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Palladium(II)-Catalyzed Domino Reaction of 2-(1-Alkynyl)-2-alken-1-ones with Nucleophiles: Scope, Mechanism and Synthetic Application in the Synthesis of 3,4-Fused Bicyclic Tetrasubstituted Furans

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Abstract: Described herein is the development of a palladium(II)-catalyzed two- or three-component reaction of 2-(1-alkynyl)-2-alken-1-ones with nucleophiles and allylic chlorides. Various types of nucleophiles such as *O*-, *N*-, *C*-based nucleophiles and olefin-tethered *O*-, *N*-, *C*-based nucleophiles were investigated. The scope, mechanism and application of this Pd(II)-catalyzed domino reaction were studied. In these transformations, the palladium catalyst exhibits a dual role, serving simultaneously as a Lewis acid and a transition metal. Two possible reaction pathways (cross-coupling reaction *vs.* Heck reaction) from the same intermediate furanylpalladium species were observed. The reaction pathway is dependent on the property of the nucleophile and the length of the tethered chain as well. When olefin-tethered *O*-based nucleophiles were used, only the cross-coupling reaction pathway was observed, in contrast, both reaction pathways were observed when olefin-tethered *C*-based nucleophiles were employed. The product ratio is dependent on the length of the tethered chain. Furthermore, ring-closing metathesis (RCM) of corresponding furans with C=C bonds provides an easy method for the preparation of functionalized oxygen-heterocycles – 3,4-fused bicyclic furans. It is also noteworthy that allylic chloride can be as an oxidant besides its well known function as an alkylating reagent.

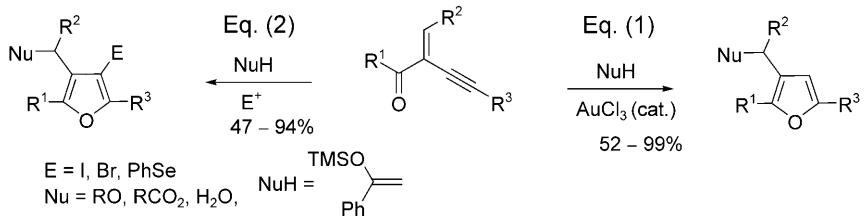
Keywords: cyclization; domino reactions; fused ring systems; palladium; synthetic methods

Introduction

As one of the most prominent classes of heterocyclic compounds, furans are important subunits in many natural products, pharmaceuticals,[1,2] and organic building blocks in organic synthesis.[3,4] It is thus not surprising that various new synthetic methods have been developed for the assembly of the furan ring.[5] It is believed that transition metal-catalyzed one- or two-component reactions are the most general and powerful approaches, which include the cyclization of allenyl ketones,[6] 3-alkyn-1-ones,[6k,7] 1-(1-alkynyl)-cyclopropyl ketones,[8] (*Z*)-2-en-4-yn-1-ols,[9] and/or cycloisomerization of cyclopropyl ketones[10]/cyclopropenyl ketones.[11] In contrast to the above-mentioned alkynyl or allenyl ketone substrates, 2-(1-alkynyl)-2-alken-1-ones bearing carbonyl, alkynyl and alkenyl groups were less explored despite the fact that they are more readily accessible and more easily manipulated than those alkynyl or allenyl ketones.[12]

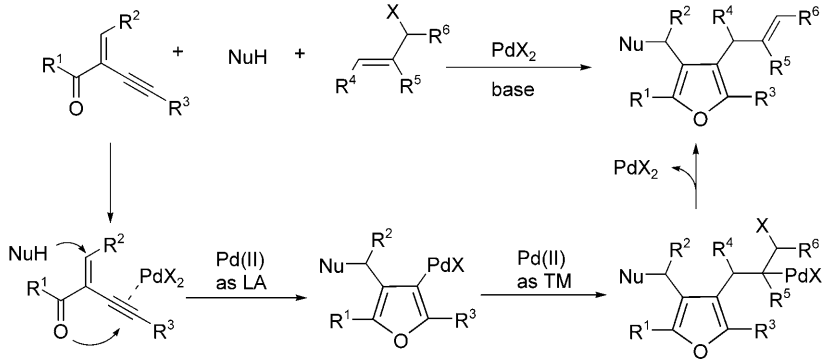
In 2004, Larock and co-workers[13] reported the first example of an $AuCl_3$-catalyzed cyclization of 2-(1-alkynyl)-2-alken-1-ones to afford highly substituted furans efficiently [Eq. (1)]. Soon after, Yamamoto,[14a] Oh,[14b] and Liang[14c] developed CuBr-, $PtCl_2$- or Bu_4NAuCl_4-catalyzed versions of this transformation independently.

Almost at the same time, Liu[15a] and Larock[15b] observed that electrophiles such as I_2 can induce the cyclization of 2-(1-alkynyl)-2-alken-1-ones with various



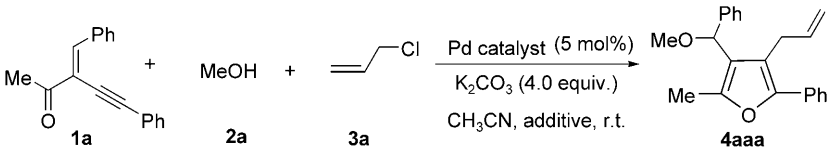
nucleophiles leading to tetrasubstituted furans in good to excellent yields [Eq. (2)].

During our study of furan synthesis, we realized that a route to efficiently synthesize tetrasubstituted furans,[16] especially tetrasubstituted 3,4-fused bicyclic furans,[17] is still a challenging topic as compared to the synthesis of trisubstituted furans. It was then envisioned that 2-(1-alknyl)-2-alken-1-ones might react with nucleophiles and an allyl halide under the catalysis of Pd(II) species, in which the Pd(II) species might exhibit a dual role: as a Lewis acid and as a transition metal (Scheme 1). To the best of our knowledge, there



Scheme 1. Proposed reaction pathway for the reaction, in the first step the Pd(II) serves as a Lewis acid, and in subsequent steps Pd(II) serves as a transition metal.

Table 1. Catalyst screening for the three-component Michael-addition/cyclization/cross-coupling reaction.[a]



Entry	Catalyst	**2a**/**3a** (equiv.)	Additive	Time [h]	Yield [%][b]
1	$Pd(PPh_3)_4$	4.0/4.0	no	36	0
2	$PdCl_2(CH_3CN)_2$	4.0/4.0	PPh_3 (20 mol%)	36	0
3	$PdCl_2(CH_3CN)_2$	4.0/4.0	no	24	88 (75)
4[c]	$PdCl_2(CH_3CN)_2$	4.0/4.0	no	24	80
5[c]	$PdCl_2(CH_3CN)_2$	2.0/2.0	no	24	53
6[c]	$PdCl_2(CH_3CN)_2$	2.0/4.0	no	24	62
7	$PdCl_2(CH_3CN)_2$	4.0/4.0	KBr (1.0 equiv.)	24	20
8[d]	$PdCl_2(CH_3CN)_2$	4.0/0.0	no	24	37
9	allylpalladium chloride dimer	4.0/4.0	no	24	78

[a] Reaction was carried out with **1a** (0.5 mmol) at room temperature.
[b] Yields were determined by NMR using CH_2Br_2 as an internal standard, isolated yields are shown in parentheses.
[c] K_2CO_3 (2.0 equiv.) was used.
[d] 10 equiv. of allyl bromide was used instead of allyl chloride .

is only one example of $Pd(OAc)_2$ serving as a dual catalyst.[18] Now, we will report a comprehensive study of this multicomponent reaction[19,20] including scope, mechanism and synthetic applications, together with a novel cascade process[21] involving Michael addition/cyclization/Heck reaction, which produces various 3,4-fused bicyclic furans in moderate to good yields. It is interesting to find that allylic chloride can play a dual role as an alkylating reagent and as an oxidant (!).

