Organic LETTERS

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Regioselective Synthesis of 2,3,4-Trisubstituted Pyrroles via Pd(II)-Catalyzed Three-Component Cascade Reactions of Amines, Alkyne Esters, and Alkenes

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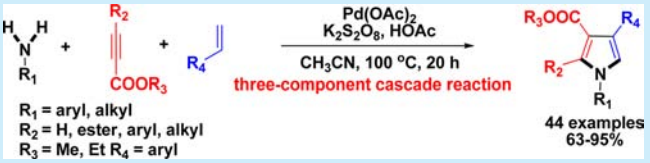
Supporting Information

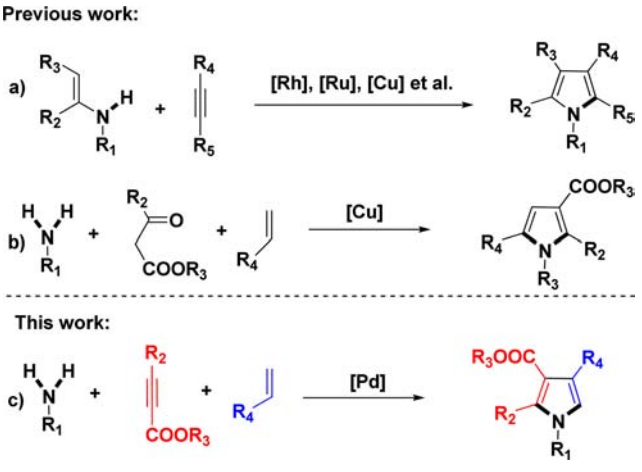
ABSTRACT: A new, efficient, and versatile Pd(II)-catalyzed oxidative three-component cascade reaction of diverse amines, alkyne esters, and alkenes is disclosed for the direct synthesis of diverse 2,3,4-trisubstituted pyrroles with broad functional group tolerance and in good to excellent yields. This transformation is supposed to proceed through the cascade formation of C(sp^2)−C(sp^2) and C(sp^2)−N bonds via Pd(II)-catalyzed regioselective alkene migratory insertion, intramolecular radical addition, and oxidation sequential processes.



Arguably, substituted pyrroles represent one of the most important classes of monocyclic *N*-heterocycles found in numerous natural products, pharmaceutical drugs, biologically active compounds, and functional materials.[1] Consequently, they have drawn considerable interest for synthetic chemists, and to date, a plethora of elegant procedures including the classical Knorr, Hantzsch, and Paal−Knorr condensation reaction have been developed for their construction.[2] However, these reactions usually proceed with limited substitution patterns of the substrates to give the relatively simple pyrrole products under harsh conditions and/or in low yields, which greatly hindered their application. Obviously, the development of new, efficient, and general methodologies for direct synthesis of multiple-substituted pyrroles using basic chemical materials remains one of the hottest topics in modern synthetic chemistry.

Recently, transition-metal-catalyzed C−H oxidative annulation of the C−H/N−H bonds has emerged as a popular and core strategy to construct the *N*-heterocycles.[3] Indeed, a large number of privileged *N*-heterocycles, such as indoles,[4] pyridines,[5] and isoquinolines,[6] have been smoothly synthesized in a more atom-economical and environmentally friendly manner with excellent substrate/functional group tolerance by employing such a versatile strategy. As one of the C−H/N−H bond annulation reaction precursors, enamines have been widely used for the synthesis of substituted pyrroles in various transition-metal-catalyzed C−H functionalization reactions (Scheme 1a).[7a−l] Despite this compelling progress, there is room for innovation. For example, the coupling partners of enamines are mostly limited to internal alkynes. Moreover, fully substituted pyrroles were often delivered in these developed catalytic systems, which would overshadow their further derivatization in a certain extent. In contrast, as far as we know, related C−H oxidative annulation of enamines with terminal alkenes toward pyrrole synthesis is still unexplored, and to date, only a beautiful example for the synthesis of 2,3,5-trisubstituted pyrroles were reported using amines and β-keto esters as enamine precursors (Scheme 1b).[7m] This is likely associated with the relatively low reactivity of terminal alkenes toward transition metals in comparison with internal alkynes. Undoubtedly, it is very challenging but highly desirable to develop a transition-metal-catalyzed direct C−H activation

