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Palladium(II)-Catalyzed Stereospecific Three-Component Domino Reactions of Diyne-enones, Nucleophiles, and Vinyl Ketones

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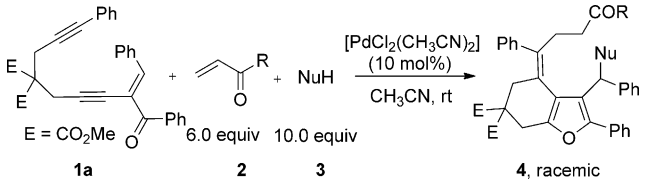
Transition-metal-catalyzed multicomponent domino reactions have received much attention due to their unrivaled power in efficient construction of architecturally complex molecules from relatively simple starting materials.[1] Furans are a class of important subunits that appear in many bioactive natural products and man-made drugs and are important building blocks in organic synthesis.[2] Among those methodologies available for synthesis of highly substituted furans,[3] much recent attention has focused on the development of metal-catalyzed single or two-component reactions of cyclopropyl ketones,[4] cyclopropenyl ketones,[5] allenyl ketones,[6] 3-alkyn-1-ones,[7] (*Z*)-2-en-4-yn-1-ols,[8] 1-(1-alkynyl)-cyclopropyl ketones,[9] 2-(1-alkynyl)-2-alken-1-ones,[10,11] and so forth.[12] However, methods for efficient synthesis of 2,3-cyclo[*b*]furans have been rarely reported.[13,14] We report herein a novel atom-economical palladium(II)-catalyzed three-component domino reaction of diyne-enones with nucleophiles and vinyl ketones or acrolein, leading to multifunctional 2,3-cyclo[*b*]furan along with a stereodefined tetrasubstituted olefin.

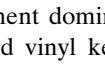
Initially, we examined the palladium-catalyzed three-component reaction of diyne-enone **1a** with MeOH and vinyl methyl ketone **2a** under different reaction conditions. After numerous attempts,[15] we obtained the best result at room temperature in CH_3CN with 10.0 equivalents MeOH as nucleophile and 6.0 equivalents vinyl methyl ketone as electrophilic acceptor and 10 mol% $[PdCl_2(CH_3CN)_2]$ as catalyst, respectively. Other catalyst such as $Pd(OAc)_2$, $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone), $[Pd(\eta^3\text{-}C_3H_5)_2Cl_2]$, and CuI are not effective at all. Reducing the catalyst loading or the amount of nucleophile and electrophile would result in slightly lower yields and longer reaction times.

With the best conditions in hand, we tested different nucleophiles (Table 1). The corresponding furans can be obtained in high yields when different alcohols are used as nucleophiles (Table 1, entries 2–4). Gratifyingly, water can act as nucleophile to give the corresponding furan with a further convertible alcohol in 58% yield (Table 1, entry 5). Furthermore, vinyl phenyl ketones **2b–2d** can also be used as electrophilic acceptors to afford the corresponding furans **4aab–4aad** in good yields (Table 1, entries 6–8), in which the weakly electron-withdrawing chlorine substituent on the aryl ring leads to higher yield. To our delight, ketone **2e** with olefinic double bonds can also act as the electrophilic acceptor to afford **4aae** selectively in high yield, in which only the terminal alkene is involved in the transformation (Table 1, entry 9). However, the acrylate **2f** cannot be applied to this transformation (Table 1, entry 10).

Table 1. Variation of nucleophiles and vinyl ketones.[a]



1a **2** **3** **4**, racemic

Entry	NuH (**3**)	R = (**2**)	*t* [h]	Product (Yield [%])[b]
1	MeOH (**3a**)	Me (**2a**)	8	**4aaa** (78)
2	*i*PrOH (**3b**)	**2a**	12	**4aba** (59)
3	BnOH (**3c**)	**2a**	12	**4aca** (61)
4	 (**3d**)	**2a**	8	**4ada** (73)
5	H_2O (**3e**)	**2a**	5	**4aea** (58)
6	**3a**	Ph (**2b**)	8	**4aab** (67)
7	**3a**	4-ClC_6H_4 (**2c**)	8	**4aac** (81)
8	**3a**	4-$MeOC_6H_4$ (**2d**)	8	**4aad** (69)
9	**3a**	CH=CHPh (**2e**)	8	**4aae** (80)
10	**3a**	OMe (**2f**)	20	**4aaf** (0)

[a] All reactions were carried out under the optimal conditions reported in the text. The product **4aaa** means that the starting materials were **1a**, **2a**, and **3a**. [b] Yield of isolated product.

We next examined the scope of the diyne-enone component under optimal conditions (Table 2). Electron-deficient and electron-rich aryl groups can be introduced to the alkyne moiety R^3 to give the corresponding products in high yields (Table 2, entries 1–6). The convertible Br group is tolerated in this reaction, providing a convenience way to

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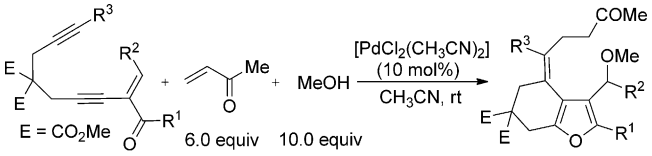
Table 2. Variation of diyne-enone components.