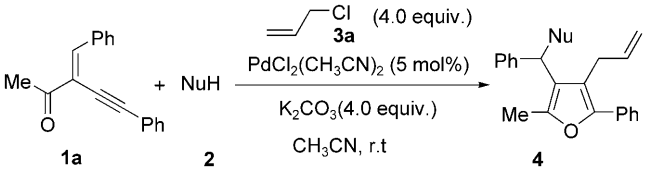
Results and Discussion

Three-Component Michael Addition/Cyclization/Cross-Coupling Reaction of 2-(1-Alkynyl)-2-alken-1-ones with *O*-, *N*-, *C*-Based Nucleophiles and Allylic Chloride: Allylic Chloride is Serving as a Crossing-Coupling Reagent

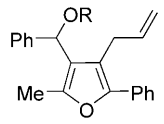
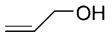
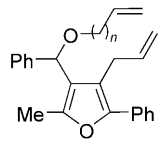
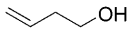
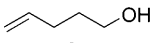
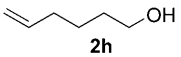
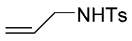
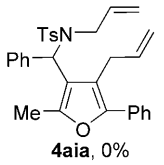
The exploration was carried out by using (*E*)-3-benzylidene-5-phenylpent-4-yn-2-one **1a**, methanol **2a** and allyl chloride **3a** as model substrates (Table 1). After catalyst screening, we found that the cyclization/cross-coupling reaction of **1a** with MeOH **2a** (4.0 equiv.), allyl chloride **3a** (4.0 equiv.) in the presence of 5 mol% of $PdCl_2(CH_3CN)_2$ and K_2CO_3 (4.0 equiv.) in CH_3CN at room temperature gives the product **4aaa** in 75% isolated yield (Table 1, entry 3, Standard Conditions). The reaction will afford the product in a lower yield upon lowering the loading of base, methanol or allyl chloride (Table 1, entries 4–6). Use of the weaker Lewis acid $PdBr_2(CH_3CN)_2$ [compared to $PdCl_2(CH_3CN)_2$], generated *via* addition of 1.0 equivalent of KBr or using allyl bromide as cross-coupling reagent instead of allyl chloride, gives the expected product in lower yield, indicating that the $PdCl_2(CH_3CN)_2$ indeed plays the role of a Lewis acid (Table 1, entries 7 and 8). Other catalysts such as $PdCl_2(PPh_3)_2$ (generated in the reaction by adding 20 mol% of PPh_3) and $Pd(PPh_3)_4$ showed no catalytic activity (Table 1, entries 1 and 2). We can then conclude that $PdCl_2(CH_3CN)_2$ is a stronger Lewis acid than $PdBr_2(CH_3CN)_2$, $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$. In addition, the allylpalladium dimer can also make this transformation work but gives a relatively lower yield (Table 1, entry 9). Thus, $PdCl_2(CH_3CN)_2$ was chosen as the catalyst for this transformation.

First, various *O*-, *N*-based nucleophiles were tested to react with (*E*)-3-benzylidene-5-phenylpent-4-yn-2-one **1a** and allyl chloride **3a** in the presence of a catalytic amount of $PdCl_2(CH_3CN)_2$, the results are listed in Table 2. The scope of the *O*-based nucleophiles is quite general. Besides methanol, other alcohols such as isopropyl alcohol, benzyl alcohol, olefin-tethered alcohols, and phenol, can act as *O*-based nucleophiles to give tetrasubstituted furans in moderate to excellent yields (Table 2, entries 1–7). The reaction of the secondary alcohol *i*-PrOH **2b** with **1a** gave a relatively lower yield (42%) and required a longer reaction time (Table 2, entry 1). This may be due to the steric effect of *i*-PrOH. Compared to other *O*-nucleophiles, the reaction with 3-butene-1-ol **2f** affords the corresponding allyl-substituted furan **4afa** in a relatively higher yield (82%) (Table 2, entry 5), it is noteworthy that no desired product was obtained, instead *N*,*N*-bisallyl-*p*-toluenesulfonamide was isolated, when *N*-

Table 2. Coupling cyclization of 2-(1-alkynyl)-2-alken-1-ones **1a** with *O*-, *N*-based nucleophiles **2b–2i**.[a]



1a 2 4

Entry	Nucleophiles **2**	Time [h]	Yield of **4**
1[b],[c]	*i*-PrOH **2b**	72	 R = *i*-Pr, **4aba**[e], 42%
2	BnOH **2c**	24	R = Bn, **4aca**, 63%
3	PhOH **2d**	24	R = Ph, **4ada**, 66%
4[b],[d]	 **2e**	72	
5	 **2f**	45	
6	 **2g**	60	*n* = 1, **4aea**, 58% *n* = 2, **4afa**, 82%
7	 **2h**	60	*n* = 3, **4aga**, 62% *n* = 4, **4aha**, 52%
8	 **2i**	60	 **4aia**, 0%

[a] Unless otherwise specified, reactions were run with **1a** (0.5 mmol, 1.0 equiv.), nucleophiles (1.0 mmol, 2.0 equiv.) in CH_3CN (2 mL). Reported yields are of the isolated product.

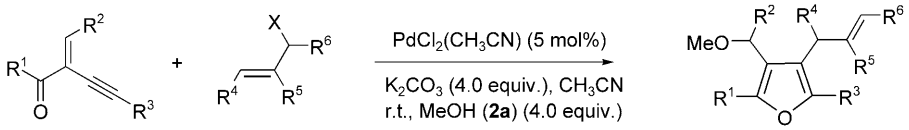
[b] Additional $PdCl_2(CH_3CN)_2$ (5 mol%) was added after 24 h.

[c] Used *i*-PrOH (6.0 equiv.) and allyl chloride (6.0 equiv.).

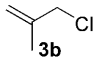
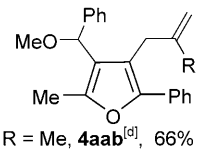
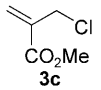
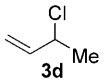
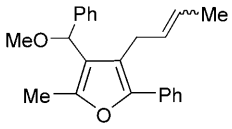
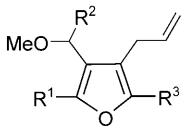
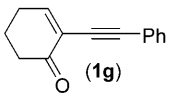
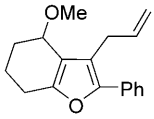
[d] Additional 2.0 equiv. of allyl alcohol and allyl chloride (4.0 equiv.) were added after 24 h.

[e] The designation **4aba** for the product indicates that the reactants used were **1a**, **2b**, and **3a**, respectively.

Table 3. Scope of 2-(1-alkynyl)-2-alken-1-ones **1** and allyl chlorides **3**.[a]



1 **3** **4**

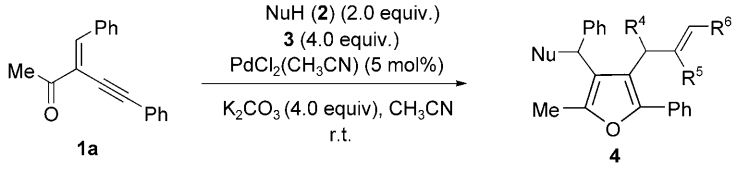
Entry	Enyne **1** R^1/ R^2/ R^3	**3**	Time [h]	**4**, Isolated Yield
1	CH_3/Ph/Ph (**1a**)	 **3b**	14	 R = Me, **4aab**[d], 66% R= CO_2Me, **4aac**, 70%
2[b]	**1a**	 **3c**	36	
3	**1a**	 **3d**	48	 **4aad**, 89%
4	*n*-C_4H_9/Ph/Ph (**1b**)	**3a**	30	 **4baa**, 77%
5	Ph/Ph/Ph (**1c**)	**3a**	24	**4caa**, 91%
6	Me/4-$MeOC_6H_4$/Ph (**1d**)	**3a**	36	**4daa**, 73%
7	Me/4-$MeOC_6H_4$/4-$MeOC_6H_4$ (**1e**)	**3a**	72	**4eaa**, 63%
8	Ph/Ph/$BnOCH_2$ (**1f**)	**3a**	24	**4faa**, 80%
9	 (**1g**)	**3a**	24	 **4gaa**, 57%
10	Me/Ph/1-naphthyl (**1h**)	**3a**	18	**4haa**, 65%
11[c]	Me/Ph/*n*-C_4H_9 (**1i**)	**3a**	43	**4iaa**, 40%

