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Ruthenium-Catalyzed Pyrrole Synthesis via Oxidative Annulation of Enamides and Alkynes

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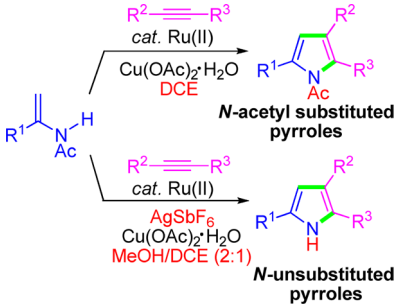
ABSTRACT



An efficient and regioselective ruthenium-catalyzed oxidative annulation of enamides with alkynes via the cleavage of C(sp^2)−H/N−H bonds is reported. The reactions can afford *N*-acetyl substituted or *N*-unsubstituted pyrroles by altering the reaction conditions slightly.

Pyrroles represent one of the most important classes of five-membered heterocycle compounds that constitute the core motif of many natural products.[1] Furthermore, they are useful building blocks in the synthesis of compounds with interesting biological and pharmaceutical activities[2] and are widely used in the field of materials chemistry.[3] As a result, many new synthetic methods have been developed for the construction of pyrroles and their derivatives over the years.[4] Among these methods, the transition-metal-catalyzed reactions play a prominent role.[5] However,

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the catalytic C−H bond functionalization[6] strategy has not been introduced into the field of pyrrole synthesis until 2010, which provides a more atom-economical and environmentally friendly approach. In this respect, to the best of our knowledge, only two reports on rhodium-catalyzed reactions were described. The seminal work by the research groups of Glorius[7] as well as Stuart and Fagnou[8] have revealed two novel polysubstituted pyrrole synthesis methods through $Cp^*Rh^{III}L_n$ ($Cp^* = C_5Me_5$) catalyzed allylic $C(sp^3)$−H activation of enamines or $C(sp^2)$−H activation of enamides followed by the cyclization with an internal alkyne. But in these transformations, an expensive catalyst was required.

Very recently, the less-expensive and readily available ruthenium complex [{$RuCl_2$(*p*-cymene)}$_2$] has been used as a catalyst in the chelation-assisted oxidative cycloaddition reactions between aromatic or alkenyl C−H bond and alkynes.[9] In this regard, methods to synthesize isoquinolones,[9a,b] pyridines,[9c] indenols,[9e] indoles,[9f] isocoumarins,[9g,h] pyrans,[9i] and isoquinolines[9j] through catalytic C−H bond activation have been developed by Ackermann et al., Jeganmohan et al., Cheng et al., and us. In contrast, as far as we know, [{$RuCl_2$(*p*-cymene)}$_2$]-catalyzed pyrrole synthesis via C−H transformation was not available in the literature. As a continuation of our interest in [{$RuCl_2$(*p*-cymene)}$_2$]-catalyzed C−H functionalization,[9b,k,10] we here disclose our development of oxidative annulation of enamides with alkynes via the cleavage of $C(sp^2)$−H/N−H bonds in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] as the catalyst and $Cu(OAc)_2\cdot H_2O$ as the oxidant to synthesize a *N*-acetyl substituted pyrrole. In addition, with the addition of $AgSbF_6$ and MeOH to the above reaction system, our ruthenium-catalyzed process also offers an interesting route of a direct synthesis to the synthetically more attractive *N*-unsubstituted pyrroles.

We began our study with the annulation reaction of methyl 2-acetamidoacrylate (**1a**) and diphenylacetylene (**2a**). Treatment of **1a** (1.0 equiv) with **2a** (1.1 equiv) in the presence of 5.0 mol % of [{$RuCl_2$(*p*-cymene)}$_2$] and 2.2 equiv of $Cu(OAc)_2\cdot H_2O$ in 1,2-dichloroethane (DCE) at 100 °C for 12 h gave the desired *N*-acetyl substituted pyrrole **3aa** in 89% yield. The structure of **3aa** was confirmed by ^1H and ^{13}C NMR analysis and mass spectrometry, which are consistent with those reported previously.[8] Other solvents, such as *t*-AmOH (*t*-Am = *tert*-amyl) and dioxane, were also effective solvents for the reaction, giving **3aa** in 84% and 83% isolated yield, respectively. But a change of solvent to CH_3CN and H_2O led to a low yield. It was interesting to find that reducing the amount of $Cu(OAc)_2\cdot H_2O$ to 0.5 equiv resulted in no loss in yield of **3aa** (90%).[11] Notably, no silver salt (such as $AgSbF_6$) was needed in our reaction system as compared to the previously reported rhodium-catalyzed transformation. In Stuart and Fagnou's catalytic system, the preactivation of the Rh(III) precursor with $AgSbF_6$ resulted in a great enhancement in catalyst efficiency to allow low temperature reactions.[8] However, we found that the addition of $AgSbF_6$ resulted in the deacetylation of **3aa** in our reaction (see below).