Scheme 1. Transition-Metal-Catalyzed C−H Oxidative Annulations of Enamines for the Synthesis of Pyrroles



Received: August 6, 2016
Published: September 13, 2016

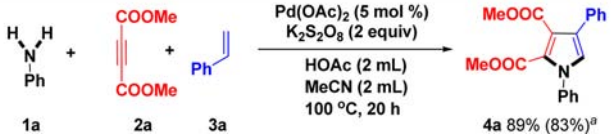
DOI: 10.1021/acs.orglett.6b02325
Org. Lett. 2016, 18, 4864−4867

strategy to build the privileged pyrroles with new substitution patterns by using low reactive terminal alkenes as efficient coupling partners.

It is well-known that enamines could be conveniently generated in situ from commercially available animes and alkyne esters.[8] Inspired by the above information, we envision that the use of simple animes and alkyne esters in place of the enamines, with alkenes in a proper transition-metal catalysis, could potentially provide a complementary method for pyrrole synthesis. Therefore, we herein report, for the first time, an efficient, general, and straightforward method for the one-pot cascade synthesis of important 2,3,4-trisubstituted pyrroles by a three-component assembly from simple and readily available amines, alkyne esters and alkenes (Scheme 1c). The versatile protocol is also novel for the Pd(II)-catalyzed sequential reactions, in which thiosulfate acts as both an radical generating reagent and an organic oxidant.[9]

Given the successful history in Pd(II)-catalyzed C−H oxidative cross-coupling reactions,[10] at the outset of this study, we chose $Pd(OAc)_2$ as the active Pd(II) catalyst and employed commercially available aniline (**1a**), dimethyl but-2-ynedioate (**2a**), and styrene (**3a**) as the model substrates for the reaction development (see the Supporting Information). After several parameters were screened, the three-component cascade reactions were optimized as follows: 5 mol % of $Pd(OAc)_2$, 2.0 equiv of $K_2S_2O_8$, and 2.0 mL of HOAc in MeCN at 100 °C for 20 h under an atmosphere of air (Scheme 2). It

Scheme 2. Optimized Results of the Pd(II)-Catalyzed Three-Component Cascade Reaction

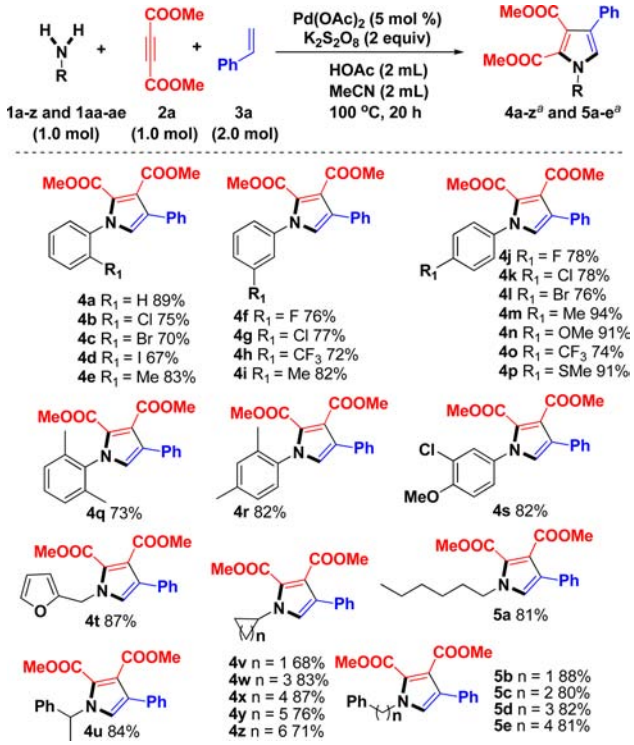


[a]The isolated yield was given when the reaction was performed on a 10 mmol scale.

was important to note that the reaction could be smoothly performed on a 10 mmol scale under the optimized conditions without a significant decrease in the product yield (83% vs 89%), which illustrated the remarkable robustness of this Pd(II)-catalyzed system.