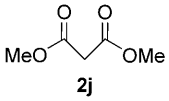
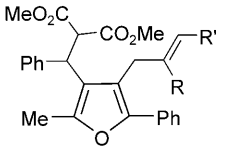
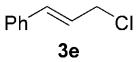
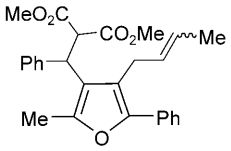
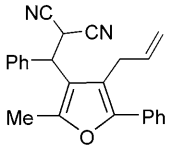
[a] Unless otherwise noted, the reactions were performed under standard conditions.
[b] Another portion of $PdCl_2(CH_3CN)_2$ (5 mol%) was added after 24 h.
[c] *Reaction conditions:* MeOH (8.0 equiv.), allyl chloride (8.0 equiv.), K_2CO_3 (6.0 equiv.), and $PdCl_2(CH_3CN)_2$ (10 mol%).
[d] The designation **4aab** for the product indicates that the reactants used were **1a**, **2a**, and **3b**, respectively.

allyl-*p*-toluenesulfonamide is used as the *N*-nucleophile (Table 2, entry 8).

Next, we examined the reaction of a series of 2-(1-alkynyl)-2-alken-1-ones **1** with various allyl chlorides **3** and methanol **2a** under standard conditions (Table 3). It should be highlighted that: (1) the reaction of **1a** with substituted allylic chlorides such as **3b–3d** proceeds very well to afford the corresponding highly functionalized furans in good yields (Table 3, entries 1–3). (2) Many functional groups are cleanly tolerated in the present transformation including the ester group, which make it be a good candidate for further organic transformations. (3) Various substituted 2-(1-alkynyl)-2-alken-1-ones **1** were examined and most of them except **1i** react well to give good to excellent yields (Table 3, entry 10). (4) We were pleased to find that the cyclic enyne **1g** can also be used as the substrate and that this reaction affords the corresponding fused bicycle furan **4gaa** in 57% yield under our conditions (Table 3, entry 9).

Table 4. Carbon-based nucleophiles **2j** and **2k** were examined under standard conditions.[a]



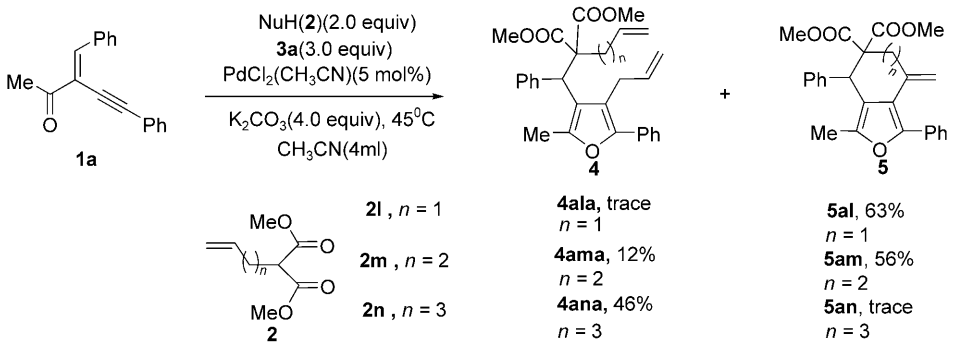
Entry	NuH (**2**)	**3**	Time [h]	**4** Isolated Yield
1	 **2j**	**3a**	10	 R = H, R' = H , **4aja**, 91%
2	**2j**	**3b**	12	R = Me, R' = H, **4ajb**, 62%
3[b]	**2j**	**3c**	20	R = CO_2Me, R' = H, **4ajc**, 54%
4	**2j**	 **3e**	24	R = H, R' = Ph, **4aje**, 79%
5	**2j**	**3d**	24	 **4ajd**, 85%
6	 **2k**	**3a**	24	 **4aka**, 0%

[a] Unless otherwise specified, reactions were carried out under standard conditions.
[b] Another 0.5 equiv. of dimethyl malonate was added after 12 h.

After studying *O*- and *N*-based nucleophiles, we turned our attention to the case of *C*-based nucleophiles such as malonates and malononitrile,[22] the results are summarized in Table 4. As expected, the reaction occurred smoothly to give tetrasubstituted furans with polyfunctional groups in moderate to excellent yields when dimethyl malonate **2j** and substituted allyl chlorides were used, respectively (Table 4, entries 1–5). On the other hand, the reaction with malononitrile failed to produce the corresponding cross-coupling product (Table 4, entry 6).

Two-Component Michael Addition/Cyclization/Heck Reaction of 2-(1-Alkynyl)-2-alken-1-ones with Olefin-Tethered *C*-Based Nucleophiles: Allyl Chloride is Serving as an Oxidant

It is surprising but also quite interesting to observe a different reaction pattern when dimethyl 2-allylmalonate **2l** was used as the *C*-based nucleophile (Scheme 2). The expected cross-coupling product, the allyl-substituted furan **4ala** was isolated in a trace amount, whereas a novel 6-membered carbocycle, the 3,4-fused bicyclic furan **5al**, was harvested in 50% yield. When the reaction was performed at 45 °C with three equivalents of allyl chloride **3a**, a slightly higher yield (63%) could be obtained. The structure of **5al** was further confirmed by single-crystal X-ray diffraction analysis (Figure 1).[23] Thus, a novel palladium-catalyzed two-component domino process involving Michael addition/cyclization/Heck reaction was explored. In this novel cascade process, two carbon-carbon bonds and one C–O bond are formed in a single operative step. Furthermore, allyl chloride is not serving as a cross-coupling reagent but, instead, as an oxidant, since two hydrogen atoms are lacking on comparing the starting materials **1a** and **2l** with the product **5al**. To evaluate the scope of this novel catalytic cascade process and in order to get seven- or



Scheme 2. Coupling cyclization reaction of **1a** with olefin-tethered *C*-based nucleophiles.

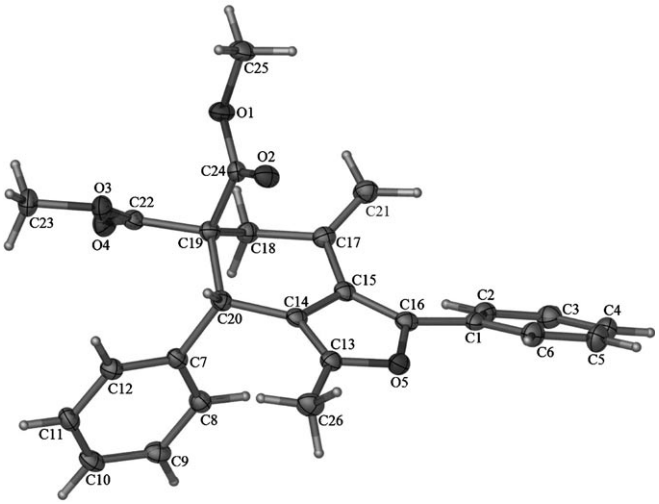


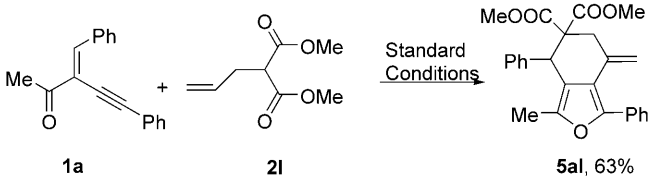
Figure 1. ORTEP depiction of compound **5al**.

eight-membered carbocyclic 3,4-fused bicyclic furans, another two 2-substituted malonate derivatives with longer tether chains, dimethyl 2-(but-3-enyl)malonate **2m** and dimethyl 2-(pent-4-enyl)malonate **2n** were prepared according to known procedures,[24] and subsequently subjected to the optimized reaction conditions, respectively. The results show that the selectivity depends much on the length of the tethered chain. When **2l** was employed, the two-component domino reaction ran prior to the three-component process to give the 3,4-fused bicyclic **5al** as the major product. In contrast, in the case of dimethyl 2-(pent-4-enyl)malonate **2n** with a longer chain, the three-component cross-coupling reaction is predominant to yield **4ana** (46%) as the major product. Moreover, the reaction gave the two-component product **5am** as the major product (56%) and the three-component cross-coupling product **4ama** (12%) as minor product in the case of **2m**.

