DOI: 10.1002/chem.200901386

Tetrasubstituted Furans by Pd^{II}-Catalyzed Three-Component Domino Reactions of 2-(1-Alkynyl)-2-alken-1-ones with Nucleophiles and Vinyl Ketones or Acrolein

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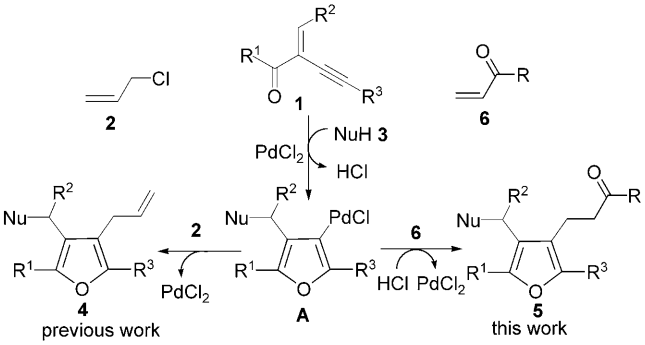
Transition-metal-catalyzed multicomponent domino reactions,[1] which can provide rapid access to architecturally complex molecules from relatively simple starting materials, are highly important in synthetic chemistry. Highly substituted furans are frequently found as subunits in many bioactive natural products and man-made drugs, and they are also important building blocks in organic synthesis.[2,3] Recently, readily available 2-(1-alkynyl)-2-alken-1-ones have demonstrated their great ability to load various substitutents onto furans under the catalysis of $AuCl_3$.[4] Very recently, we also developed a Pd^{II}-catalylzed three-component domino reaction of 2-(1-alkynyl)-2-alken-1-ones with nucleophiles and allylic chlorides, which lead to tetrasubstituted furans (Scheme 1).[5a]

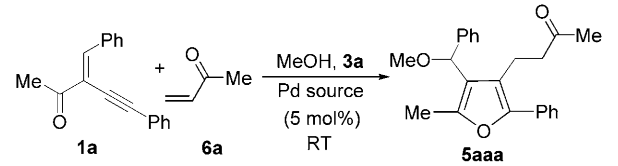


Scheme 1. Previous and current work.

In our ongoing efforts to develop cascade reactions to synthesize heterocyclic compounds,[5] we envisaged that furanyl palladium intermediates **A**, generated from the cyclization of ketones **1** and nucleophiles, might react with other electrophiles such as vinyl ketones or acrolein[6] to afford terasubstituted furans with 100 % atom economy. Herein, we report a novel, atom-economic Pd^{II}-catalyzed three-component domino reaction of 2-(1-alkynyl)-2-alken-1-ones with nucleophiles and vinyl ketones or acrolein, which lead to multifunctionalized tetrasubstituted furans.[7]

First, we examined this palladium-catalyzed three-component domino reaction under different reaction conditions by using ketone **1a**, MeOH, and vinyl methyl ketone as model substrates (Table 1). After numerous attempts, the desired product **5aaa** could be obtained in 85 % isolated yield after running the reaction for 9 h at room temperature in CH_3CN

Table 1. Screening reaction conditions.



Entry[a]	Pd source (5 %)	Solvent	Time [h]	Isolated yield [%]
1	$PdCl_2$	CH_3CN	12	83
2	$Pd(OAc)_2$	CH_3CN	24	NR
3	$[Pd_2(dba)_3]$	CH_3CN	24	trace
4	$[Pd(\eta^3\text{-}C_3H_5)_2Cl_2]$	CH_3CN	24	NR
5	$[PdCl_2(CH_3CN)_2]$	CH_3CN	9	85
6	$[PdCl_2(CH_3CN)_2]$	DMF	2.5	75
7	$[PdCl_2(CH_3CN)_2]$	DMA	9	55
8	$[PdCl_2(CH_3CN)_2]$	THF	24	81
9	$[PdCl_2(CH_3CN)_2]$	1,4-dioxane	24	65
10[b]	$[PdCl_2(CH_3CN)_2]$	CH_3CN	12	82

[a] Unless otherwise specified, vinyl methyl ketone (4 equiv) and MeOH (4 equiv) were used. [b] Vinyl methyl ketone (2 equiv) and MeOH (2 equiv) were used. NR = no reaction.