Having the established standard conditions in hand, we first examined the substrate scope of this reaction with respect to amines (Scheme 3). Pleasingly, the results demonstrated that a wide range of aryl amine substrates reacted smoothly with **2a** and **3a** to deliver the desired products in good to excellent yields (67−94%). Both electron-donating and electron-withdrawing substituents either at the ortho- (**4a**−**e**), meta- (**4f**−**i**), or para- (**4j**−**p**) position were all well tolerated. Importantly, the reaction also showed good compatibility with many valuable functional groups such as chloro (**4b**,**g**,**k**,**m**,**s**), bromo (**4c**,**l**), iodine (**4d**), methyl (**4e**,**i**,**m**,**q**−**r**), fluoro (**4f**), methoxy (**4n**,**s**), trifluoromethyl (**4h**,**o**), and methylthio (**4q**) substituents. Moreover, disubstituted aryl amines, such as 2,6-dimethylaniline (**1q**), 2,4-dimethylaniline (**1r**), and 3-chloro-4-methoxyaniline (**1s**), are also applicable to give the pyrrole products in good yields. Of note, replacement of the aryl amines with various alkyl amines including phenyl- and heteroaromatic ring-substituted alkyl amines were perfectly

Scheme 3. Scope of Amines

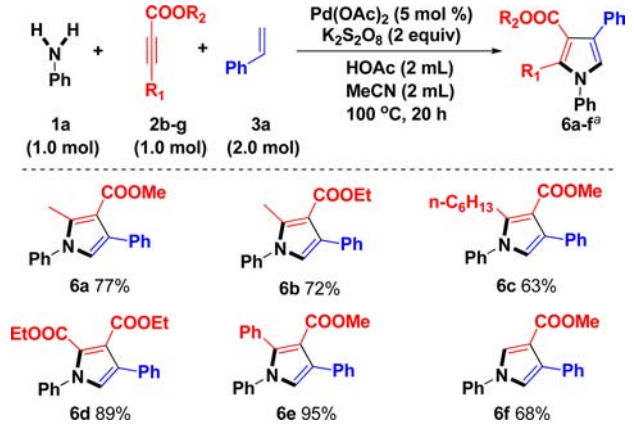


[a]Yields refer to isolated yields.

tolerated, producing their corresponding products (**4t**−**z** and **5a**−**e**) in decent isolated yields.

Next, we evaluated the substrate scope with respect to alkyne esters (Scheme 4). To our delight, the reaction was well

Scheme 4. Scope of Alkyne Esters



[a]Yields refer to isolated yields.

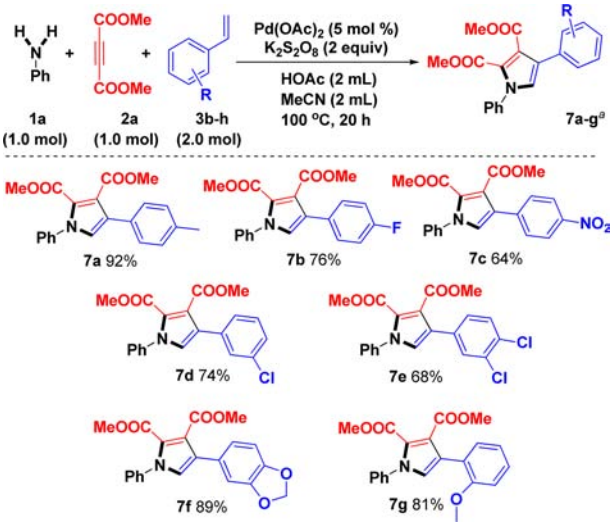
compatible with alkyl- as well as aryl-substituted internal alkyne esters, such as methyl but-2-ynoate (**2b**), ethyl but-2-ynoate (**2c**), methyl non-2-ynoate (**2d**), diethyl but-2-ynedioate (**2e**), and methyl 3-phenylpropiolate (**2f**), thus providing the corresponding pyrroles **6a**−**e** in generally good yields. Gratifyingly, terminal alkyne ester (**2g**) also smoothly reacted with **1a** and **3a** to deliver the desired product **6f** in 68% yield, which further demonstrated the versatility of this reaction.

