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Efficient synthesis of highly substituted pyrroles through a $Pd(OCOCF_3)_2$-catalyzed cascade reaction of 2-alkenal-1,3-dicarbonyl compounds with primary amines†

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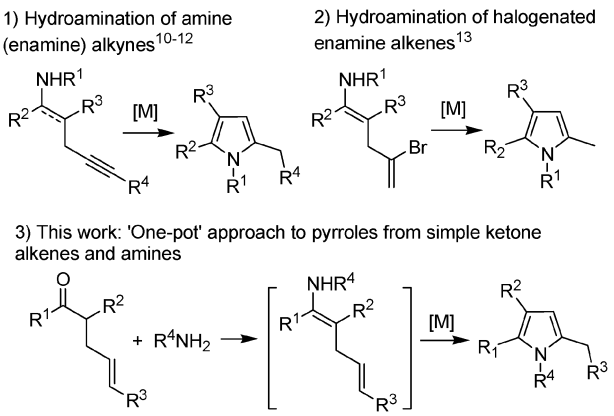
We describe an unprecedented $Pd(OCOCF_3)_2$-catalyzed cascade process for the synthesis of highly functionalized 1,2,3,5-tetra-substituted pyrroles with high efficiency. Unlike documented methods relying on preformed enamines and active halogenated terminal alkenes, the process employs simple 2-alkenal-dicarbonyls and primary amines in 'one-pot'.

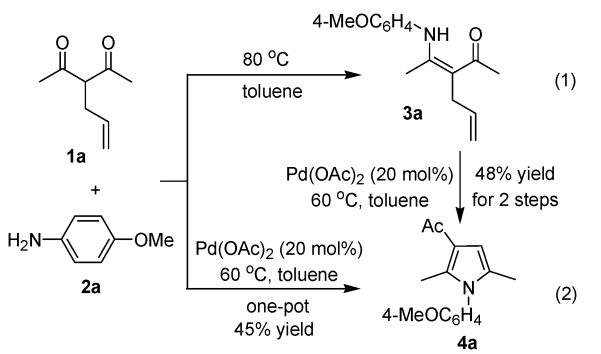
Pyrrole units feature in a number of natural products and biologically active molecules[1] with a broad spectrum of biological properties such as antitumor,[2] antibacterial,[3] and antiviral activities.[4] Moreover, they are also widely employed as versatile building blocks in organic synthesis.[5] Therefore, there has been a long-standing interest in the development of efficient methods for their preparation. The classical synthetic methods include the Barton–Zard,[6] Paal–Knorr[7] and Hantzsch reactions.[8] The increasing applications of this class of compounds demand more efficient synthetic approaches and significant progress has been made.[9] A popular strategy uses transition metal-catalyzed hydroamination of functionalized amine alkynes (eqn (1), Scheme 1).[10–12] The palladium catalyzed cyclization of less reactive alkene-Wacker-type cyclization reactions[13] is promising. However, it has limited success in the formation of pyrroles.[14,15] Other methods rely on the use of halogenated terminal alkenes (eqn (2))[16] or 2-step halogen activation of terminal alkenes.[17] Nevertheless, the preformation of enamines is required for these processes. To the best of our knowledge, the intermolecular Wacker-type reaction of unactivated alkenes with amines for the synthesis of pyrroles has not been reported.



Scheme 1 Hydroamination approaches to pyrroles.

Toward this end, we wish to report an unprecedented highly efficient Pd-catalyzed cascade Wacker-type process in 'one-pot' for the synthesis of highly substituted pyrroles (eqn (3)).

In the initial attempt to synthesise pyrroles, we probed a 2-step sequence process *via* a model reaction of 3-allylpentane-2,4-dione (**1a**) with *p*-anisidine (**2a**) (Scheme 2, eqn (1)). A mixture of **1a** and **2a** in toluene was heated at 80 °C leading



Scheme 2 Exploration of Pd-catalyzed enamination–alkenyl hydroamination for the preparation of substituted pyrroles **4a**: (1) two step reactions; (2) 'one-pot' reaction.

