Tandem Cyclization

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Palladium-Catalyzed Three-Component Cascade Cyclization Reaction of Bisallenes with Propargylic Carbonates and Organoboronic Acids: Efficient Construction of *cis*-Fused Bicyclo[4.3.0]nonenes**

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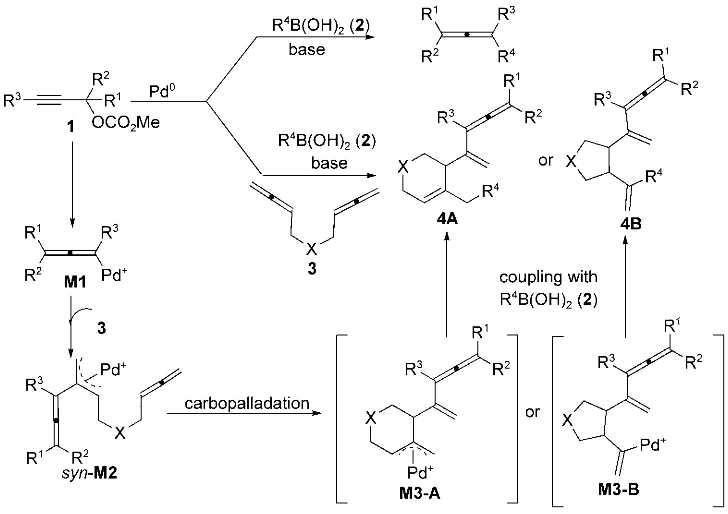
The palladium-catalyzed coupling reaction involving propargylic/allenic metallic reagents provides one of the most straightforward pathways for the formation of allenes.[1–3] In this area, we have noticed that the palladium-catalyzed coupling reaction of propargylic carbonates with boronic acids or organozinc reagents affords alkynes or allenes depending on the steric hindrance of the starting materials.[4] Moreover, multicomponent cascade reactions (MCRs) are among the most efficient synthetic methods for the construction of complex organic molecules.[5] Such processes avoid the time-consuming and costly protection–deprotection steps as well as purification processes and thus are inherently environmentally benign and atom economical.[6] We envisioned that a three-component reaction[7] of 2-alkynylic carbonates, bisallenes, and organoboronic aicds would provide an efficient route for the synthesis of vinyl-substituted allenes **4A** or **4B** via the intermediate allylic palladium species **M3-A**[8] or the vinylic palladium species **M3-B**[9] formed from the two consecutive carbopalladations (Scheme 1). Herein, we report our observation that this three-component reaction afforded *cis*-fused bicyclo[4.3.0]nonenes highly regio- and stereoselectively with high efficiency, in which only the vinylic **M3-B** intermediate was involved in forming the first five-membered ring, and the newly formed allene moiety was further carbopalladated subsequently to form the second six-membered ring.



Scheme 1. Possible pathways for the palladium(0)-catalyzed reaction of bisallenes with propargylic carbonates and boronic acids.

Our initial efforts were based on the reaction of propargylic carbonate **1a**, phenyl boronic acid **2a**, and bisallene **3a**. When the reaction was carried out in dichloroethane (DCE) at 80 °C catalyzed by 5 mol % $Pd(OAc)_2$ and 10 mol % tri(2′-furyl)phosphine (TFP) in the presence of two equivalents Na_2CO_3, the bicyclic conjugate triene *cis*-**5a** was obtained in 58 % yield (entry 1, Table 1). The structure and relative configuration of this product was confirmed unambiguously by X-ray diffraction (Figure 1).[10] The product could not be obtained in the absence of K_2CO_3 (entry 2, Table 1). The reaction proceeded better at 90 °C, affording *cis*-**5a** in 64 % yield (entry 3, Table 1). The catalyst is also important for this reaction: it was noted that $[Pd(dba)_2]$/TFP (dba = *trans,trans*-dibenzylidenacetone) is better than the $Pd(OAc)_2$/TFP combination (compare entries 3 and 4, Table 1). In addition, the reaction did not proceed when 1,2-bis(diphenylphosphanyl)ethane (dppe) was used as the ligand (entry 5, Table 1). After screening the effect of solvent (entries 6–10, Table 1), we defined **3a**, 1.2 equivalents **1a**, and 2.0 equivalents **2a** catalyzed by 5 mol % $[Pd(dba)_2]$ and 10 mol % TFP in the presence of 2.0 equivalents Na_2CO_3 in DCE at 90 °C as the standard conditions. Under the standard reaction conditions, only the *cis* diastereoisomer was detected, and the formation of **4**-type allenes **4A** and **4B** or bicyclic products **5a′** and **5a″** did not occur, as judged by ^1H NMR spectroscopic analysis of the crude reaction mixture.

