Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 7313

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Pd-Catalyzed cyclization reaction: a convenient domino process for synthesis of α-carbonyl furan derivatives†

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Received 7th July 2011, Accepted 5th September 2011
DOI: 10.1039/c1ob06105d

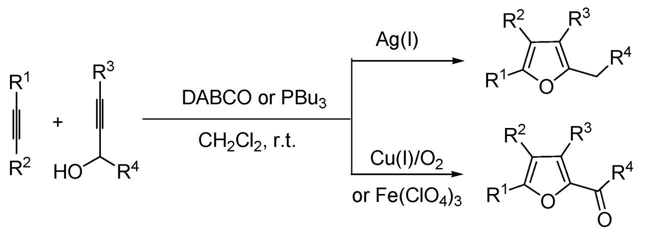
Today Pd-catalyzed reactions are probably the most versatile and extensively used processes for the synthesis of heterocyclic compounds in one single operation without isolation of intermediates.[1–11] Due to their synthetic efficiency they have attracted significant attention in modern organic synthesis.[12–14] Therefore, the discovery of new and convenient transformations for the synthesis of various heterocyclic compounds through Pd-catalyzed reactions continues to attract broad interest. In this paper, we have described an efficient Pd-catalyzed process to construct α-carbonyl furan derivatives.

Furans are extremely important heterocyclic compounds[15–20] and worth our attention because they exhibit a wide range of biological activities,[21–27] and the furan skeleton often exists as a key structural unit in many drugs and natural products.[28–30] In addition, furan derivatives can be extensively used not only as synthetic building blocks for the synthesis of more complex compounds, but also as communicating moieties in materials science. Generally, there are mainly two routes to obtain furan derivatives:[31–42] (i) cyclization of allenyl ketones,[43,44] alkynyl ketone,[45,46] enynols,[47,48] alkynyl epoxides[49] or propargyl ethers;[50] (ii) cyclization of 1,4-dicarbonyl compounds (Paal–Knorr synthesis).

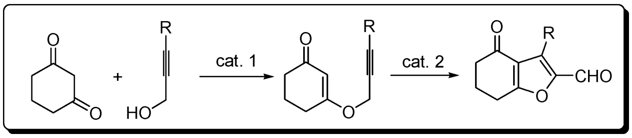
Recently, our group has reported convenient one-pot domino processes for regiospecific synthesis of highly functionalized polysubstituted furans through different transition metal-catalyzed cyclizations (Scheme 1).[39–42] These furans derivatives were obtained through intramolecular Claisen rearrangement from substrates electron-deficient alkynes and 2-yn-1-ols. With these fruitful results in hand, we attempted to explore the scope of these transformations. Thus, we anticipated to design and develop a new efficient two-step one pot protocol for the preparation of novel bicyclic α-carbonyl furans from readily accessible propargyl alcohols and commercially available 1,3-dicarbonyl compounds (Scheme 2).

Based on the previous study on etherization of 1,3-dicarbonyl compounds, **1a** (1.0 equiv) was reacted with **2a** (1.2 equiv) catalyzed by iron(III) *p*-toluenesulfonate in DCE for 12 h at 80 °C to give intermediate product **3a**[51,52] under an atmosphere of nitrogen. Our endeavors centered on optimizing the reaction conditions for the transformation of **3a** into **4aa**. The results were summarized in Table 1. Initially, various Cu(I) and Fe(III) catalysts used in our previous work were tested. As seen in Table 1, Fe^{III} catalysts such as $Fe(C_7H_7SO_3)_3$, $Fe(ClO_4)_3$, $FeCl_3$ were of no effect (Table 1, entries 1–3), and trace amounts of the product were detected under the catalysis of CuI or nano-Cu_2O (entries 4, 5). The cyclization reaction of **3a** could not proceed when various palladium species were respectively used as catalysts alone (entries 6–8). Excitingly, the desired product **4aa** was produced in 41% yield in the presence of $PdCl_2$ with CuI as co-catalyst (entry 9). Then, other co-catalysts, such as CuCl, CuBr and $FeCl_3$, were evaluated and it was found that they were inferior to CuI (entries 10–12). To improve the transformation under the catalysis of $PdCl_2$ with CuI as co-catalyst, we attempted to employ various additives in the reaction system (entries 13–20). Our investigations indicated that $Bu_4N^+Cl^-$ was the most helpful (entry 18). Finally, with regard to the solvent, DMF, DMSO and DMA proved to be suitable in the presence of $PdCl_2$/CuI and **3aa** was given in 60–65% yields, while other solvents such as toluene (entry 23), 1,2-dichloroethane (entry 24), 1,4-dioxane (entry 25) led to lower yields.