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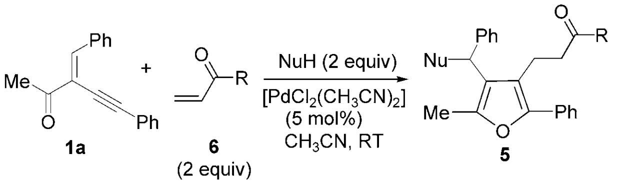
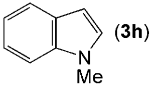
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200901386 and contains the preparative procedures and spectroscopic data for all of the new compounds reported.

(Table 1, entry 5). Interestingly, different from the results obtained by Lu et al.,[6] the presence of extra lithium halides such as LiBr was not necessary for this transformation. It is not surprising that $PdCl_2$ gave a similar yield in CH_3CN. However, other palladium salts such as $Pd(OAc)_2$, $[Pd_2(dba)_3]$, and $[Pd(\eta^3\text{-}C_3H_5)_2Cl_2]$ were not effective at all. Other solvents such as DMF, DMA, THF, and 1,4-dioxane gave relatively lower yields. Further screening indicated that only two equivalents of methanol and vinyl methyl ketone were required for this transformation, giving 82 % yield of the corresponding product (Table 1, entry 10).

Next, we investigated the scope and limitation of this transformation under optimized conditions. We first tested different nucleophiles and the results are listed in Table 2.

Table 2. Scope of Pd^{II}-catalyzed cascade reaction of **1a** with various nucleophiles and vinyl ketones.



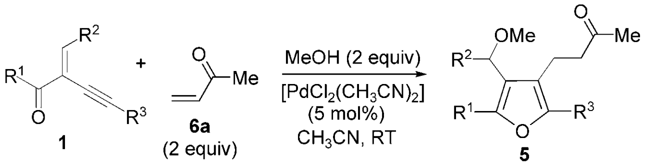
Entry	NuH (**3**)	R = **6**	Time [h]	Yield of **5** [%]
1	MeOH (**3a**)	Me (**6a**)	9	**5aaa** (82)
2	*i*PrOH (**3b**)	**6a**	52	**5aba** (67)
3	*t*BuOH (**3c**)	**6a**	24	**5aca** (30)
4	BnOH (**3d**)	**6a**	26	**5ada** (76)
5	4-$MeOC_6H_4OH$ (**3e**)	**6a**	24	**5aea** (50)
6[b]	AcOH (**3g**)	**6a**	24	**5afa** (44)
7	 **(3h)**	**6a**	12	**5aga** (81)
8	**3a**	Ph (**6b**)	20	**5aab** (87)

[a] Unless otherwise specified, the reactions were carried out with NuH (2 equiv) and vinyl ketone (2 equiv); [b] AcOH (4 equiv) was used.

Several points should be noted from these results: 1) The corresponding products could be obtained in high yields when MeOH, *iso*-propanol, and benzyl alcohol were used as nucleophiles; 2) The treatment of *para*-methoxyphenol, bulky *tert*-butanol, or weak nucleophilic acetic acid with **1a** and **6a** could still give the corresponding products in moderate yields; 3) *N*-Methyl indole could be used as a carbon-nucleophile to give furan **5aga** in 81 % yield. Furthermore, vinyl phenyl ketone **6b** could also be used as an electrophile instead of vinyl methyl ketone to afford the corresponding furan **5aab** in excellent yield (Table 2, entry 8).

We next examined the scope of the ketone **1** component under optimized conditions, and the results are summarized in Table 3. In general, moderate to high yields were obtained for most substrates under standard conditions. Various substitutents could be introduced into the corresponding furan products. In some cases DMF was found to be a better solvent than CH_3CN based on the yield and reaction rate (Table 3, entries 8 and 9, and 11 and 12).

