ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 4698–4700

www.rsc.org/chemcomm

COMMUNICATION

Synthesis of 4*H*-cyclopenta[*c*]furans *via* cooperative $PdCl_2$–$FeCl_2$ catalyzed cascade cyclization reaction involving a novel acyl rearrangement process†

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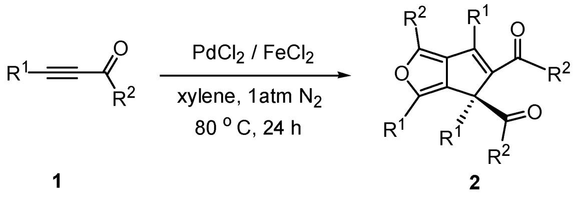
Received 15th February 2012, Accepted 15th March 2012
DOI: 10.1039/c2cc31138k

We have discovered a novel $PdCl_2$–$FeCl_2$ catalyzed cascade cyclization reaction, which involves a novel acyl rearrangement process. This reaction affords a diverse set of poly-substituted 4*H*-cyclopenta[*c*]furan products. The reaction scope of this cascade process is quite broad and various internal acetylenes can be employed.

Transition metal catalyzed cascade cyclization processes are fascinating strategies in the synthesis of natural products and biologically-active agents, because multiple bonds can be formed in a single transformation with exceptional selectivity.[1] However, dual-metal catalysis has attracted much attention.[2] Palladium catalyzed cascade reactions have been demonstrated to be versatile tools for the synthesis of numerous polycyclic compounds, and cooperative catalysts like copper complexes have been employed to enhance the reaction efficiency and selectivity.[3] However, synthetic methodologies employing homogeneous cooperative palladium and iron catalysts are fairly rare, even though iron catalysis is being exhaustively investigated.[4,6d] Herein, we wish to report a novel synthesis of 4*H*-cyclopenta[*c*]furans *via* cooperative $PdCl_2$–$FeCl_2$ catalyzed cascade cyclization reaction. This chemistry presumably goes through two consecutive processes, the palladium-catalyzed cycloaddition and the iron-catalyzed acyl rearrangement.

Recently, palladium-catalyzed cycloaddition reactions of alkynes have emerged as a privileged approach for the rapid construction of cyclic rings.[5] For instance, we and others have reported a number of unique palladium-catalyzed cyclization and cyclotrimerization reactions employing commonly available acetylenes to afford diverse heterocyclic and carbocyclic compounds.[6] 4*H*-Cyclopenta[*c*]furan derivatives possess interesting molecular skeletons and electronic features, which should exhibit remarkable biological and physical properties. However, the state of art synthetic methodology is far behind satisfactory, posing an obstacle to the investigation of its potential applications.

Table 1 $PdCl_2$-catalyzed cyclization of 2-yn-1-one (**1**) to multi-substituted 4*H*-cyclopenta[*c*]furan (**2**)[a]



Entry	Alkynone	R^1	R^2	Product	Yield[b] [%]
1	**1a**	Ph	Ph	**2a**	70
2	**1b**	Ph	4-$CH_3C_6H_4$	**2b**	65
3	**1c**	Ph	2-$MeOC_6H_4$	**2c**	60
4	**1d**	Ph	4-BrC_6H_4	**2d**	61
5	**1e**	Ph	4-FC_6H_4	**2e**	68
6	**1f**	Ph	Me	**2f**	67

[a] Reaction conditions: substrate 1 (1 mmol), $PdCl_2$ (0.1 mmol), $FeCl_2$ (0.05 mmol), LiCl (2 equiv.) in 3.0 mL of xylene at 80 °C under an atmosphere of 1 atm N_2 for 24 h. [b] Yield of isolated products.