With the optimal reaction conditions in hand, we then probed the generality of the reaction using a variety of 1,3-dicarbonyl compounds and propargyl alcohols. As depicted in Table 2,



Scheme 1 Transition metal-catalyzed synthesis of furans by our group.



Scheme 2 New synthetic route to α-carbonyl furans.

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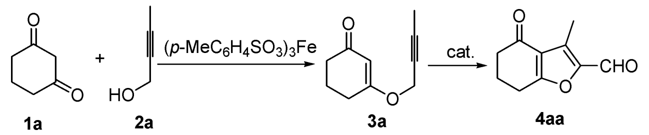
† Electronic supplementary information (ESI) available: Experimental protocols and NMR spectra for products **4aa–4eg**. See DOI: 10.1039/c1ob06105d

Table 1 Screen of reaction conditions[a]



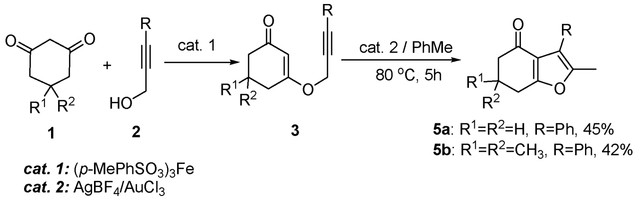
Entry	Catalyst	Additive	Solvent	Yield (%)[b]
1	$Fe(C_7H_7SO_3)_3$	—	DMF	—
2	$Fe(ClO_4)_3$	—	DMF	—
3	$FeCl_3$	—	DMF	—
4	CuI	—	DMF	trace
5	nano-Cu_2O	—	DMF	trace
6	$PdCl_2$	—	DMF	—
7	$Pd(OAc)_2$	—	DMF	—
8	$Pd_2(dba)_3$	—	DMF	—
9	$PdCl_2$/CuI	—	DMF	41
10	$PdCl_2$/CuCl	—	DMF	35
11	$PdCl_2$/CuBr	—	DMF	38
12	$PdCl_2/FeCl_3$	—	DMF	—
13	$PdCl_2$/CuI	CH_3CO_2H	DMF	33
14	$PdCl_2$/CuI	1,10-phenanthroline	DMF	22
15	$PdCl_2$/CuI	$Bu_4N^+Br^-$	DMF	35
16	$PdCl_2$/CuI	$Bu_4N^+F^-$	DMF	29
17	$PdCl_2$/CuI	$Bu_4N^+I^-$	DMF	44
18	$PdCl_2$/CuI	$Bu_4N^+Cl^-$	DMF	65
19	$PdCl_2$/CuI	pyridine	DMF	54
20	$PdCl_2$/CuI	DABCO	DMF	40
21	$PdCl_2$/CuI	$Bu_4N^+Cl^-$	DMSO	63
22	$PdCl_2$/CuI	$Bu_4N^+Cl^-$	DMA	60
23	$PdCl_2$/CuI	$Bu_4N^+Cl^-$	Toluene	24
24	$PdCl_2$/CuI	$Bu_4N^+Cl^-$	1,2-dichloroethane	31
25	$PdCl_2$/CuI	$Bu_4N^+Cl^-$	1,4-dioxane	46

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), catalyst (0.1 equiv), additive (0.1 equiv), CuI : $PdCl_2$ = 1.2 : 1, solvent (2.0 mL $mmol^{-1}$); [b] Yield of isolated product after flash chromatography.

the reaction of **1a** with **2a** afforded product **4aa** in 65% yield (Table 2, entry 1). As expected, the product **4ab** was obtained in 62% yield when **1a** reacted with **2b** carrying a phenyl group on the alkynyl carbon. Unfortunately, when unsubstituted propargyl alcohol was tested, the desired product **4ac** was not formed under the optimized conditions. The reason might be that **2c** was unstable in the presence of Pd and this result was coincident with our previous studies. We then examined the reaction scope of this Pd/Cu catalytic system and its tolerance of functional groups in the case of other cyclic 1,3-dicarbonyl compounds. As illustrated in Table 2, substrates **1b** and **1c** were employed and the desired products **4ba–4ca** were formed in 59% to 67% yields (entry 4–6).