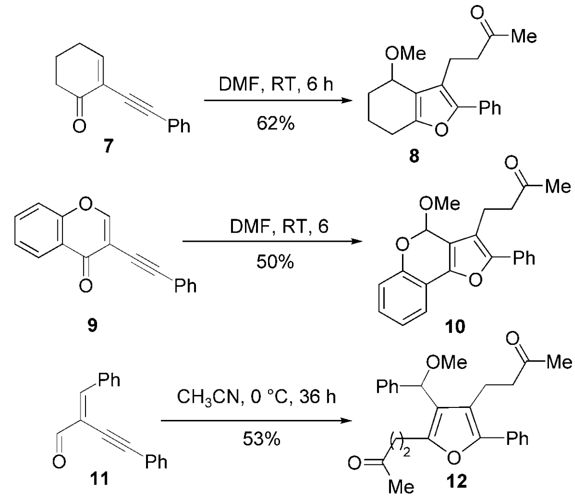
Table 3. The scope of ketone component **1**.



Entry	Ketone **1** $R^1/R^2/R^3$	Time [h]	Yield of **5** [%]
1	Me/4-$MeOC_6H_4$/1-naphthyl (**1b**)	12	**5baa** (91)
2	Me/4-$MeOC_6H_4$/Ph (**1c**)	12	**5caa** (70)
3[a]	Me/Ph/*n*Bu (**1d**)	12	**5daa** (50)
4	*n*Bu/Ph/Ph (**1e**)	24	**5eaa** (78)
5	Ph/Ph/Ph (**1f**)	10	**5faa** (91)
6	Ph/Ph/1-cyclohexenyl (**1g**)	30	**5gaa** (67)
7	Ph/Ph/*n*Bu (**1h**)	16	**5haa** (77)
8[a]	Ph/Ph/4-$NO_2C_6H_4$ (**1i**)	48	**5iaa** (44)
9[a]	**1i**	16	**5iaa** (60)[b]
10[a]	Ph/Ph/4-$MeOC_6H_4$ (**1j**)	9	**5jaa** (60)
11[a]	Ph/4-$MeOC_6H_4$/4-$MeOC_6H_4$ (**1k**)	24	**5kaa** (51)
12[a]	**1k**	6	**5kaa** (64)[b]
13	Me/*n*Bu/Ph (**1l**)	16	**5laa** (62)

[a] Vinyl methyl ketone (4 equiv) and MeOH (4 equiv) were used. [b] Carried out in DMF.

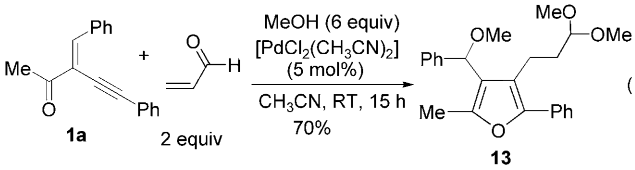
The generality of this transformation was also investigated by using the cyclic ketone **7**, the chromanone derivative **9**, and aldehyde **11** (Scheme 2). The reaction of ketone **7** gave the bicyclic 2,3-fused furan **8** in 62 % yield, and the reaction of the ketone **9** produced a tricyclic furan **10** in 50 % isolated yield. The reaction of aldehyde **11** with MeOH and vinyl methyl ketone at 0 °C for 36 h gave 53 % yield of tetrasubstituted furan **12** rather than the corresponding trisubstituted furan, which indicated that the electron-rich trisubstituted furan would undergo a rapid Friedel–Crafts reaction with another molecule of vinyl methyl ketone under these reaction conditions. Au^{III}-catalyzed Friedel–Crafts reactions of



Scheme 2. The domino reactions of cyclic ketones **7**, **9**, and aldehyde **11**. Conditions: MeOH (4 equiv), **6a** (4 equiv) and $[PdCl_2(CH_3CN)_2]$ (5 mol %).

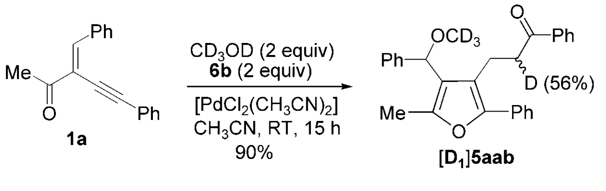
vinyl methyl ketone with furan were first explored by Hashmi et al., and later extensively studied by He et al..[8]

Furthermore, acrolein could be used as an electrophile instead of vinyl methyl ketone, but the reaction produced an acetal **13**, rather than the free aldehyde, in 70 % isolated yield under the optimized conditions shown in [Eq. (1)].