It is obvious that a better yield of the two-component product **5al** will be formed if the competitive three-component reaction can be suppressed, in which allyl chloride serves as a cross-coupling reagent. Thus, if we can find an oxidant to replace the allyl chloride which plays as the oxidant role, the reaction will become much cleaner and give a higher yield of **5al**. Thus, (*E*)-3-benzylidene-5-phenylpent-4-yn-2-one **1a** and dimethyl 2-allylmalonate **2l** were selected as representative substrates for optimization of reaction conditions (Table 5). In this domino process, the key problem that needs to be solved is to find an appropriate oxidant that enables the conversion of Pd(0) into Pd(II) and thus accomplishes the catalytic cycle. To increase the yield, many oft-used oxidants such as O_2,[25] benzoquinone/MnO_2,[26] the α-halocarbonyl compound desyl chloride,[27] and $CuCl_2$ were tested.[28] Unfortunately, all of these oxidants as well as additives such as LiCl, $(n\text{-Bu})_4NCl$ [could stabilize the Pd(0) complex and not convert it into Pd black[29]] were not suitable for the present transformation. Among these oxidants, allyl chloride is the only working oxidant for this transformation (Table 5, entries 1 and 2). The desired product **5al** was obtained in 63% isolated yield when the reaction was carried out in CH_3CN at 45 °C for 36 h with allyl chloride (3.0 equiv.) and K_2CO_3(4.0 equiv.). Other changes, such as lowering the amount of the base or use of different solvent or base, lead to a lower yield or no product at all (Table 5, entries 1–18).

To further explore the scope of this transformation, a variety of 2-(1-alkynyl)-2-alken-1-ones **1** were examined and the results are listed in Table 6. It is shown that: (1) alkynes containing aryl groups afford relatively higher yields than those with alkyl groups (Table 6, compare entries 1–4 with entry 5); (2) the reaction of those substrates with alkynes bearing an electron-rich aryl ring requires a longer reaction time and gives relatively lower yields (Table 6, compare entries 1 and 2 with entries 3 and 4); (3) it is surprising that the reaction mixture became very complicated and no product was isolated when cyclic substrate **1g** was treated with **2l** (Table 6, entry 6).

Table 5. Screening reaction conditions for Pd(II)-catalyzed double cyclization of **1a** with **2l**.[a]



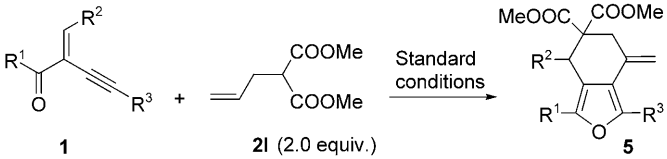
1a **2l** **5al**, 63%

Standard Conditions: 1a (0.5mmol,1.0 equiv.), allylic chloride (3.0 equiv.), K_2CO_3 (4.0 equiv.), **2l** (2.0 equiv), $PdCl_2(CH_3CN)_2$ (5 mol%), CH_3CN, 45 °C.

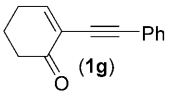
Entry	Different from standard conditions	Yield[b]
1	r.t.	50%
2	K_2CO_3 (2 equiv.)	40%
3	no base	0
4	under O_2 protection	0
5	same as entry 4, LiCl (1.0 equiv.)	0
6	same as entry 4, $(n\text{-}Bu)_4NCl$ (1.0 equiv.)	0
7	1,4-benzoquinone (1.0 equiv.)	0
8	1,4-benzoquinone (0.1equiv.), MnO_2 (1.0 equiv.)	0
9	$CuCl_2$ (1.1 equiv.)	0
10	2-chloro-1,2-diphenylethanone	0
11	$K_3PO_4{\cdot}3H_2O$ was used instead of K_2CO_3	0
12	K_2HPO_4 was used instead of K_2CO_3	0
13	Cs_2CO_3 was used instead of K_2CO_3	28%
14	Na_2CO_3 was used instead of K_2CO_3	0
15[c]	NMP was used instead of CH_3CN	0
16	DMF was used instead of CH_3CN	8%
17	$Pd(OAc)_2$ was used instead of $PdCl_2(CH_3CN)_2$	0
18	$Pd(dba)_2$ was used instead of $PdCl_2(CH_3CN)_2$	0

[a] Unless otherwise stated, reaction were carried out with **1a** (0.5 mmol), **2l** (1.0 mmol), base (2.0 mmol), catalyst (5 mol%), oxidant and additives in solvent (2 mL) at room temperature for 36 h.
[b] Yield of the isolated product.
[c] NMP = 1-methyl-2-pyrrolidinone.

Table 6. Cascade two-component reaction of **1** with dimethyl 2-allylmalonate **2l** under the standard conditions[a]



1 **2l** (2.0 equiv.) **5**

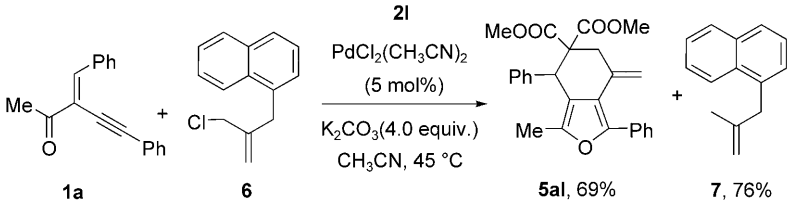
Entry	enyne 1 $R^1/R^2/R^3$	Time [h]	Yield 5[b] [%]
1	$n\text{-}C_4H_9$/Ph/Ph (**1b**)	36	**5bl** (60)
2	Ph/Ph/Ph (**1c**)	30	**5cl** (68)
3	Me/4-$MeOC_6H_4$/Ph (**1d**)	48	**5dl** (55)
4	Me /4-$MeOC_6H_4$/4-$MeOC_6H_4$ (**1e**)	72	**5el** (47)
5	Ph/Ph/$BnOCH_2$ (**1f**)	70	**5fl** (40)
6	 (**1g**)	72	**5gl** (0)

[a] Reactions were carried out with **1** (0.25 mmol) under standard conditions.
[b] Isolated yield.

Mechanism Insights

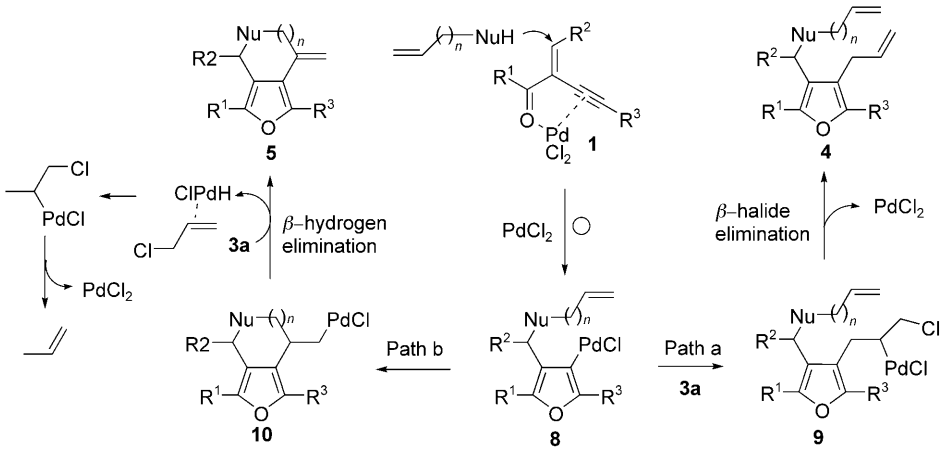
In order to clarify where allyl chloride goes after the reaction, a 2-substituted allyl chloride, 1-[2-(chloromethyl)allyl]naphthalene **6**, was prepared from the commercially available 1-bromethylnaphthalene and prop-2-yn-1-ol in two steps according to known procedures.[30] Then, we examined the reaction of **1a** with dimethyl 2-allylmalonate **2l** under standard conditions using 2-(naphthalen-1-y1-methyl)allyl chloride **6** instead of allyl chloride as oxidant reagent [Eq. (3)]. We were pleased to find that the reaction proceeds smoothly under standard conditions to afford the desired product, the 3,4-fused bicyclic furan **5al** in 69% yield along with 2-methylallylnaphthalene **7** derived from **6** in 76% isolated yield.