The results mentioned above demonstrated the remarkable functional group compatibility on both reagents. Other 1,3-dicarbonyl compounds and propargyl alcohols were employed as substrates for this Pd/Cu co-catalyzed domino reaction. We discovered that the reaction of 1,3-diphenylpropane-1,3-dione (**1d**) or ethyl phenylpropiolate (**1e**) with differently substituted propargyl alcohols ($R^3 = CH_3$, phenyl, *m*-tolyl, 4-methoxyphenyl, 4-nitrophenyl, 2-thienyl) had a beneficial effect on the reaction outcomes, and in most cases the corresponding products were obtained in moderate to good yields under our standard experimental conditions (Table 2, entries 7–17). Pleasingly, these results indicated that this domino reaction tolerated functional groups on the aromatic ring. There was no effect on this transformation with either the electron-rich (**2d**) or electron-withdrawing groups (**2e**) at the aromatic ring of the propargyl alcohols. When asymmetric ethyl 3-oxo-3-phenylpropanoate was employed, only one regioisomer was detected, indicating that this cyclization was highly regioselective.

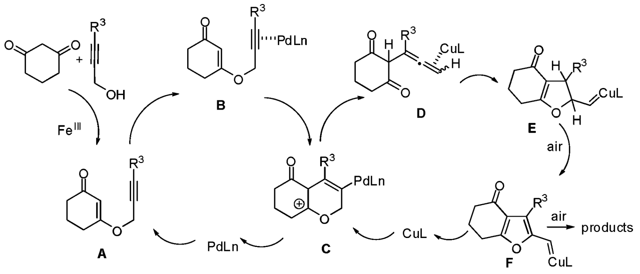
Subsequently, we were interested in whether the propargyl vinyl ethers **3** could be converted to α-CH_3 furan derivatives **5**[53] through intramolecular Claisen rearrangement (Scheme 3).



Scheme 3 $AgBF_4/AuCl_3$ co-catalyzed synthesis of furans.

The cyclization was completed rapidly with the use of $AuCl_3/AgBF_4$ catalytic system under mild conditions, and gave the corresponding furan derivatives (**5a** and **5b**) in 45% and 42% yields respectively. This synthetic route provided a further example of Au and Ag co-catalyzed C–C and C–O bond formation for synthesis of α-CH_3 furan derivatives.

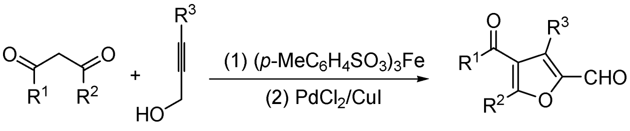
On the basis of the experimental results, it was demonstrated that $PdCl_2$ and CuI were essential for the domino reaction. Therefore, a plausible mechanism for this transformation is described in Scheme 4. The dehydration product **A** was formed in the presence of iron catalyst. A 6-*endo* dig addition of the enol ether onto Pd(II)–alkyne complex **B** resulted in the formation of intermediate **C**, which collapsed into the β-allenic ketone **D**.[54,55] And then, β-allenic ketone **D** underwent rearrangement to form carbene intermediate **E**[56–59] in the presence of copper catalyst. Finally, carbene complex **E** underwent sequential dehydrogenation oxidation and carbene-oxidation [60–62] to give product in the presence of air.



Scheme 4 Proposed mechanism.

In summary, a practical and mild new method for the palladium-catalyzed synthesis of highly functionalized α-carbonyl furan has been developed. Under these conditions, various functional groups were well tolerated and the product furans were usually isolated in moderate to good yields. In addition, this synthetic route could prepare a variety of α-carbonyl furans which are useful synthetic intermediates for bioactive and natural compounds.