We then explored the internal alkyne scope of our ruthenium-catalyzed oxidative annulation transformation of **1a** under the optimized reaction conditions (Scheme 1). With both the electron-poor and -rich tolanes, the reaction proceeded smoothly and provided the corresponding adducts **3ab**−**3ag** in good to excellent yields. Gratifyingly, functional groups such as fluoro, chloro, bromo, carboxylic ester, and methoxy substituents were very compatible in the present catalytic reaction. These functional groups offer the opportunity for further functionalization to construct more complex molecules. The symmetrically aliphatic or heteroaryl-substituted alkynes, such as 3-hexyne (**2h**) and 4-octyne (**2i**) or di(2-thiophenyl)ethylene (**2j**), were successfully coupled with **1a** to yield **3ah**−**3aj** but generally exhibited lower reactivity (62−72%). When unsymmetrical aryl alkyl-disubstituted alkynes (**2k**−**2m**) were employed, the reactions exhibit high regioselectivity: **3ak**−**3am** were isolated as single regioisomers with an aryl-substituted carbon center connected to nitrogen. Good results were also obtained from using ethyl (**1b**) and benzyl (**1c**) ester-substituted enamides together with various internal alkynes, providing the products **3ba**, **3bi**, **3bk**, **3bl**, **3ca**, **3ci**, **3ck**, **3cl**, and **3cj** in up to 85% yield. Replacement of the ester with a phenyl group led to the formation of **3da** in low yield.

In addition, by using (*E*)-1-cyanopropenyl-2-acetamide (**4**) as the substrate, the formation of pentasubstituted pyrroles (**5**) was achieved in moderate yield (55−61%) and high regioselectivity (eq 1).

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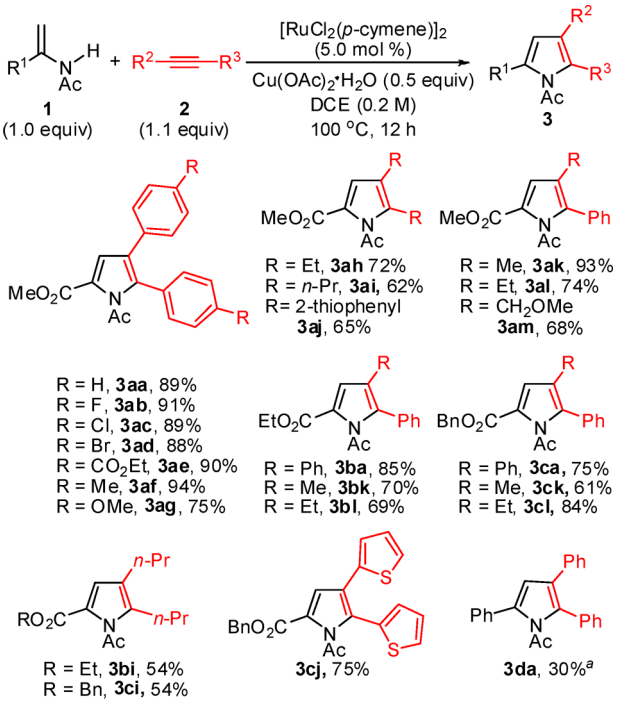
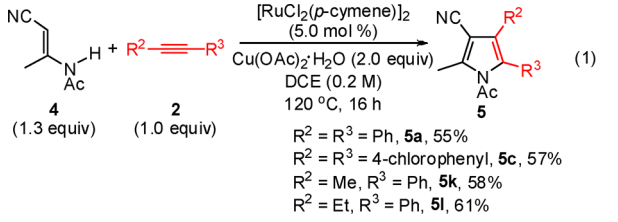
(11) For detailed optimization studies, see Table S1 in the Supporting Information.