According to the above control experiment result, two plausible mechanisms, a Pd(II) (Scheme 3) and a Pd(0) [Pd(II) as the precursor] catalytic cycle (Scheme 4), are proposed, respectively. In the Pd(II) catalytic cycle (Scheme 3), the Pd(II) catalyst plays a dual role as a Lewis acid and transition metal to facilitate the nucleophilic addition step and the subsequent cyclization step[18,20] to afford a key intermediate, the furanyl-palladium **8**, which would undergo two possible pathways. One is the intermolecular cross-coupling reaction with allyl chloride *via* regioselctive insertion of the double bond of allyl chloride into the C–Pd bond of intermediate **8**, followed by β-halide elimination to afford the allyl-substituted tetra-

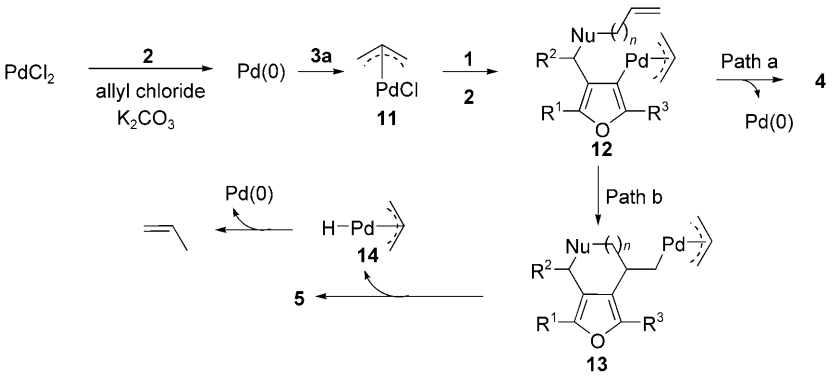


1a **6** **5al**, 69% **7**, 76%

Eq. (3)



Scheme 3. Proposed Pd(II) catalytic cycle.

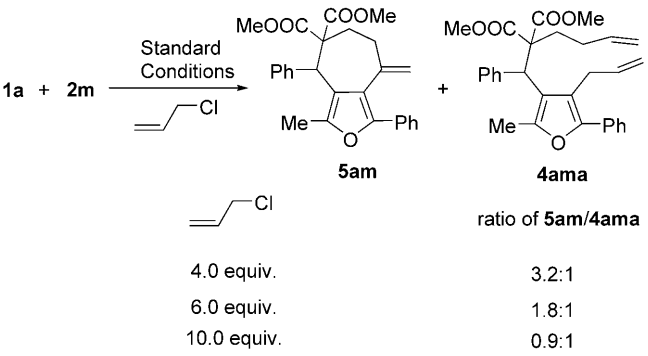


Scheme 4. Proposed Pd(0) catalytic cycle.

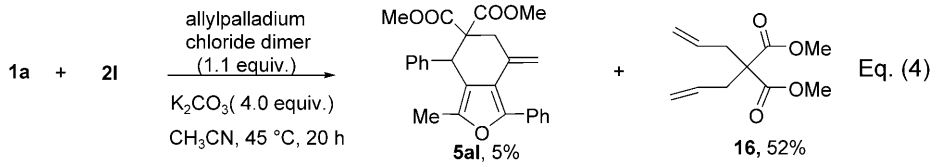
substituted furan **4**[31] and regenerate $PdCl_2$ (path a). The other one is the intramolecular Heck reaction *via* the intramolecular regioselective insertion of the double bond followed by β-H elimination to afford tetrasubstitued furan **5** and generate an allyl chloride-coordinated intermediate $(CH_2CHCH_2Cl)HPdCl$ in the presence of excess allylic chloride. The $(CH_2CHCH_2Cl)HPdCl$ intermediate would not undergo reductive elimination to generate Pd(0) under the basic conditions,[32] instead, a regioselective addition reaction followed by β-halide elimination to regenerate $PdCl_2$ (path b) occurs.

In the Pd(0)-catalyzed cycle (Scheme 4),[20] Pd(0) could be generated from Pd(II) in the presence of base and nucleophiles.[33] The oxidative addition of allyl chloride with Pd(0) generates allylpalladium chloride **11** which may also facilitate both the nucleophilic addition step and the cyclization step to afford a furanyl allyl-palladium intermediate **12**, which could also undergo subsequently two possible pathways. One is the direct reductive elimination to give the cross-coupling product **4** and regenerate Pd(0). The other is the intramolecular Heck reaction *via* the intramolecular regioselective insertion of the double bond followed by β-H elimination to afford furan **5** and generate **14**. Subsequent reductive elimination would regenerate Pd(0).

Some further control experiments were then performed in order to find out which mechanism is more reasonable. The coupling cyclization reaction of **1a** with dimethyl butene-3-yl-1-malonate **2m** under different concentrations of allyl chloride catalyzed by $PdCl_2(CH_3CN)_2$ was investigated in detail (Scheme 5).



Scheme 5. Coupling cyclization reaction of **1a** with **2m** under different concentration of allyl chloride **3a**.

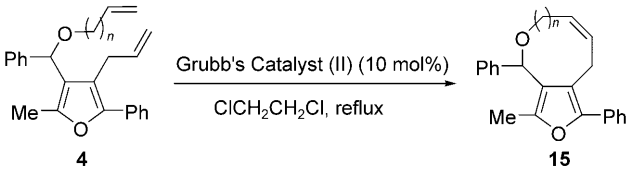


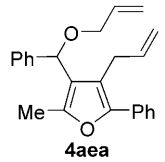
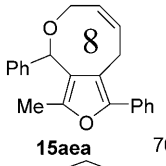
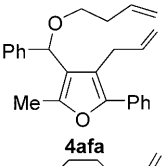
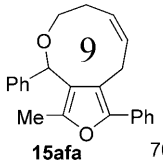
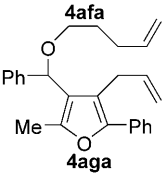
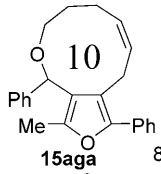
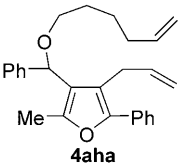
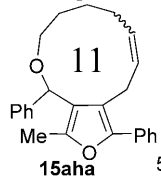
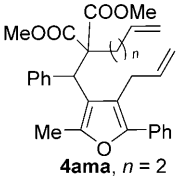
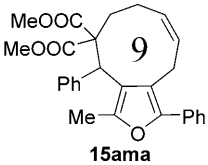
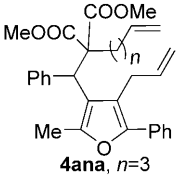
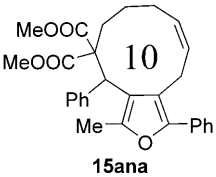
The results showed that with the increasing concentration of allyl chloride, the ratio of **5am/4ama** is becoming lower. However, treatment of **1a** and dimethyl 2-allylmalonate **2l** with a stoichiometric amount of allylpalladium chloride dimer under the basic conditions makes the reaction very complicated to give the desired **5al** in only 5% isolated yield (caculated based on **1a**), the main isolated product was dimethyl 2,2-diallylmalonate **16** in 52% yield {calculated based on **2l** [Eq. (4)]}. Although these results cannot exclude the Pd(0) catalytic cycle exclusively, we prefer the Pd(II) catalytic cycle (Scheme 3) as the more reasonable possible mechanism for this cascade transformation.