Table 2 $PdCl_2$/CuI-Catalyzed Synthesis of α-Carbonyl Furans[a]



1a-1e **2a-2g** **4aa-4eg**

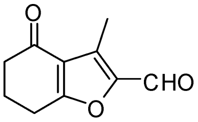
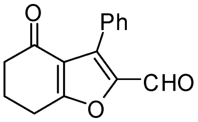
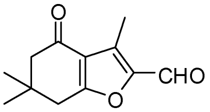
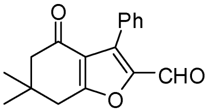
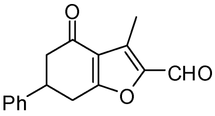
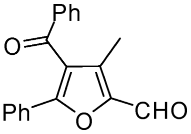
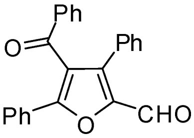
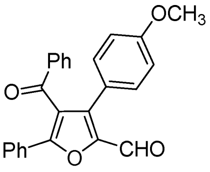
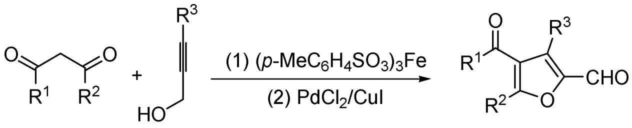
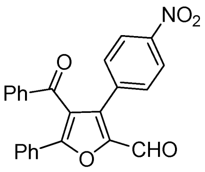
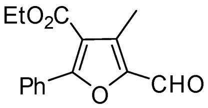
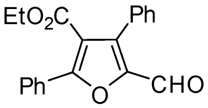
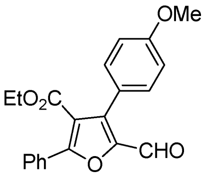
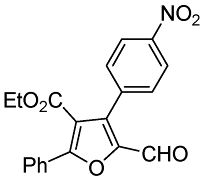
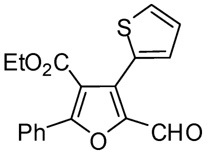
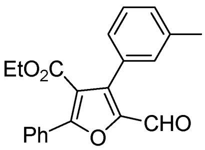
Entry	1,3-Dicarbonyl compounds	Propargyl alcohols	Product (yield%)[b]
1	**1a** (R^1,R^2 = $CH_2CH_2CH_2$)	**2a** (R^3 = CH_3)	 **4aa** 65%
2	**1a**	**2b** (R^3 = Ph)	 **4ab** 62%
3	**1a**	**2c** (R^3 = H)	—
4	**1b** (R^1,R^2 = $CH_2CMe_2CH_2$)	**2a**	 **4ba** 67%
5	**1b**	**2b**	 **4bb** 59%
6	**1c** (R^1,R^2 = $CH_2CHPhCH_2$)	**2a**	 **4ca** 60%
7	**1d** (R^1 = R^2 = Ph)	**2a**	 **4da** 74%
8	**1d**	**2b**	 **4db** 71%
9	**1d**	**2c**	—
10	**1d**	**2d** (R^3 = C_6H_4-*p*-OMe)	 **4dd** 69%

Table 2 (*Contd.*)



1a-1e **2a-2g** **4aa-4eg**

Entry	1,3-Dicarbonyl compounds	Propargyl alcohols	Product (yield%)[b]
11	**1d**	**2e** ($R^3 = C_6H_4$-*p*-NO_2)	 **4de** 70%
12	**1e** (R^1 = Ph; R^2 = OEt)	**2a**	 **4ea** 68%
13	**1e**	**2b**	 **4eb** 65%
14	**1e**	**2d**	 **4ed** 67%
15	**1e**	**2e**	 **4ee** 60%
16	**1e**	**2f** (R^3 = 2-C_4H_3S)	 **4ef** 66%
17	**1e**	**2g** ($R^3 = C_6H_4$-*m*-Me)	 **4eg** 67%

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.2 equiv), $PdCl_2$ (0.1 equiv), CuI (0.1 equiv), $Bu_4N^+Cl^-$ (0.1 equiv), DMF 3 mL. [b] Isolated yields.

Acknowledgements

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

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