To explore the substrate scope further, different arylethylenes were also investigated in the three-component process (Scheme

DOI: 10.1021/acs.orglett.6b02325
Org. Lett. 2016, 18, 4864−4867

5). In general, we found that the developed catalytic system proved to be broadly applicable, thus delivering the desired

Scheme 5. Scope of Alkenes

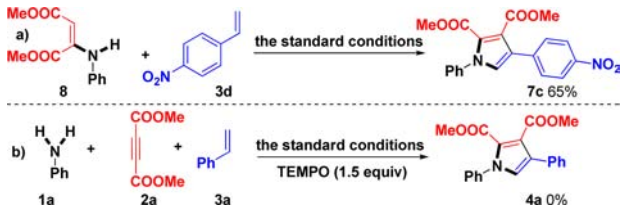


[a]Yields refer to isolated yields.

products **7a**–**g** in 64–92% yields. It should be emphasized that the electron-withdrawing alkenes gave relatively lower yields than the electron-donating substrates (e.g., 64% for **7c** and 68% for **7e** vs 92% for **7a** and 89% for **7f**), suggesting that the electrical property of the substituent on the benzene ring of arylethylene had an obvious influence on the outcome of the reaction.

Motivated by the aforementioned results and literature precedents,[7,11] we speculated that the enamines might be used as a key intermediate for the Pd(II)-catalyzed cascade reaction (Scheme 6a). Thus, enamine **8** were prepared and designated

Scheme 6. Experimental Investigation for the Reaction Mechanism

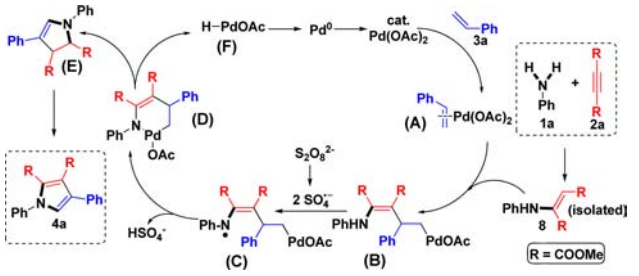


as substrates to probe the reaction mechanism. As expected, the designed reaction occurred successfully under the standard conditions to give the predicted product **7c** in 65% yield.

We also conducted a radical capture experiment to unveil both the role of $K_2S_2O_8$ and the nature of the reaction mechanism. As shown in Scheme 6b, when the Pd(II)-catalytic system was treated with a representative radical inhibitor, TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl), no desired product was detected upon addition of TEMPO. The results revealed that, in addition to the organic oxidant, $K_2S_2O_8$ acted as the radical-generating reagent[9] for the catalytic cycle.

With these observations in mind, we finally proposed a plausible reaction mechanism for the three-component cascade sequence (Scheme 7). Initially, styrene (**3a**) was activated by $Pd(OAc)_2$ to form intermediate **A**.[12] Moreover, enamine **8** is

Scheme 7. Plausible Reaction Mechanism



generated from in situ nucleophilic addition of amine **1a** to alkyne ester **2a**. Subsequently, regioselective alkene migratory insertion via intermolecular nucleophilic attack by the β-position of enamine moiety **8** to intermediate **A** gives the Pd complex **B**. Radical intermediate **C** is produced by hydride abstraction from **B** facilitated by the sulfate radical anion that is generated from the heated $K_2S_2O_8$.[9,13] Next, an intramolecular radical addition/cyclization leads to the formation of the six-membered intermediate **D**. Protonolysis of **D** yields intermediate **E** and HPdOAc (**F**), and the latter undergoes a reductive elimination/oxidation sequence to regenerate the active Pd(II) catalyst by the aid of $K_2S_2O_8$. Finally, intermediate **E** is oxidized by $K_2S_2O_8$ to deliver the desired pyrrole product **4a**.

In summary, we have successfully developed an efficient Pd-catalyzed three-component cascade reaction of simple amines, alkynes, and alkenes for the direct synthesis of novel 2,3,4-trisubstituted pyrroles with high diversity, where thiosulfate acted as both the radical generating reagent and the organic oxidant. Through experimental investigation, a plausible regioselective alkene migratory insertion for the formation of a $C(sp^2)$–$C(sp^2)$ bond–intramolecular radical addition/oxidation for the formation of $C(sp^2)$–N bond sequential pathway was proposed. Further studies on the scope, mechanism, and application of this three-component cascade reaction are actively ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02325.

Experimental procedures, characterization of products, and ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Youth Innovation Promotion Association CAS, the National Natural Science Foundation of China (21502100 and 81502909), the Shanghai Municipal Natural Science Foundation (15ZR1447800), and the Shanghai Rising-Star Program (16QB1400200).

DOI: 10.1021/acs.orglett.6b02325
Org. Lett. 2016, 18, 4864–4867

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