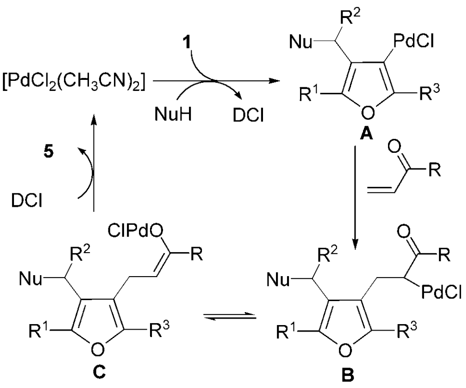
(1)

The reaction of ketone **1a**, vinyl phenyl ketone **6b**, and deuterated methanol produced the corresponding **[D$_1$]5aab** in excellent yield, and about 56 % of deuterium was incorporated at the α carbon of the ketone as shown in [Eq. (2)].



(2)

This result led us to propose a plausible mechanism for this Pd^{II}-catalyzed three-component domino reaction (Scheme 3). The reaction of a nucleophile with ketone **1** would give a furanyl palladium intermediate **A** and the release of one molecule of HCl in the presence of [PdCl$_2$(CH$_3$CN)$_2$]. The insertion of a C=C double bond of vinyl ketone into the C−Pd bond of intermediate **A** would produce two interconvertible intermediates **B** and **C** through a Michael-addition type mode. Subsequent protonation by HCl would provide the final product and regenerate the catalyst.



Scheme 3. Proposed mechanism for the Pd^{II}-catalyzed domino reaction.

In summary, we have developed a novel Pd^{II}-catalyzed three-component domino reaction of 2-(1-alkynyl)-2-alken-1-ones with nucleophiles and vinyl ketones, which has provided an efficient, general, and atom-economic route to multifunctionalized tetra-substituted furans. It was also interesting to find that when (*E*)-2-benzylidene-4-phenylbut-3-ynal was used as substrate, the reaction would undergo a double addition reaction of two molecules of vinyl methyl ketones. The reaction produced a furan with an acetal by acetalization of the aldehyde group when acrolein was used as the electrophile.

Experimental Section

Typical procedure for the synthesis of 5aaa: [PdCl$_2$(CH$_3$CN)$_2$] (6.5 mg, 0.025 mmol) was added to a solution of **1a** (123 mg, 0.5 mmol), MeOH (32 mg, 1.0 mmol) and vinyl methyl ketone (70 mg, 1.0 mmol) in CH$_3$CN (2 mL) at room temperature. The reaction mixture was stirred for 12 h, after which **1a** was completely consumed according to the TLC analysis, and then the reaction mixture was concentrated in vacuum. The residue was purified by column chromatography on silica gel (hexanes/EtOAc = 5:1) to give the desired product **5aaa** (142 mg) as a colorless oil. Yield = 82 %; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta_H = 7.58$ (d, 2H, $J = 7.8$ Hz), 7.33–7.43 (m, 6H), 7.21–7.30 (m, 2H), 5.35 (s, 1H), 3.44 (s, 3H), 2.80–2.91 (m, 1H), 2.64–2.75 (m, 1H), 2.40–2.52 (m, 1H); 2.39 (s, 3H), 2.07–2.15 (m, 1H), 2.05 ppm (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta_C = 207.90$, 148.93, 147.06, 141.25, 131.28, 128.43, 128.08, 126.98, 126.56, 126.14, 124.75, 120.48, 119.82, 77.00, 56.34, 42.77, 29.40, 18.12, 12.00 ppm; MS (70 eV): *m*/*z* (%): 348 (47.59), 258 (100); HRMS calcd for C$_{23}$H$_{24}$O$_3$ $[M]^+$: 348.1725; found: 348.1722.

Acknowledgements

Financial support from NSFC (20702015), STCSM (07DZ-22937, 08dj1400101), Shanghai Shuguang Program (07SG27), Shanghai Pujiang Program (07pj14039), and Shanghai Leading Academic Discipline Project (B409) is greatly appreciated.

Keywords: cyclization · domino reactions · furans · multicomponent reactions · palladium

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Received: May 25, 2009