One viable approach to synthesize 4*H*-cyclopenta[*c*]furans could be transition metal catalyzed cycloaddition reaction of acetylenes bearing oxygen-containing functionalities, like 2-yn-1-one derivatives.[7]

To test this hypothesis, 1,3-diphenyl-propynone was treated with $PdCl_2$ (10 mol%) and LiCl (2 equiv.) in xylene (3.0 mL) at 80 °C under 1 atm N_2 for 24 h. To our delight, a small amount of cyclopenta[*c*]furan product was formed and isolated by flash chromatography (ESI†; Table 1, entry 2). The structure of this compound was subsequently determined by NMR and X-ray crystallography analyses of **2a** and **2k** (Fig. 1). Further study indicated that 47% yield of the product **2a** was obtained while an additional catalyst $Cu(OTf)_2$ was employed. Encouraged by these results, a diverse set of cooperative metal catalysts were screened and $FeCl_2$ appears to be the most suitable one. Surprisingly, a moderate yield can also be achieved when this reaction is conducted in the presence of a strong Brønsted acid HCl. In order to understand the intrinsic role of the $FeCl_2$ catalyst, this reaction was performed in the absence of $PdCl_2$, and no desired product was obtained. Finally, this reaction was carried out in air and oxygen. Interestingly, a much lower yield was obtained when this reaction was conducted in the presence of oxygen. These results indicate that this chemistry

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† Electronic supplementary information (ESI) available: Experimental section, characterization of all compounds, copies of ^1H and ^{13}C NMR spectra for isolated compounds. See DOI: 10.1039/c2cc31138k

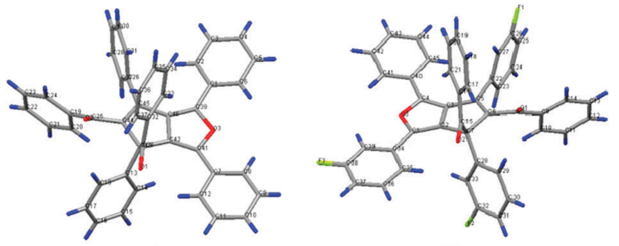


Fig. 1 X-Ray molecular structures of **2a** and **2k**.

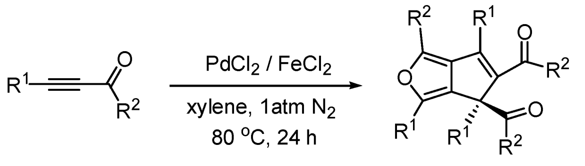
should be a palladium(0)-mediated reaction, yet we cannot rule out other possibilities since the overall reaction mechanism is still under investigation (for information on the optimization of **2a**, see ESI†).

With the "optimal" reaction conditions in hand, we subsequently explored the reaction scope. First, we examined the steric and electronic effects of the aryl substituents adjacent to the carbonyl group of the acetylenes, as shown in Table 1. It appears that the reaction yields were slightly lower when electron-donating or electron-withdrawing group substituted 2-yn-1-ones were employed (entries 2–5), possibly suggesting that the catalytic cycles involved have distinct preference over the electronic nature of the acetylenes.

To understand the effect of the substituent adjacent to the triple bond, acetylenes in which R^1 is aryl or alkyl group were employed in this transformation (Table 2). It appears that both electron-donating and electron-withdrawing group substituted aryl acetylenes afforded respectable yields of the desired products (entries 1–5). In addition, when alkyl substituted alkyne **1l** was allowed to react under the "optimal" conditions, a 65% yield of the desired product was obtained. Acetylenes lacking aromatic rings like compound **1m** were employed in this chemistry (Table 2, entry 7). To our delight, the cascade cyclization reaction of **1m** gave 68% yield of the desired product **2m** after purification.

These results demonstrated that the cascade reaction developed by us has broad scope and can afford a diverse set of 4*H*-cyclopenta[*c*]furans bearing both alkyl and aryl groups with different electronic characters. In addition, quaternary carbon centers can be constructed at the 4 position of the cyclopenta[*c*]furan ring by using internal acetylenes.

