of vinylpyrroles and alkylated pyrroles occurred to give multi-substituted indoles under various conditions, respectively. Diels–Alder reactions of 2-vinylpyrroles with maleimides, and 2- or 3-nitropyrroles with dienes, were realized for the same purpose. Lewis acid-catalyzed pyrrolyl-supported enynals with enols or enol ethers, and ruthenium(0)-mediated annulation of pyrroles with propargyl alcohols yielded indoles under relatively harsh conditions. Palladium-catalyzed oxidative decarboxylative annulation of N-methylpyrrole-2-carboxylic acid with alkynes generated indoles as reaction intermediates. Substituted indoles were also obtained from one-pot, two-step reactions of pyrroles with β-nitroacrylates. Benzannellation of pyroles with rhodium enalcarbenoids formed substituted indoles. Because establishment of an indole core is often encountered in the synthesis of functionalized molecules, 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 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, direct oxidative cross-coupling of pyroles 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, and later Yao’s lab achieved palladium-catalyzed solvent-controlled switchable olefination of 3,4-disubstituted pyroles with electron-deficient olefins (Scheme 1a). Under acid, iodine, or organocatalysis 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, we reasonably envisioned the oxidative annulation reactions of β-chloroalkyl ketones to pyroles. 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...
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, tBuOOtBu, 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 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)²

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Additive (equiv.)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)₂·H₂O</td>
<td>DMSO</td>
<td></td>
<td>100</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)₂·H₂O</td>
<td>DMF</td>
<td></td>
<td>100</td>
<td>42</td>
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<tr>
<td>3</td>
<td>Cu(OAc)₂·H₂O</td>
<td>DMF/DMSO</td>
<td></td>
<td>100</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)₂</td>
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<td></td>
<td>100</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)₂</td>
<td>DMF/DMSO</td>
<td></td>
<td>100</td>
<td>&lt;1</td>
</tr>
<tr>
<td>6</td>
<td>Air</td>
<td>DMF/DMSO</td>
<td></td>
<td>100</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OAc)₂·H₂O</td>
<td>DMF/DMSO</td>
<td>TBAB (0.5)</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OAc)₂·H₂O</td>
<td>DMF/DMSO</td>
<td>PivOH (1.0)</td>
<td>100</td>
<td>66</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OAc)₂·H₂O</td>
<td>DMF/DMSO</td>
<td>TBAB/PivOH</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OAc)₂·H₂O</td>
<td>DMF/DMSO</td>
<td>TBAB/PivOH</td>
<td>100</td>
<td>60</td>
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<tr>
<td>11</td>
<td>Cu(OAc)₂·H₂O</td>
<td>DMF/DMSO</td>
<td>TBAB/PivOH</td>
<td>80</td>
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<tr>
<td>12</td>
<td>Cu(OAc)₂·H₂O</td>
<td>DMF/DMSO</td>
<td>TBAB/PivOH</td>
<td>130</td>
<td>68</td>
</tr>
<tr>
<td>13</td>
<td>Cu(OAc)₂·H₂O</td>
<td>DMF/DMSO</td>
<td>TBAB/PivOH</td>
<td>140</td>
<td>52</td>
</tr>
</tbody>
</table>

² 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. Isolated yields based on 1a. DMF/DMSO (v:v = 9:1). Under 0.1 MPa N₂ atmosphere. Cu(OAc)₂·H₂O (0.8 mmol). TBAB (0.1 mmol) and PivOH (0.2 mmol).
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,
3a was formed in 50% isolated yield. Without Pd(OAc)_2 the reaction occurred to form 3a in 65% yield, and using Cu(OAc)_2·H_2O 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 Pd(OAc)_2 only acted as the catalyst for the oxidative alkenylation of pyrrole 1a, Cu(OAc)_2·H_2O 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 Cu(OAc)_2·H_2O 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 palladated species A and HOOAc 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 Pd(0) species. A Diels–Alder cycloaddition of enone 6 to 5b forms tetrahydroindole 7, which is subsequently oxidized to indole 3a. Both the Cu(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), Pd(OAc)_2 (4.5 mg, 0.02 mmol), Cu(OAc)_2·H_2O (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)/EtOAc/CH_2Cl_2 (30:1:3, v/v/v) to afford 3a as a yellow liquid (56 mg, 68%).
Acknowledgements

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Notes and references