Synthetic Application in Syntheses of 3,4-Fused Bicyclic Furans *via* Ring-Closing Metathesis of Three-Component Products

Ring-closing metathesis (RCM), one of the most powerful methods for the construction of a wide variety of complex molecules with multiple functional groups, has emerged as an effective strategy in organic synthesis.[34] It occurred to us that the two terminal olefins of the obtained allyl-substituted furans (**4aea–4aha**, **4ama**, **4ana**) might undergo a ring-closing metathesis(RCM) reaction to construct a new ring. To the best of our knowledge, only few reports concerning the synthesis of 3,4-fused fully substituted furans have been published.[17] It is well documented that seven-, eight-, and nine-membered heterocyclic ring systems are characteristic structural frameworks of various natural products.[35] To demonstrate the synthetic utility of the obtained allyl-substituted furans, we examined their RCM reaction catalyzed by the commercially available second generation Grubbs catalyst. The results are summarized in Table 7. Initially, allyl-substituted furan **4afa** was chosen as model substrate for screening the RCM reaction conditions. It was pleasing to find that the RCM reaction of allyl-substituted furan **4afa** under highly diluted concentration proceeds smoothly in refluxing DCE to afford the corresponding 9-membered oxygen fused furan **15afa** in 70% yield (Table 7, entry 2). The reaction proceeds very slowly and **4afa** could not be consumed completely after 72 h at room temperature. Similar results were obtained when Grubbs catalyst (II) (5 mol%) was employed even if the reaction was carried out in refluxing DCE. Under these conditions, the RCM reactions of other allyl-substituted furans **4aea**, **4aga** and **4aha** give the corresponding 8-, 10- and 11-membered oxygen fused furans **15aea, 15aga** and **15aha** in moderate to good yields, respectively

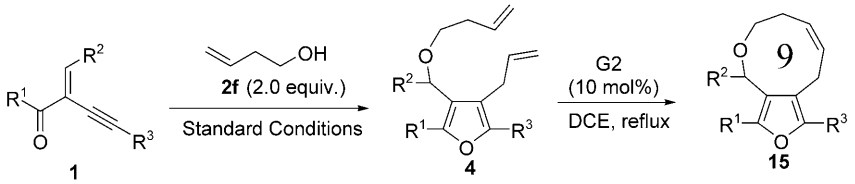
Table 7. Ring-closing metathesis of allyl-substituted furans catalyzed by Grubbs' catalyst (II).[a]

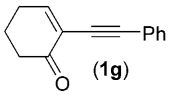
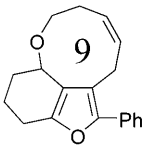


Entry	Substrate	Time [h]	Yield of **15**[b]
1	 **4aea**	15	 **15aea** 76%
2	 **4afa**	8	 **15afa** 70%
3	 **4aga**	10	 **15aga** 84%
4	 **4aha**	12	 **15aha** 56%
5	 **4ama**, *n* = 2	12	 **15ama** 0%
6	 **4ana**, *n*=3	12	 **15ana** 0%

[a] Reactions run with **4** (0.25 mmol scale) in $ClCH_2CH_2Cl$ (40 mL).
[b] Isolated yield.

Table 8. Synthesis of [5,9]-bicycles *via* a two-step strategy.[a,b]



Entry	enyne 1 $R^1/R^2/R^3$	4[c] Yield [%]	15[c] Yield(%)
1	*n*-C_4H_9/Ph/Ph (**1b**)	**4bfa** (75)	**15bfa** (89)
2	Ph/Ph/Ph (**1c**)	**4cfa** (93)	**15cfa** (75)
3	Me/4-$MeOC_6H_4$/Ph (**1d**)	**4dfa** (77)	**15dfa** (74)
4	Me/4-$MeOC_6H_4$/4-$MeOC_6H_4$ (**1e**)	**4efa** (57)	**15efa** (50)
5	Ph/Ph/$BnOCH_2$ (**1f**)	**4ffa** (85)	**15ffa** (50)
6	 (**1g**)	**4gfa** (59)	 **15gfa** (61)
7	Me/Ph/1-naphthyl (**1h**)	**4hfa** (67)	**15hfa** (70)
8	Me/Ph/ *n*-C_4H_9 (**1i**)	**4ifa** (29)	**15ifa** (44)
9	Me/4-$MeOC_6H_4$/1-naphthyl (**1j**)	**4jfa** (79)	**15jfa** (53)

[a] The first step was run with **1a** (0.5 mmol scale) in CH_3CN (2.0 mL).
[b] The second step was run with **4** (0.25 mmol) in $ClCH_2CH_2Cl$ (40 mL).
[c] Isolated yields.

(Table 7, entries 1, 3, and 4). With respect to the enlarged 11-membered oxygen heterocyclic fused furan **15aha**, the reaction affords a mixture of two inseparable *E*/*Z* isomers (Table 7, entry 4). Interestingly, the RCM reactions of the corresponding allyl substituted furans **4ama**, **4ana** derived from carbon-based nucleophiles failed to yield the desired bicyclic products. Only decomposed products were obtained according to ^{1}H NMR spectroscopy.

Encouraged by the above successful results, this expedient access to nine-membered oxygen fused furans *via* a two-step operation was examined with respect to other substrates. First, we evaluated the scope of the coupling cyclization of **1** with 3-butene-1-ol **2f** under the standard conditions, subsequently, the RCM reaction of the resulting allyl-substituted furans **4** was executed to afford nine-membered oxygen-heterocyclic fused furans **15**. As shown in Table 8, this easy access to nine-membered fused furans can be successfully extended to a variety of 2-(1-alkynyl)-2-alken-1-ones **1**. Both the three-component Michael addition/cyclization/cross-coupling reaction and the subsequent ring-closing metathesis reaction proceeded uneventfully to furnish the desired product under standard conditions. The results in Table 7 and Table 8 show that this new strategy provides an easy access to functionalized fused bicyclic furans containing nine- to eleven-membered rings in moderate to good yields.

Conclusions

In summary, we have developed a Pd(II)-catalyzed domino reaction of 2-(1-alkynyl)-2-alken-1-ones with nucleophiles for the preparation of tetrasubstituted furans. Its advantage is clear in some aspects: (1) it provides an efficient route to cyclic 3,4-fused tetrasubstituted furans *via* a two-component cascade double cyclization and tetrasubstituted furans *via* a three-component cascade reaction; the type of nucleophiles and the length of the tethered chain affect the efficiency of two-component reaction. (2) It is easy to introduce various substituents to the furan ring by the appropriate choice of 2-(1-alkynyl)-2-alken-1-ones, nucleophiles and chlorides. (3) Ring-closing metathesis reactions of allyl-substituted tetrasubstituted furans provide an efficient route to synthesize 3,4-fused bicyclic furans; (4) Some control reactions for mechanistic studies showed that this domino reaction proceeds *via* a Pd(II) catalytic cycle. (5) Allyl chloride can act as an oxidant besides its well known behaviour as an alkylating reagent.

Experimental Section

The starting materials, 2-(1-alkynyl)-alken-1-ones **1**, were prepared according to known procedures.[13,15b] For preparative procedures and spectroscopic data for all new compounds, see the Supporting Information.

