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Highly Selective Cascade C−C Bond Formation via Palladium-Catalyzed Oxidative Carbonylation−Carbocyclization−Carbonylation−Alkynylation of Enallenes

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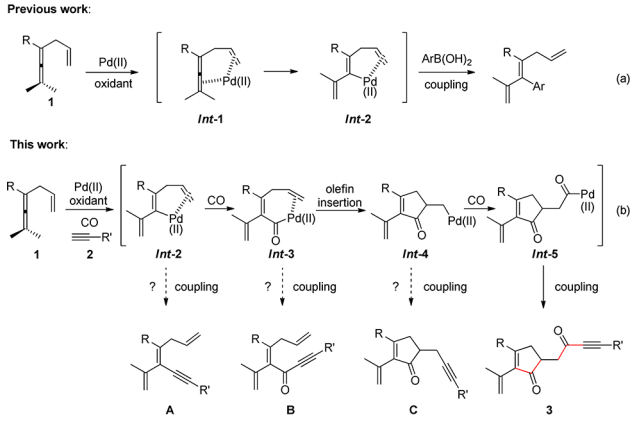
Supporting Information

ABSTRACT: A highly efficient palladium-catalyzed oxidative cascade reaction of enallenes undergoing overall four C−C bond formations has been developed. The insertion cascade proceeds via carbonylation−carbocyclization−carbonylation−alkynylation involving sequential insertion of carbon monoxide, olefin, and carbon monoxide. Furthermore, different types of terminal alkynes and functionalized enallenes have been investigated and found to undergo the cascade reaction under mild reaction conditions.

The construction of carbon−carbon (C−C) bonds is a basic yet crucial element in organic synthesis.[1] Therefore, much attention has been focused on the development of novel and efficient approaches toward C−C bond formation.[2] In recent years, transition-metal-catalyzed C−C bond formation has emerged as an effective strategy,[3] especially those catalyzed by palladium.[4] On the other hand, cascade reactions, in which a consecutive series of reactions occur involving multibond formation, have shown high efficiency to build complicated molecule skeletons with high stereocontrol in an atom-economical transformation.[5] Thus, a cascade strategy for the construction of C−C bonds would definitely be a significant efficiency improvement compared to stepwise approaches.[6] However, the challenge will be the identification of suitable catalytic systems, which should work nicely in each step during the reaction and the control of the involved selectivity.

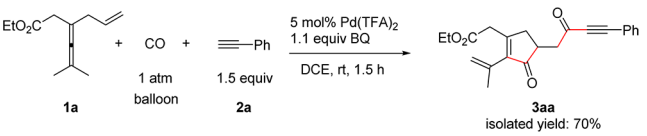
Very recently, we reported an olefin-directed palladium-catalyzed oxidative regio- and stereoselective arylation of allenes (Scheme 1a).[7] As the initial step, the coordination of the olefin unit to palladium is a crucial element for the subsequent allene attack on the metal to form the key intermediate ***Int*-2**. On the basis of these observations, we anticipated that, in the presence of carbon monoxide (CO), insertion of CO into the C−Pd bond of ***Int*-2** would lead to carbonyl palladium complex ***Int*-3** (Scheme 1b).[8,9] Subsequent carbocyclization of ***Int*-3** via olefin insertion would produce ***Int*-4**,[10] followed by carbonylative Sonogashira coupling reaction to produce ynone **3** via ***Int*-5** as the last step.[11] This envisioned insertion cascade would undergo carbonylation-carbocyclization-carbonylation-alkynylation involving four C−C bond formations. However, the control of the chemoselectivity during the reaction is challenging,[12] considering the probable coupling reaction of terminal alkyne **2** with palladium species ***Int*-2**, ***Int*-3**, or ***Int*-4**, which would lead to compounds **A**, **B**, and **C**, respectively, as side products.

Scheme 1. Previous Work and Proposal for This Work



Based on this concept, our initial attempt began with coupling reactions of allyl-substituted 3,4-dienoate **1a**[13] and alkyne **2a** using BQ (*p*-benzoquinone, 1.1 equiv) as the oxidant in the presence of $Pd(TFA)_2$ (TFA = trifluoroacetate) (5 mol %) under 1 atm of CO (balloon). When the reaction was run in DCE (dichloroethane) at room temperature for 1.5 h, inspiringly, the envisioned ynone **3aa** was obtained in 70% isolated yield (Scheme 2). To our delight, the insertion cascade showed

Scheme 2. Initial Attempt



exclusive chemoselectivity since ynone **3aa** was the only observed product, while **A**, **B**, or **C**-type side products in Scheme 1b were not detected.[14]