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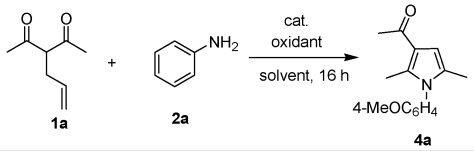
† Electronic supplementary information (ESI) available: Experimental procedures, compound characterizations, and ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c3cc42216j

Table 1 Optimization of reaction conditions



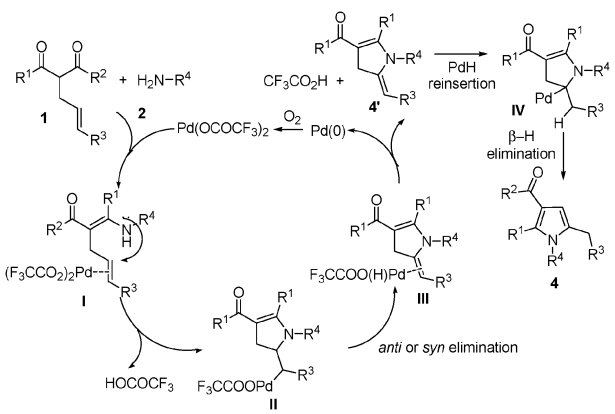
1a 2a 4a

Entry[a]	Solvent	Catalyst	Oxidant	Yield[b] (%)
1	Toluene	$Pd(OAc)_2$	Air	45
2	Xylenes	$Pd(OAc)_2$	Air	50
3	Xylenes	$Pd(OAc)_2$	O_2	58
4	Xylenes	$PdCl_2$	O_2	28
5	Xylenes	$PdCl_2(PPh_3)_2$	O_2	14
6	Xylenes	$PdCl_2(CH_3CN)_2$	O_2	Trace
7	Xylenes	$Pd(PPh_3)_4$	O_2	17
8[c]	Xylenes	$Pd(OCOCF_3)_2$	O_2	82
9[d]	Toluene	$Pd(OCOCF_3)_2$	O_2	86
10[e]	Toluene	$Pd(OCOCF_3)_2$	O_2	88

[a] A solution of **1a** (1.2 mmol) and **2a** (0.6 mmol) with catalyst (0.12 mmol) in the solvent (2 mL) was stirred at 60 °C for 16 h. [b] Isolated yield. [c] The reaction time is 2 h. [d] The reaction time is 1.5 h. [e] 5 mol% catalyst used with a reaction time of 16 h.

to the formation of the enaminone derivative **3a**. Without the isolation of intermediate **3a**, it was then treated with a catalytic amount of $Pd(OAc)_2$ (20 mol%) at 60 °C for 16 h. Under the reaction conditions, the desired product pyrrole **4a** was obtained in 48% yield. Encouraged by the outcome, we combined the two steps in 'one-pot' aiming to further improve the synthetic efficiency in a cascade manner. A toluene solution of **1a** (2.0 equiv.) and **2a** (1.0 equiv.) in the presence of $Pd(OAc)_2$ (20 mol%) was stirred at 60 °C overnight. To our delight, the desired product **4a** was obtained in a similar yield (45%) (Scheme 2, eqn (2)).

Next, we made an effort to optimize the reaction conditions to improve reaction yields (Table 1). Screening of reaction solvents revealed that most of them afforded reaction yields lower than that in toluene (23–40%, see ESI,† Table S1). The reaction yield in xylenes was slightly higher than that in toluene (50%, entry 2). It was found that elevating the reaction temperature to 80 °C was not beneficial. An almost identical yield was observed (data not shown). If the reaction was carried out under nitrogen, the reaction yield dropped significantly and only a trace of amount of the product was obtained.



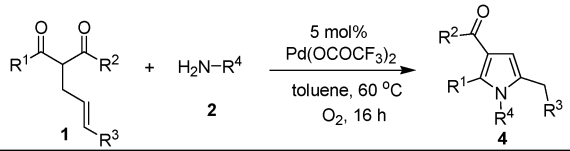
Scheme 3 A proposed mechanism for the cascade reaction.

This indicates that the oxygen is essential for the catalyst recycling (see Scheme 3). Different oxidants including $Cu(OAc)_2$ (1.0 equiv.) and AgOAc were probed instead of air (see Table S1, ESI†), and the reaction yields decreased dramatically. When O_2 was used instead of air, the reaction yield increased to 58% (entry 3). These results further demonstrated that the oxidant was optimal for the reaction. When different palladium catalysts with O_2 as the oxidant were tested, all reactions gave poor yields (entries 4–7). However, the reaction catalyzed by $Pd(OCOCF_3)_2$ in xylenes completed in 2 h with a high yield of 82% (entry 8). Moreover, the reaction in toluene proceeded faster (1.5 h) with higher yields (86%, entry 9). Lowering the catalyst loading from 20 mol% to 5 mol% did not affect the reaction yields albeit prolonging the reaction time (88%, 16 h, entry 10).