General Procedure for the Pd(II)-Catalyzed Domino Reaction of 2-(1-Alkynyl)-alken-1-ones 1 with Nucleophiles using Allyl Chloride as Oxidant or Cross-Coupling Reagent

$PdCl_2(CH_3CN)_2$ (6.0 mg, 0.025 mmol) was added to a mixture of **1** (0.5 mmol), nucleophile (1.0 mmol, 2.0 equiv.), allyl chloride (1.5–2.0 mmol, 3.0–4.0 equiv.) in CH_3CN (2.0–4.0 mL) followed by addition of solid K_2CO_3(2.0 mmol, 4.0 equiv.) as the base. The reaction mixture was stirred at room temperature or 45 °C until **1** was consumed completely as determined by TLC analysis. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O = 10:1–100:1) to give desired product **4** or **5**.

General Procedure for Ring-Closing Metathesis Reaction of Allyl-Substituted Furans 4 Catalyzed by Second Generation Grubbs' Catalyst

To a solution of allyl-substituted furan **4**(0.25 mmol) in dry CH_2ClCH_2Cl (40 mL), second generation Grubbs' catalyst (21.2 mg, 10 mol%) was added at room temperature under N_2 protection, the mixture was then stirred at reflux. After **4** was consumed completely as determined by TLC analysis. The reaction mixture was concentrated under vacuum and the residue was purified by column chromatography on silica gel (petroleum ether/Et_2O = 10:1–100:1) to give the desired product **15**.

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References

[1] a) M. V. Sargent, F. M. Dean, in: *Comprehensive Heterocyclic Chemistry*, Vol. 4, (Eds.: A. R. Katrizky, C. W. Rees), Pergamon Press, New York, **1984**, pp 599–656; D. M. X. Donnelly, M. J. Meegan, in: *Comprehensive Heterocyclic Chemistry*, Vol. 4, (Eds.: A. R. Katrizky, C. W. Rees), Pergamon Press, New York, **1984**, pp 657–712; b) *Natural Products Chemistry*, (Ed.: K. Nakanishi), Kodansha, Toyko, **1974**, pp 392–403; c) M. Shipman, *Contemp. Org. Synth.* **1995**, *2*, 1.

[2] G. Vernin, in: *Chemistry of Heterocyclic Compounds in Flavours and Aromas*, (Ed.: G. Vernin), Ellis Horwood, Chichester, **1982**, pp 74–85; G. Vernin, C. Parknanyi, in: *Chemistry of Heterocyclic Compounds in Flavours and Aromas*, (Ed.: G. Vernin), Ellis Horwood, Chichester, **1982**, pp 161–165.

[3] a) B. H. Lipshutz, *Chem. Rev.* **1986**, *86*, 795; b) R. Benassi, in: *Comprehensive Heterocyclic Chemistry II*, (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon: Oxford, **1996**; Vol. 2, pp 259–295; c) H. Heaney, J. S. Ahn, in: *Comprehensive Heterocyclic Chemistry II*, (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, Vol. 2, pp 297–357; d) W. Friedrichsen, in: *Comprehensive Heterocyclic Chemistry II*, (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**; Vol. 2, pp 351–393; e) B. A. Keay, P. W. Dibble, in: *Comprehensive Heterocyclic Chemistry II*, (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, Vol. 2, pp 395–436; f) *Comprehensive Organic Synthesis*, (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**.

[4] a) E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, John Wiley, New York, **1989**; b) K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, VCH, Weinheim, **1996**.

[5] For reviews, see: a) X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. T. Tong, H. N. C. Wong, *Tetrahedron* **1998**, *54*, 1955; b) B. A. Keay, *Chem. Soc. Rev.* **1999**, *28*. 209; c) T. L. Gilchrist, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2849; d) S. Cacchi, *J. Organomet. Chem.* **1999**, *576*, 42; e) X. L. Hou, Z. Yang, K. S. Yeung, H. N. C. Wong, in: *Progress in Heterocyclic Chemistry*, Vol. 19, (Eds.: G. W. Gribble, J. A. Joule), Pergamon, Oxford, **2008**, p 176; f) S. F. Kirsch, *Org. Biomol. Chem.* **2006**, *4*, 2076.

[6] a) J. A. Marshall, E. D. Robinson, *J. Org. Chem.* **1990**, *55*, 3450; b) J. A. Marshall, G. S. Bartley, *J. Org. Chem.* **1994**, *59*, 7169; c) J. A. Marshall, E. M. Wallace, *J. Org. Chem.* **1995**, *60*, 796; d) A. S. K. Hashmi, *Angew. Chem.* **1995**, *107*. 1749; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1581; e) A. S. K. Hashmi, T. L. Ruppert, T. Knofel, J. W. Bats, *J. Org. Chem.* **1997**, *62*, 7295; f) A. S. K. Hashmi, L. Schwarz, J. H. Choi, T. M. Frost, *Angew. Chem.* **2000**, *112*, 2382; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; g) S. Ma, L. Li, *Org. Lett.* **2000**, *2*, 941; h) S. Ma, Z. Yu, *Angew. Chem.* **2002**, *114*, 1853; *Angew. Chem. Int. Ed.* **2002**, *41*, 1775; i) S. Ma, ; J. Zhang, L. Lu, *Chem. Eur. J.* **2003**, *9*, 2447; j) J. T. Kim, A. V. Kel′in, V. Gevorgyan, *Angew. Chem.* **2003**, *115*, 102; *Angew. Chem. Int. Ed.* **2003**, *42*, 98; k) A. W. Sromek, A. V. Kel′in, V. Gevorgyan, *Angew. Chem.* **2004**, *116*, 2330; *Angew. Chem. Int. Ed.* **2004**, *43*, 2280; l) M. H. Suhre, M. Reif, S. F. Kirsch, *Org. Lett.* **2005**, *7*, 3925; m) A. W. Sromek, M. Rubina, V. Gevorgyan, *J. Am. Chem. Soc.* **2005**, *127*, 10500; n) A. Dudnik, V. Gevorgyan, *Angew. Chem.* **2007**, *119*, 5287; *Angew. Chem. Int. Ed.* **2007**, *46*, 5195; o) T. Schwier, A. W. Sromek, D. M. L. Yap, D. Chernyak, V. Gevorgyan, *J. Am. Chem. Soc.* **2007**, *129*, 9868.

[7] a) Y. Fukuda, H. Shiragami, K. Utimoto, H. Nozaki, *J. Org. Chem.* **1991**, *56*, 5816; b) A. V. Kel′in, V. Gevorgyan, *J. Org. Chem.* **2002**, *67*, 95.

[8] J. Zhang, H. G. Schmalz, *Angew. Chem.* **2006**, *118*, 6856; *Angew. Chem. Int. Ed.* **2006**, *45*, 6704.

[9] Y. H. Liu, F. Song, Z. Song, M. Liu, ; B. Yan, *Org. Lett.* **2005**, *7*, 5409.

[10] a) S. Ma, J. Zhang, *Angew. Chem.* **2003**, *115*, 193; *Angew. Chem. Int. Ed.* **2003**, *42*, 183; b) S. Ma, L. Lu, J. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 9645.

[11] a) A. Padwa, J. M. Kassir, S. L. Xu, *J. Org. Chem.* **1991**, *56*, 6971; b) S. Ma, J. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 12386.

[12] M. W. Miller, C. R. Johnson, *J. Org. Chem.* **1997**, *62*, 1582.

[13] T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164.

[14] a) N. T. Patil, H. Wu, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 4531; b) C. Oh, V. Reddy, A. Kim, C. Rhim, *Tetrahedron Lett.* **2006**, *47*, 5307; c) X. Liu, Z. Pan, X. Shu, X. Duan, Y. liang, *Synlett* **2006**, *12*, 1962.

[15] a) Y. H. Liu, S. Zhou, *Org. Lett.* **2005**, *7*, 4609; b) T. Yao, X. Zhang, R. C. Larock, *J. Org. Chem.* **2005**, *70*,7679.