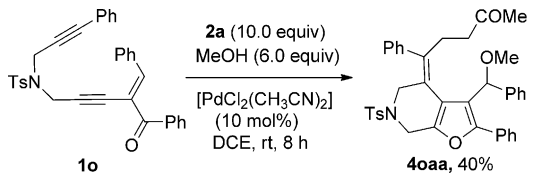


Entry	Ketone **1** $R^1/R^2/R^3$	t [h]	Product (Yield [%])[b]
1	Ph/Ph/4-MeC_6H_4 (**1b**)	8	**4baa** (71)
2	Ph/Ph/4-$MeOC_6H_4$ (**1c**)	8	**4caa** (70)
3	Ph/Ph/4-$MeCOC_6H_4$ (**1d**)	8	**4daa** (76)
4	Ph/Ph/4-$EtO_2CC_6H_4$ (**1e**)	8	**4eaa** (71)
5	Ph/Ph/3-$CF_3C_6H_4$ (**1f**)	8	**4faa** (75)
6	Ph/Ph/4-BrC_6H_4 (**1g**)	8	**4gaa** (72)
7	Me/Ph/Ph (**1h**)	6	**4haa** (42)
8	Ph/4-ClC_6H_4/Ph (**1i**)	8	**4iaa** (71)
9	Ph/Ph/4-$NO_2C_6H_4$ (**1j**)	8	**4jaa** (78)
10	4-ClC_6H_4/Ph/Ph (**1k**)	10	**4kaa** (61)
11[a]	Ph/Ph/H (**1l**)	20	**4laa** (44)
12[a]	Ph/Ph/*n*-C_4H_9 (**1m**)	20	**4maa** (47)
13[a]	Me/*n*Bu/Ph (**1n**)	16	**4naa** (32)

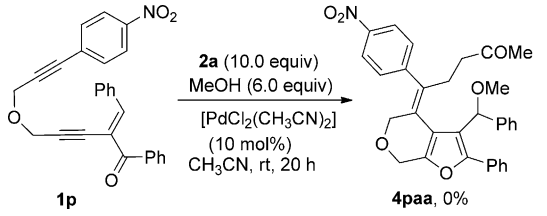
[a] 20 mol% $[PdCl_2(CH_3CN)_2]$ was used. [b] Yield of isolated product.

bring in other groups (Table 2, entry 6). It is noteworthy that the terminal alkyne is compatible in this transformation. For example, diyne-enone **1l** with a terminal alkyne still affords the desired **4laa** with a stereodefined trisubstituted alkene in a reasonable yield (Table 2, entry 11). Diyne-enone **1n** containing aliphatic R^1 and R^2 groups displays a relatively low reactivity and affords the corresponding products in only 32% yield, because the substrate is unstable (Table 2, entry 13). It is also noteworthy that various functional groups such as ester, ketone, nitro, and halogen are also compatible in this Pd^{II}-catalyzed multicomponent domino reaction, which provides an opportunity for further modification.

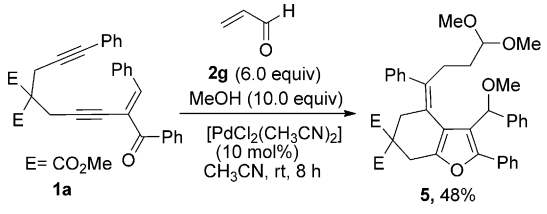
To our delight, 4-methylbenzenesulfonamide (TsN) can be used as the tether group to give the corresponding product **4oaa** in moderate yield [Eq. (1), DCE = 1,2-dicholoroethane]. Compound **1p** with oxygen tether decomposed under the reaction conditions and failed to give the corresponding product [Eq. (2)]. Furthermore, when acrolein **2g** is used instead of vinyl ketone, the reaction produces an acetal **5** in 48% yield along with a small amount of free aldehyde under the standard conditions owing to the HCl generated in the process [Eq. (3)]. The generality of this transformation was further investigated by employing compound **6** with a terminal alkene instead of the alkyne as substrate [Eq. (4)]. It is quite surprising to find that no reaction occurs even at higher temperature, thus indicating that the olefin shuts down the reaction.