The studies reveal that the process serves as a general approach to the synthesis of structurally diverse pyrroles **4**. Significant structural variations in the amine components can be tolerated. The substitution pattern of the methoxy group on the phenyl ring of the anilines has a very limited impact (**4a–c**, entries 1–3). Yields drop only slightly indicating the role of the steric effect. Neutral aniline also proceeds smoothly with 77% yield (**4d**, entry 4). Furthermore, the anilines bearing other electron-donating groups on the phenyl ring are also suitable for this protocol (**4e–4g**, entries 5–7). Even two substituents on the phenyl rings such as 2-naphthalenamine, 3,4-dimethyaniline and 4-methoxy-2-methylaniline can be present in the substrates as illustrated by the formation of the pyrrole products **4h–j** in good yields (74–85%, entries 8–10). However, the anilines with electron-withdrawing groups (EWG) on the phenyl ring give lower yields under the same reaction conditions (**4k** and **l**, 40–50%, entries 11 and 12). It is believed that the EWG significantly reduce the nucelophilicity of the nitrogen of aniline. We noted that in addition to aromatic amines, the aliphatic amines could smoothly involve in the process to afford the corresponding pyrroles **4m** and **n** with excellent yields (entries 13 and 14). Probing the diketone substrates implies that the more hindered R^1 = Et group appears to be a good candidate for this cascade reaction (**4o**, entry 15). Moreover, the variation of R^2 functionalities on **1** such as phenyl and OEt groups can afford the structurally diverse pyrroles **4p–r** (entries 16–18). Finally, we examined the challenging non-terminal alkene substrates. Such a reactant could form two possible products pyrrole and pyridine. We found that the process proceeded with high regioselectivity. Only pyrrole **4s** was afforded with acceptable yield (R^3 = Ph, entry 19) (Table 2).

A mechanism for the palladium-catalyzed Wacker-type reaction of 2-alkenal-1,3-dicarbonyl compounds with primary amines leading to substituted pyrroles is proposed in Scheme 3. The enamine **3** generated from dicarbonyl compound **1** and primary amine **2** is coordinated with $Pd(OCOCF_3)_2$ to form palladium–alkene complex intermediate **I**, followed by the Wacker-type reaction of the nitrogen to the palladium activated alkene in an *anti* manner[18] with the loss of HOAc to generate Pd–alkyl intermediate **II**. **II** undergoes β-hydride elimination to form Pd(H)(alkene) complex **III**. The resulting intermediate **III** forms dihydropyrrole **4′** upon alkene dissociation and Pd(H). Alternatively, alkene **4′** can reinsert into the Pd(H) to form

Table 2 Scope of $Pd(OCOCF_3)_2$-catalyzed synthesis of pyrroles **4**[a]



Entry[a]	R^1, R^2, R^3, R^4, **4**	Yield[b] (%)
1	Me, Me, H, 4-MeOPh, **4a**	88
2	Me, Me, H, 3-MeOPh, **4b**	86
3	Me, Me, H, 2-MeOPh, **4c**	70
4	Me, Me, H, Ph, **4d**	77
5	Me, Me, H, 4-MePh, **4e**	82
6	Me, Me, H, 4-CF_3OPh, **4f**	81
7	Me, Me, H, 4-PhOPh, **4g**	84
8	Me, Me, H, 2-naphthyl, **4h**	84
9	Me, Me, H, 3,4-MePh, **4i**	85
10	Me, Me, H, 2-Me-4-MeOPh, **4j**	74
11[c]	Me, Me, H, 3-FPh, **4k**	50
12[c]	Me, Me, H, 4-NO_2Ph, **4l**	40
13	Me, Me, H, 4-MeO-benzyl, **4m**	91
14	Me, Me, H, isopentyl, **4n**	90
15	Et, Et, H, 4-MeOPh, **4o**	83
16	Me, Ph, H, 4-MeOPh, **4p**	78
17	Me, Ph, H, Ph, **4q**	75
18	Me, OEt, H, 4-MeOPh, **4r**	85
19	Me, Me, Ph, 4-MeOPh, **4s**	60

[a] A solution of **1** (1.2 mmol) and **2** (0.6 mmol) with catalyst (0.12 mmol) in xylenes (2 mL) was stirred at 60 °C for 16 h. [b] Isolated yield. [c] 20 mol% catalyst used.

Pd–alkyl intermediate **IV**,[19] which can undergo second β-hydride elimination to aromatize the system to give pyrrole **4**. Catalyst Pd(II) is regenerated through Pd(0) oxidized by O_2. Finally, pyrrole **4** is formed *via* acid-catalyzed isomerization of **4′** (Scheme 3).

In summary, we have developed an unprecedented palladium-catalyzed cascade Wacker-type process for the 'one-pot' synthesis of synthetically and biologically meaningful pyrroles. Unlike reported methods relying on preformed enamines and active halogenated terminal alkenes, the process uses simple 2-alkenal-dicarbonyl compounds and primary amines to synthesise highly substituted pyrroles in a cascade fashion in moderate to excellent yields for a diverse range of substrates. Moreover, non-terminal alkenes can be applied in a highly regioselective manner.

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