With these results in hand, we turned to optimizing the reaction conditions (Table 1). Catalyst screening showed that $Pd(OAc)_2$ produced the corresponding ynone **3aa** in a lower yield (48%) compared to $Pd(TFA)_2$, while $Pd(PPh_3)_2Cl_2$ and $Pd(MeCN)_2Cl_2$ failed to realize such a transformation (Table 1, entries 2−4). Solvent screening revealed that toluene was the best solvent, improving the yield further to 80% with $Pd(TFA)_2$

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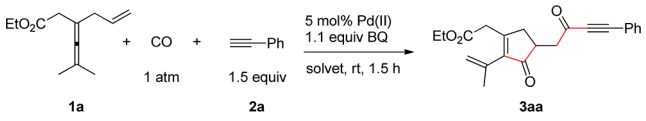
Table 1. Optimization of the Reaction Conditions[a]



entry	cat. (Pd)	solvent	yield of **3aa** (%)[b]	recovery of **1a** (%)[b]
1	$Pd(TFA)_2$	DCE	78	–
2	$Pd(OAc)_2$	DCE	48	–
3	$Pd(PPh_3)_2Cl_2$	DCE	–	90
4	$Pd(MeCN)_2Cl_2$	DCE	–	84
5	$Pd(TFA)_2$	acetone	64	–
6	$Pd(TFA)_2$	MeCN	69	–
7	$Pd(TFA)_2$	THF	65	–
8	$Pd(TFA)_2$	dioxane	79	–
9	$Pd(TFA)_2$	toluene	80	8
10[c]	$Pd(TFA)_2$	toluene	73	–
11[d]	$Pd(TFA)_2$	toluene	61	27
12[e]	$Pd(TFA)_2$	toluene	80	4
13[f]	$Pd(TFA)_2$	toluene	79	5
14[g]	**$Pd(TFA)_2$**	**toluene**	**84**	–

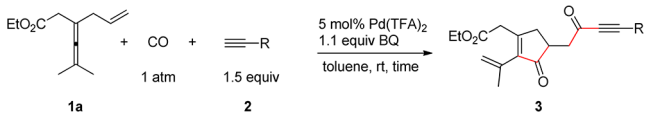
[a]The reaction was conducted in the indicated solvent (1 mL) at room temperature using **1a** (0.2 mmol), phenylacetylene (0.3 mmol), and BQ (1.1 equiv) in the presence of palladium catalyst (5 mol %). [b]Yield determined by ^{1}H NMR analysis using anisole as the internal standard. [c]The reaction was run at 40 °C. [d]The reaction was run at 0 °C for 2.5 h. [e]1.2 equiv of BQ was used. [f]1.0 equiv of BQ was used. [g]Reaction was run for 3 h.

as catalyst, with enallene **1a** recovered in 8% (Table 1, entries 5–9). Moreover, room temperature was found to be the best temperature for this reaction (Table 1, entries 10 and 11), while the amount of BQ was kept at 1.1 equiv (Table 1, entries 12 and 13). Finally, the yield of the desired product **3aa** was increased to 84% by extending the reaction time to 3 h (Table 1, entry 14).

Under the optimized reaction conditions, the scope of terminal alkynes **2** was investigated with enallene **1a** (Table 2). First, a range of substituted phenylacetylenes were examined: the analogues substituted with *o*-MeO, *m*-MeO, *p*-Me, *p*-F, and *p*-CF_3 groups all reacted smoothly and afforded the corresponding products **3ab–af** in good yields (Table 2, entries 2–6). Moreover, the cascade reaction worked equally well using heteroaryl acetylenes (Table 2, entries 7 and 8). It is noteworthy that both aliphatic acyclic and cyclic terminal alkynes could be introduced as substrates for this insertion cascade (Table 2, entries 9–12). Finally, functional groups, such as chloro and TMS (trimethylsilyl) turned out to be compatible under the standard reaction conditions, thus leading to the corresponding products **3am** and **3an** in 72 and 73% yield, respectively (Table 2, entries 13 and 14).