[16] For selected recent examples see: a) R. Sanz, D. Miguel, A. Martinez, J. M. Alvarez-Gutierrez, F. Rodriguez, *Org. Lett.* **2007**, *9*, 727; b) V. Cadierno, J. Gimeno, N. Nebra, *Adv. Synth. Catal*, **2007**, *349*, 382; c) I. Yavari, A. Mokhtarporyani-Sanandaj, L. Morad, A. Mirzaei, *Tetrahedron* **2008**, *64*, 5221; d) X. Feng, Z. Tan, D. Chen, Y. Shen, C. Guo, J. Xiang, C. Zhu, *Tetrahedron Lett.* **2008**, *49*, 4110; e) Z. Chai, Z. Xie, X. Liu, G. Zhao, J. Wang, *J. Org. Chem.* **2008**, *73*, 2947.

[17] a) M. Suzuki, H. Ohtaka, Y. Kameya, N. Hamanaka, R. Noyori, *J. Org. Chem.* **1989**, *54*, 5292; b) M. E. Price, N. E. Schore, *J. Org. Chem.* **1989**, *54*, 2777; c) Y. Siquot, P. Frere, T. Nozdryn, J. Cousseau, M. Salle, M. Jubauct, J. Orduna, J. Carin, A. Corguesa, *Tetrahedron Lett*, **1997**, *38*, 1919; d) G. Zhang, X. Huang, G. Li, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 1814.

[18] $Pd(OAc)_2$ acts as both a Lewis acid and a transition metal, see: N. Asao, T. Nogami, K. Takahashi, Y. Yammamoto, *J. Am. Chem. Soc.* **2002**, *124*, 764.

[19] For recent reviews, see: a) A. Dömling, *Curr. Opin. Chem. Biol.* **2002**, *6*, 306; b) R. V. A. Orru, M. de Greef, *Synthesis* **2003**, 1471; c) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51; d) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133; e) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, L. Balagopal, *Acc. Chem. Res.* **2003**, *36*, 899; f) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602; g) A. Dondoni, A. Massi, *Acc. Chem. Res.* **2006**, *39*, 451; h) A. Dömling, *Chem. Rev.* **2006**, *106*, 17; i) D. M. D′Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095; j) T. J. J. Müller, in: *Topics in Organometallic Chemistry* (Ed. T. J. J. Müller), Springer, Berlin, **2006**, Vol. 19, pp 149; k) *Multicomponent Reactions*, (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**.

[20] Part of this work has been published in the preliminary communication, see: Y. Xiao, J. Zhang, *Angew. Chem.* **2008**, *120*, 1929; *Angew. Chem. Int. Ed.* **2008**, *47*, 1903.

[21] For reviews, see: a) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131; b) R. A. Bunce, *Tetrahedron Tetrahedron.* **1995**, *51*, 13103; c) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; d) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137; e) P. J. Parsons, C. S. Penkett and A. J. Shell, *Chem. Rev.***1996**, *96*, 195; f) H. Pellissier, *Tetrahedron* **2006**, *62*, 2143; g) H. Pellissier, *Tetrahedron* **2006**, *62*, 1619; h) L. F. Tietze, G. Brasche, K. Gercke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**, p 672; i) *Metal Catalyzed Cascade Reactions,* (Ed: T. J. J. Müller), Springer, Berlin, Heidelberg. *Top. Organomet. Chem.* **2006**, Vol 19; j) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; k) D. M. D′Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095; l) S. F. Kirsch, *Synthesis* **2008**, 3183.

[22] The reaction of 2-(1-alkynyl)-2-alken-1-ones with 1, 3-diketones as *C*-based nucleophiles readily affords 4*H*-pyrans under basic reaction conditions, see: X. Yu, H. Ren, Y. Xiao, J. Zhang, *Chem. Eur. J.* **2008**, *14*, 8481, and unpublished results.

[23] X-ray data for compound **5al**: $C_{26}H_{24}O_5$, MW = 416.45, triclinic, space group-1, Mo-Kα, final *R* indices [I > 2σ(I)], *R*1 = 0.0384, *wR*2 = 0.0980, *a* = 9.4172(3) Å, *b* = 9.4598(3) Å, *c* = 11.1284(2) Å, α = 93.5100(10)°, β = 107.1180(10)°, γ = 95.7700(10)°, *V* = 1058.48(6) Å^3, *T* = 123(2) K, *Z* = 2, reflections collected/unique: 24662/3689 (R_{int} = 0.0199), number of observations [I > 2σ(I)] 3289, parameters 288. CCDC 698140 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[24] S. Ma, B. Xu, Bukuo. Ni, *J. Org. Chem.* **2000**, *65*, 8532.

[25] For selected recent examples see: a) K. Akiyama, K. Wakabayashi, K. Mikami, *Adv. Synth. Catal.* **2005**, *347*,1569; b) K. S. Yoo, C. H. Yoon, R. K. Mishra, Y. C. Jung, S. W. Yi, K. W. Jung, *J. Am. Chem. Soc.* **2006**, *128*, 16384; c) K. S. Yoo, C. P. Park, C. H. Yoon, S. Sakaguchi, J. O'Neill, K. W. Jung, *Org. Lett*, **2007**, *9*, 3933; d) For a review, see: E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318.

[26] For selected recent examples, see: a) J. D. Crowley, K. D. Hanni, A. L. Lee, D. A. Leigh, *J. Am. Chem. Soc.* **2007**, *129*, 12092; b) J. Lindh, P.-A. Enquist, A. Pilotti, P. Nilsson, M. Larhed, *J. Org. Chem*, **2007**, *72*, 7957; c) R. Giri, N. Maugel, J. Li, D. Wang, S. Breazzano, L. Saunders, J. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510; d) C. Peng, Y. Wang, J. Wang, *J. Am. Chem. Soc.* **2008**, *130*, 1566.

[27] For selected recent examples see: a) A. Lei, X. Zhang, *Org. Lett*, **2002**, *4*, 2285; b) Y. Zhao, H. Wang, X. Hou, Y. Hu, A. Lei, H. Zhang, L. Zhu, *J. Am. Chem. Soc.* **2006**, *128*, 15048; c) Y. Zhao, L. Jin, P. Li, A. Lei, *J. Am. Chem. Soc.* **2008**, *130*, 9429.

[28] a) C. Liu, X. wang, T. Pei, R. A. Widenhoefer, *Chem. Eur. J.* **2004**, *10*, 6343; b) Z. Wang, S. Sugiarti, C. Morales, C. Jensen, D. Morales-Morales, *Inorg. Chim. Acta* **2006**, *359*, 1923; c)14d.

[29] W. Liu, Y. Xie, Y. Liang, J. Li, *Synthesis* **2006**, 860.

[30] a) J. G. Duboudin, B. Jousseaume, A. Saux, *J. Organomet. Chem*, **1979**, *168*, 1; b) M. Frederick Hawthorne, *J. Am. Chem. Soc.* **1960**, *82*, 1886.

[31] For the Pd-catalyzed allylation-cyclization reactions, see: a) Y. Wakabayashi, Y. Fukuda, H. Shiragami, K. Utimoto, H. Nozaki, *Tetrahedron* **1985**, *41*, 3655; b) M.

Kimura, K. Fugami, S. Tanaka, Y. Tamaru, *J. Org. Chem*, **1992**, *57*, 6377; c) see refs.[6g,7a]
[32] See the catalytic cycle of Heck reaction: a) F. Alonso, I. P. Beletskaya, M. Yus, *Tetrahedron* **2005**, *61*, 11771; b) S. Brase, A. de. Meijere, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley, Chichester, **1998**, pp 99–166.
[33] a) T. Nishimura, T. Onoue, K. Ohe, S. Uemura, *Tetrahedron. Lett*, **1998**, *39*, 6011; b) T. Nishimura, T. Onoue, K. Ohe, S. Uemura, *J. Org. Chem*, **1999**, *64*, 6750; c) T. Nishimura, K. Ohe, S. Uemura, *J. Am. Chem. Soc.* **1999**, *121*, 2645.
[34] For reviews, see: a) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036; b) R. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413.
[35] D. J. Faulkner, *Nat. Prod. Rep.* **1986**, *3*, 1.