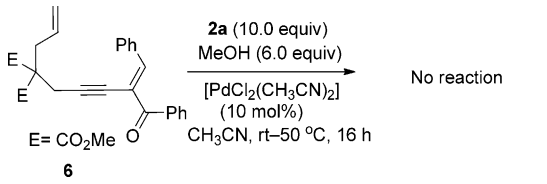
(1)



(2)

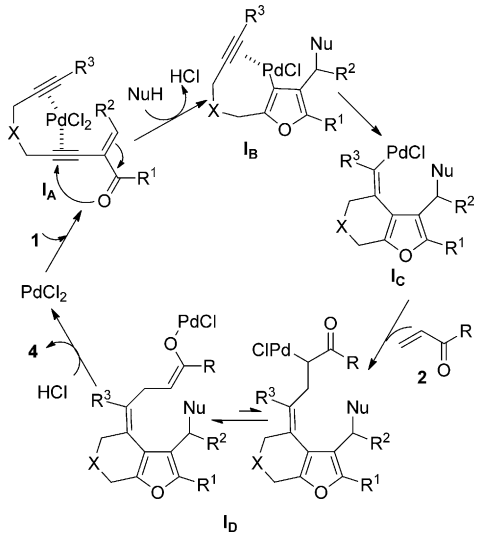


(3)



(4)

A plausible mechanism of this palladium(II)-catalyzed domino reaction is depicted in Scheme 1. According to our previous results,[13] we believe that in this process, $[PdCl_2(CH_3CN)_2]$ also plays a dual role, that is, as Lewis acid and transition metal. First, $[PdCl_2(CH_3CN)_2]$ as a π acid would coordinate to the two alkyne moieties of the diyne-enone **1** to form intermediate $\mathbf{I_A}$. This coordination would mediate a tandem heterocyclization and nucleophilic addition to give furanyl palladium intermediate $\mathbf{I_B}$ and release one molecule of HCl. The s*yn* addition of sp^2 C–Pd bond of $\mathbf{I_B}$ to the unconjugated alkyne would generate a bicyclic vinylpalladium species $\mathbf{I_C}$, with subsequent conjugate addition of the vinyl-



Scheme 1. Plausible mechanism that accounts for the stereochemistry.

palladium species to the vinyl ketone **2** to produce intermediate $\mathbf{I_D}$ with two interconvertible forms but with palladium enolate as the major form, which would prefer protonation by the HCl generated in situ to produce the final product **4** rather than the Heck type product via β-H elimination of $\mathbf{I_D}$. Lu and co-workers have established that the palladium enolate prefers protonation in the presence of excess halide.[16] The excess halide accelerates the protonation step, which may explain why higher catalyst loading (10 mol%) gives better results. Accordingly, the corresponding $\mathbf{I_D}$-type intermediate generated from methyl acrylate **2f** would prefer β-H elimination and generate Pd^0, which would shut down the reaction (Table 1, entry 10). The terminal olefin of compound **6** may bind to the Pd^{II} species strongly, and the Lewis acid Pd^{II} might not be strong enough to activate the alkyne bond.

In summary, we have developed a novel palladium(II)-catalyzed steroselective three-component domino reaction of readily available diyne-enones with nucleophiles and vinyl ketones under mild conditions, which provides a general, efficient, and atom-economical route to multifunctionalized 2,3-cyclo[*b*]furan with a stereodefined tri- or tetrasubstituted olefin. Further studies including the scope, mechanism, and design of new reactions based on the diyne-enones are ongoing.

Experimental Section

$[PdCl_2(CH_3CN)_2]$ (5.6 mg, 0.02 mmol) was added to a mixture of **1a** (98.0 mg, 0.2 mmol), MeOH (**3a**, 64.0 mg, 2.0 mmol), and vinyl methyl ketone (**2a**, 84.0 mg, 1.2 mmol) in CH_3CN (2.0 mL) at room temperature. After the mixture was stirred for 8 h, **1a** was completely consumed according to TLC analysis. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 5:1) to give the desired product **4aaa** (92.3 mg) in 78% yield as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.61 (d, 2H, J = 7.8 Hz), 7.39 (d, 2H, J = 6.6 Hz), 7.15–7.33 (m, 9H), 7.01 (d, 2H, J = 7.5 Hz), 5.46 (s, 1H), 3.65 (s, 3H), 3.59 (s, 3H), 3.55 (d, 1H, J = 17.7 Hz), 3.36 (s, 3H), 3.14 (d, 1H, J = 17.7 Hz), 2.98 (d, 1H, J = 12.9 Hz), 2.67–2.77 (m, 1H), 2.65 (d, 1H, J = 12.9 Hz), 2.48–2.59 (m, 1H), 2.04 (t, 2H, J = 7.8 Hz), 1.63 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C = 207.55, 171.19, 170.68, 152.35, 149.24, 140.75, 140.08, 139.08, 130.62, 128.80, 128.21, 128.12, 128.02, 127.49, 127.44, 127.20, 127.12, 127.00, 122.54, 122.47, 117.03, 77.43, 56.79, 54.97, 52.80, 52.72, 41.45, 36.94, 29.77, 29.53, 29.25 ppm; MS (70 eV): *m*/*z* (%): 592 (0.88) [M^+], 502 (100); HRMS calcd for $C_{37}H_{36}O_7$ $(M)^+$: 592.2461, found: 592.2465.

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Keywords: domino reactions · enynes · furans · palladium · stereoselectivity

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