We next studied the reactivity of substrates with different substituents on the enallene moiety (Scheme 3). Under the optimal conditions, cyclopentylidene enallene afforded **3b** in a relatively lower yield, while cyclohexylidene enallene gave the corresponding product **3c** in good yield. In order to exhibit the broad scope of enallenes in this cascade reaction, we chose different types of allene-containing structures: 2,3-dienoate **1d**[15] could also be employed, thus producing ynone **3d** in 63% yield. To our delight, benzyl and tosyl 3,4-dienol worked equally well as shown by the formation of **3e** and **3f** in 75 and 76% yield, respectively. It is worth noting that a phenyl or ethyl substituent on the olefin moiety (R^2 = Ph or Et) has a great influence on the reaction: enallenes **1g** and **1h**[16] only produced ynones **3g** and **3h** in 41 and 40% yield, respectively. Finally, the reaction of a dissymmetric allene **1i**, bearing Me and *i*-Pr, produced **3i** and **3i′** in 30 and 40% yield, respectively. The formation of **3i** and **3i′** was due to the selective allenic C–H cleavage (***Int*-1** → ***Int*-2** in Scheme 4).

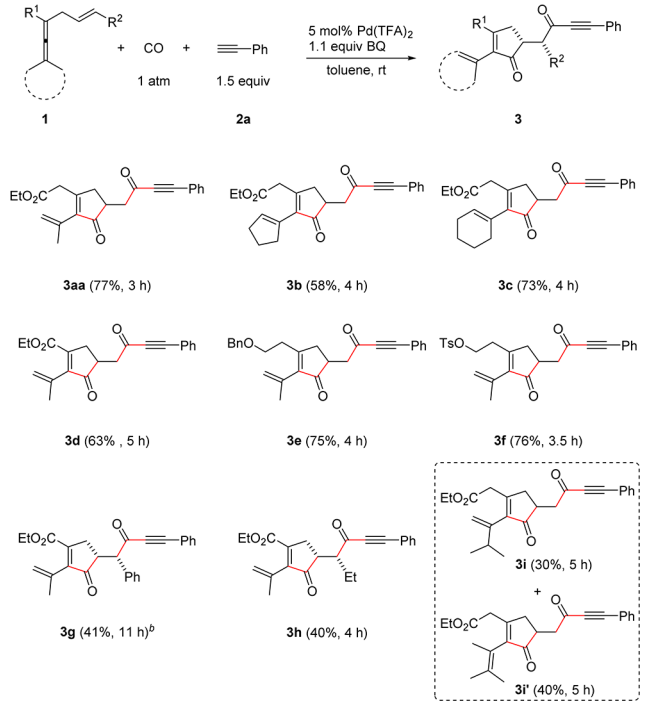
Table 2. Scope of Terminal Alkynes[a]



entry	R	time (h)	yield of **3** (%)[b]
1	Ph	3	77 (**3aa**)
2	2-$MeOC_6H_4$	3	80 (**3ab**)
3	3-$MeOC_6H_4$	3	71 (**3ac**)
4	4-MeC_6H_4	3	72 (**3ad**)
5	4-FC_6H_4	3	81 (**3ae**)
6	4-$CF_3C_6H_4$	3	70 (**3af**)
7	2-thiophenyl	3	66 (**3ag**)
8	3-thiophenyl	3	75 (**3ah**)
9	*n*-hexyl	4	75 (**3ai**)
10	cyclopentyl	5	74 (**3aj**)
11	cinnamyl	3	83 (**3ak**)
12	2-phenylethyl	3	82 (**3al**)
13	3-chloropropyl	4	72 (**3am**)
14[c]	TMS	8	73 (**3an**)

[a]The reaction was conducted in toluene (1 mL) at room temperature using **1a** (0.2 mmol), **2** (0.3 mmol), and BQ (1.1 equiv) in the presence of $Pd(TFA)_2$ (5 mol %). [b]Isolated yield after column chromatography. [c]TMS-acetylene (3.0 equiv) was used. TMS = trimethylsilyl.

Scheme 3. Scope of Enallenes 1 for the Pd-catalyzed cascade Reaction[a]



[a]The reaction was conducted in toluene (1 mL) at room temperature using **1** (0.2 mmol), **2a** (0.3 mmol), and BQ (1.1 equiv) in the presence of $Pd(TFA)_2$ (5 mol %). [b]The reaction was run at 0 °C.