Scheme 1. Results of Ruthenium-Catalyzed *N*-Acetyl Substituted Pyrrole (**3**) Synthesis[a]



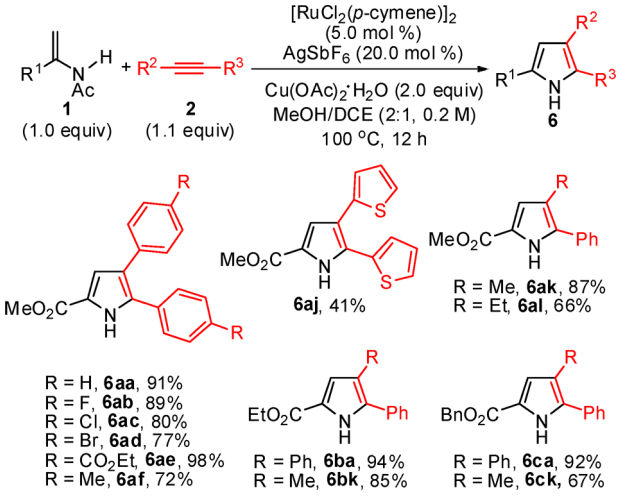
[a] 20.0 mol % of $AgSbF_6$ and 2.0 equiv of $Cu(OAc)_2 \cdot H_2O$ in CH_3CN were used.

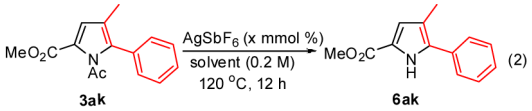


It was demonstrated that a separate deprotection step is necessary for the synthesis of *N*-unsubstituted pyrroles in previously reported Rh-catalyzed reactions.[7,8] Intriguingly, the combination of pyrrole formation and subsequent deacetylation in one process was realized in our ruthenium-catalyzed process. When the above-mentioned reaction conditions were altered slightly—5.0 mol % of $[\{RuCl_2(p\text{-cymene})\}_2]$, 20 mol % of $AgSbF_6$, and 2.0 equiv of $Cu(OAc)_2 \cdot H_2O$ in a mixed solvent system of MeOH/DCE (2:1, 0.2 M) at 100 °C for 12 h—the synthetically more attractive *N*-unsubstituted pyrroles **6** were isolated as single products in high yield.[12] Control experiments reveal that deacetylation of **3** results in the generation of **6** and both $AgSbF_6$ and MeOH are essential for this transformation (eq 2): **6ak** was isolated in 98% yield from **3ak** under the standard reaction conditions, whereas in the absence of $AgSbF_6$ or MeOH, only part of **3ak** was converted. As shown in Scheme 2, the internal alkynes **2a**–**2f**, **2j**, **2k**, and **2l** were all successfully reacted with **1a** as well as **1b** and **1c**, providing the corresponding trisubstituted pyrroles **6** in moderate to excellent yield and high regioselectivity.

(12) For detailed optimization studies, see Table S2 in the Supporting Information.

Scheme 2. Results of Ruthenium-Catalyzed *N*-Unsubstituted Pyrrole (**6**) Synthesis

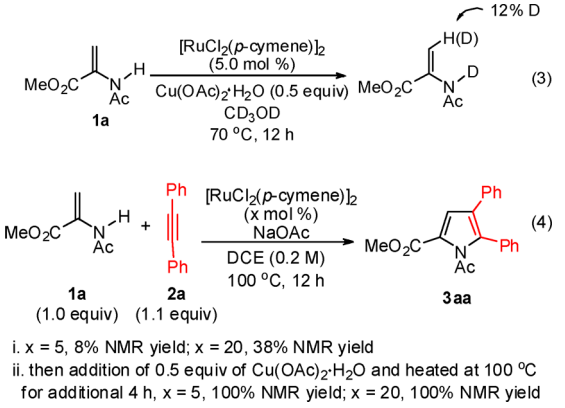


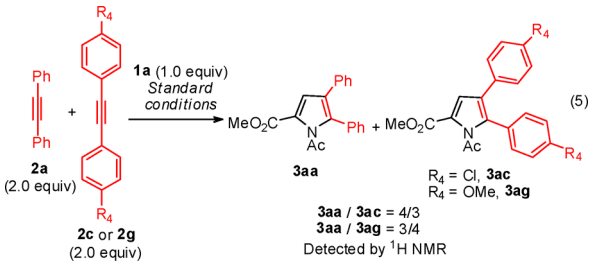


[a] 42% of **3ak** was recovered. [b] 62% of **3ak** was recovered.