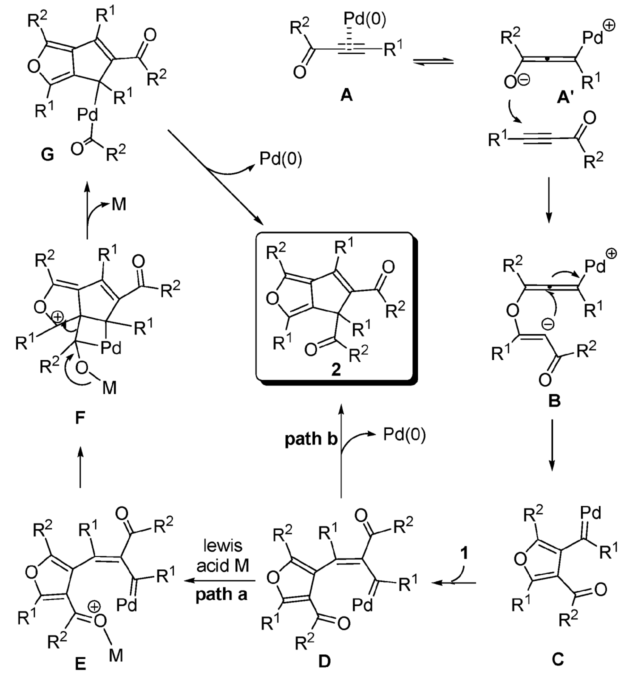
Table 2 $PdCl_2$-catalyzed cyclization of 2-yn-1-one (**1**) to multi-substituted 4*H*-cyclopenta[*c*]furan (**2**)[a]



1 **2**

Entry	Alkynone	R^1	R^2	Product	Yield[b] [%]
1	**1g**	4-$MeOC_6H_4$	Ph	**2g**	58
2	**1h**	4-*t*-BuC_6H_4	Ph	**2h**	51
3	**1i**	4-$CH_3C_6H_4$	4-FC_6H_4	**2i**	57
4	**1j**	2-FC_6H_4	Ph	**2j**	68
5	**1k**	3-FC_6H_4	Ph	**2k**	69
6	**1l**	*n*-Hexyl	Ph	**2l**	65
7	**1m**	Et	Me	**2m**	68

[a] Reaction conditions: substrate 1 (1 mmol), $PdCl_2$ (0.1 mmol), $FeCl_2$ (0.05 mmol), LiCl (2 equiv.) in 3.0 mL of xylene at 80 °C under an atmosphere of 1 atm N_2 for 24 h. [b] Yield of isolated products.



Scheme 1 Proposed mechanism.

A proposed mechanism of this unprecedented $PdCl_2$–$FeCl_2$ catalyzed cascade cyclization reaction is illustrated in Scheme 1. This chemistry presumably goes through two consecutive processes, the palladium-catalyzed cycloaddition and the iron-catalyzed acyl rearrangement. Allene intermediate **A′**,[8] generated from the Pd(0)[9]-catalyzed isomerization of acetylene **A**, undergoes nucleophilic addition to another acetylene **A** to produce intermediate **B**. This addition process could possibly be assisted by the $FeCl_2$ co-catalysts, which may serve to stabilize the intermediates involved. The palladium complex **B** subsequently undergoes an intramolecular cyclization to afford a palladium carbene intermediate **C**.[10] Another molecule of **A** could react with intermediate **C** to afford palladium carbene intermediate **D**.[11] At this stage, intermediate **D** could either undergo a direct carbene insertion reaction to afford the final product **2** (path b), or it could react with the Lewis acid co-catalyst to generate intermediate **E** (path a),[12] which rapidly goes through an unprecedented rearrangement process to afford intermediate **G** and release the Fe co-catalyst. Subsequent reductive elimination of intermediate **G** should afford the 4*H*-cyclopenta[*c*]furan products. Given the fact that Brønsted acids or Lewis acids are essential for the success of this chemistry, a mechanism going through path b appears to be more likely.

In conclusion, we have discovered a novel $PdCl_2$–$FeCl_2$ catalyzed cascade cyclization reaction, which affords a diverse set of poly-substituted 4*H*-cyclopenta[*c*]furan products. The reaction scope of this cascade process is quite broad and various internal acetylenes can be employed. This reaction appears to involve two consecutive processes, the palladium-catalyzed cycloaddition and the iron-catalyzed acyl rearrangement. However, the exact reaction mechanism has not been well understood yet. We are continuing to study this process in order to better understand the reaction mechanism and its potential applications.

We thank the National Natural Science Foundation of China (20932002 and 21172076), National Basic Research Program of China (973 Program) (2011CB808600), Doctoral Fund of Ministry of Education of China (20090172110014) and Guangdong Natural Science Foundation (10351064101000000) for financial support.

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