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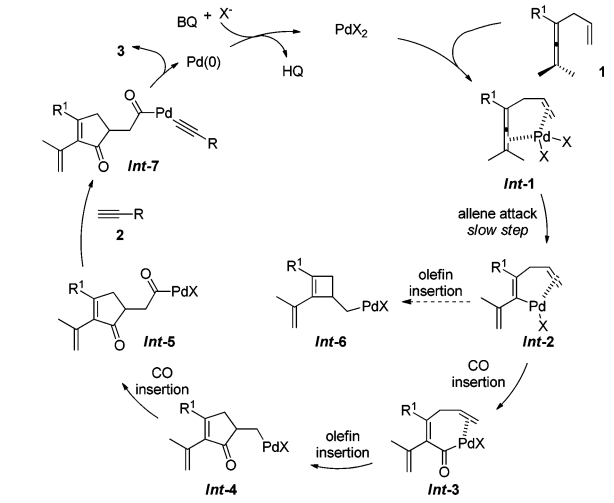
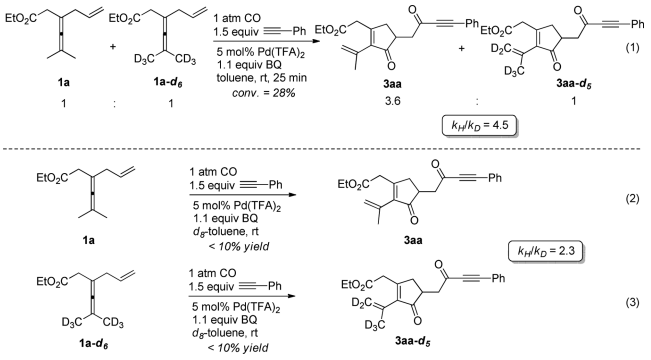
Scheme 4. Proposed mechanism



To gain a deeper insight into the insertion cascade, the deuterium kinetic isotope effects (KIE) were studied. An intermolecular competition experiment was conducted using a 1:1 mixture of **1a** and **1a-d_6** at room temperature for 25 min eq 1.



The product ratio **3aa**/**3aa-d_5** (ca. 28% conv.) measured was 3.6:1, while the ratio of the recovered **1a** and **1a-d_6** was observed as 1:1.6. From these ratios, the competitive KIE was determined to k_H/k_D = 4.5.[17] Furthermore, parallel kinetic experiments provided a KIE (k_H/k_D from initial rate) value of 2.3 ± 0.1 eqs 2 and 3.[17] The observed KIE in both competition and parallel experiments indicate that the initial allenylic C−H bond cleavage occurred during the rate-limiting step. However, the difference in KIE values in these two experiments suggested that this step is not totally, but only partially, rate-limiting. Moreover, the large competitive isotope effect in the C−H bond cleavage (k_H/k_D = 4.5) requires that this step is the first irreversible step.[7,18]

Based on the observations of KIE, a possible mechanism for this cascade reaction is proposed in Scheme 4. As the initial step, simultaneous coordination of the allene and olefin unit to the Pd(II) center would promote allene attack to afford vinylpalladium intermediate ***Int*-2** involving allenylic C−H bond cleavage. The additional coordination of olefin to Pd(II) is essential for the allene attack,[19] which has been definitely proven in the previous work.[7] The following step would proceed via a selective insertion of CO to C−Pd bond of ***Int*-2** to afford ***Int*-3** instead of an olefin insertion, which in principle could take place to form a highly strained cyclobutene complex ***Int*-6**.[20] Further cascade olefin and CO insertion reactions would produce ***Int*-5** via ***Int*-4** involving carbocyclization. Finally, reaction of terminal alkyne **2** with Pd in ***Int*-5** would produce ***Int*-7**, which on subsequent reductive elimination would lead to ynone **3**. The released Pd(0) is reoxidized to Pd(II) by *p*-benzoquinone, which closes the cycle.

In conclusion, we have developed a one-pot palladium-catalyzed oxidative cascade reaction of enallenes via carbonylation−carbocyclization−carbonylation−alkynylation. This insertion cascade is highly efficient and exclusively chemoselective, which proceeds via sequential CO-olefin-CO insertion involving overall four C−C bond formations. Mechanistic studies have shown that the allenylic C−H bond cleavage is the partially rate-limiting step. Furthermore, an exclusive chemoselectivity was observed in this transformation as ynone **3** was the only product obtained, while the possible side products via coupling reaction of terminal alkyne **2** with palladium intermediates were not detected (see Scheme 1b). Finally, because of the highly efficient construction of complicated skeletons, this chemistry will be useful in synthetic and materials chemistry. Further studies on the mechanism, synthetic application, and asymmetric variants of this cascade reaction are currently under way in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06828.

Experimental procedures and compound characterization data, including the $^1H/^{13}C$ NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(16) When the reaction was run using a mixture of stereoisomers (*Z*)- and (*E*)-**1h** (*Z*/*E* = 4.5/1), two diastereoisomers were obtained in 26 and 8% yield, respectively. For details, see the SI.
(17) For details, see the SI.
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