We then conducted a series of experiments to unveil the nature of the reaction mechanism.[13] First, reactions with isotopically labeled solvents were studied. Only N–H deuteration was observed in the absence of the Ru catalyst, and an additional 12% deuterium incorporation at the CH_{olefin} was found in the presence of Ru (eq 3). This result suggests that, under the reaction conditions, the C–H bond metalation step is probably irreversible. Then, in the absence of $Cu(OAc)_2 \cdot H_2O$, two reactions between **1a** and **2a** were conducted using 5.0 mol % $[\{RuCl_2(p\text{-cymene})\}_2]$ and 20.0 mol % $[\{RuCl_2(p\text{-cymene})\}_2]$, repectively. After 12 h at 100 °C, **3aa** was formed in 8% and 38% NMR yield, respectively. Afterwards, the addition of 0.5 equiv of $Cu(OAc)_2 \cdot H_2O$ to these mixtures and prolonged heating for 4 h at 100 °C led to a quantitative NMR yield of **3aa** for both reactions (eq 4). These results indicate that Cu(II) is not essential for product formation. Finally, competition experiments between tolane and its derivative **2c** or **2g** reveal that the reaction slightly favors the electron-rich alkyne (electron-poor **2c** < **2a** < electron-rich **2g**, eq 5). This finding is in contrast with the reported Rh-catalyzed pyrrole synthesis by Glorius et al.

(13) See Supporting Information for details.





Based on the above information and the known metal-catalyzed oxidative annulation reactions,[7−9] a potential mechanism is proposed. As shown in Scheme 3, [{$RuCl_2$-(*p*-cymene)}$_2$] reacts with $Cu(OAc)_2 \cdot H_2O$ to form an acetate-ligated species. It may also be coordinated by **1a** via the amide oxygen. Then an irreversible C−H bond cleavage process occurs to afford a six-membered ruthenacycle **B** with concomitant formation of acetic acid via an acetate-assisted mechanism.[6e,14] Alkyne **2k** may then coordinate **B**, followed by insertion into the Ru−C bond and cleavage of N−H to form a six-membered ruthenacycle intermediate **C**. Subsequently, the oxidative coupling of the C−N bond takes place to form the pyrrole product **3ak** with the reduction of the ruthenium center from Ru(II) to Ru(0). The Ru(0) undergoes oxidation to regenerate the catalytically active Ru(II) complex with the aid of a copper oxidant.

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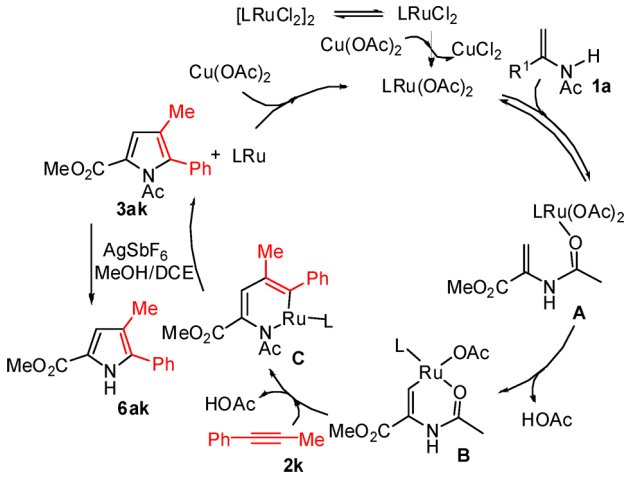
After removal of the acetyl group of **3ak** in the presence of $AgSbF_6$ and MeOH, **6ak** is formed in situ.

In conclusion, we have developed a ruthenium-catalyzed oxidative annulation of enamides with alkynes to synthesize *N*-acetyl substituted pyrroles via the cleavage of C(sp^2)−H/N−H bonds. The catalytic reaction exhibits excellent regioselectivity. With the addition of $AgSbF_6$ and MeOH, our ruthenium-catalyzed process can afford *N*-unsubstituted pyrroles directly. Further studies to explore ruthenium-catalyzed oxidative C−H bond transformations are ongoing in our laboratory and will be reported in due course.

Scheme 3. Proposed Mechanism (L = *p*-Cymene)



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Supporting Information Available. Detailed experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.