With the optimized conditions in hand, we turned to examine the substrate scope of the reaction. The reaction is

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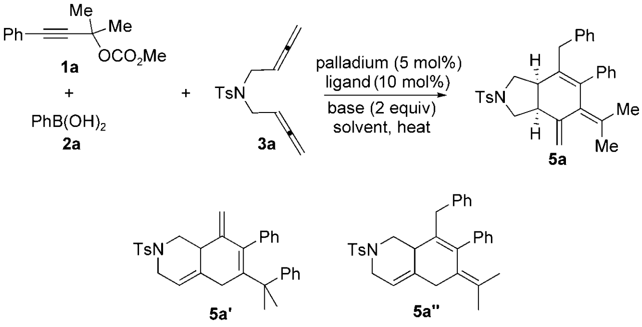
Table 1: Optimization of the reaction conditions for the Pd-catalyzed three-component cyclization of **3a** with **1a** and **2a**.[a]



Entry	Catalyst	Base	Solvent	T [°C]	Yield [%][b]
1	$Pd(OAc)_2$/TFP	Na_2CO_3	DCE	80	58
2	$Pd(OAc)_2$/TFP	–	DCE	80	trace[c]
3	$Pd(OAc)_2$/TFP	Na_2CO_3	DCE	90	64
4	$[Pd(dba)_2]$/TFP	Na_2CO_3	DCE	90	70
5	$[Pd(dba)_2]$/dppe	Na_2CO_3	DCE	90	n.r.[d]
6	$[Pd(dba)_2]$/TFP	Na_2CO_3	DMSO	90	trace[c]
7	$[Pd(dba)_2]$/TFP	Na_2CO_3	CB	90	49
8	$[Pd(dba)_2]$/TFP	Na_2CO_3	dioxane	90	19
9	$[Pd(dba)_2]$/TFP	Na_2CO_3	toluene	90	24
10	$[Pd(dba)_2]$/TFP	Na_2CO_3	CH_3NO_2	90	trace[c]

[a] The reaction was carried out with 0.2 mmol **3a**, 0.24 mmol **1a**, and 0.4 mmol **2a** at the indicated temperature. CB = chlorobenzene, DCE = dichloroethane, DMSO = dimethyl sulfoxide, dppe = 1,2-bis(diphenylphosphanyl)ethane, TFP = tri(2'-furyl)phosphine, Ts = toluene-4-sulfonyl. [b] Yield of isolated **5a**. [c] The starting material **3a** was completely consumed. [d] n.r. = no reaction.

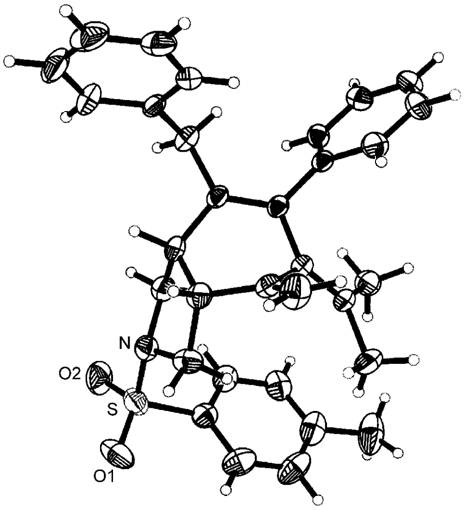
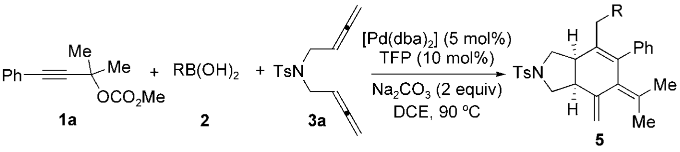


Figure 1. ORTEP plot of *cis*-**5a** shown with ellipsoids at the 30% probability level.

very general for bisallenes **3**, propargylic carbonates **1**, and boronic acids **2**, affording *cis*-fused bicyclo[4.3.0]nonenes **5** in good yields (Tables 2 and 3). Phenyl boronic acids and phenyl boronic acids with electron-withdrawing and electron-donating substituents are all good substrates (entries 1–7, Table 2); polysubstituted phenylboronic acids are also suitable for this MCR process (entries 8 and 9, Table 2). However, the reaction with terminal methyl 2-methylbut-3-yn-2-yl carbonate does not work, which may be because the presence of Na_2CO_3 is problematic for the acidic terminal alkynic proton.

Table 2: The coupling–cyclization of **3a** and **1a** with various boronic acids **2**.[a]

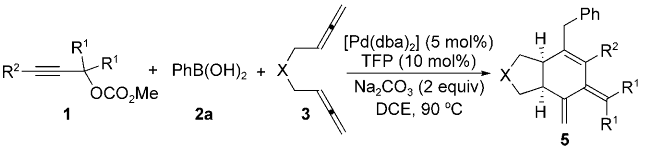


Entry	R	t [h]	Yield of **5** [%][b]
1	C_6H_5	3	70 (**5a**)
2	4-ClC_6H_4	5	63 (**5b**)
3	4-MeC_6H_4	3	70 (**5c**)
4	4-$MeCOC_6H_4$	5	64 (**5d**)
5	3-$MeOC_6H_4$	6	66 (**5e**)
6	4-$C_6H_5C_6H_4$	3	65 (**5f**)
7	2-$MeOC_6H_4$	4	65 (**5o**)
8	benzo[*d*][1,3]dioxol-5-yl	3	65 (**5g**)
9	3,5-$Me_2C_6H_3$	3	77 (**5h**)

[a] The reaction was carried out with 0.2 mmol **3a**, 0.24 mmol **1a**, 0.4 mmol **2**. [b] Yield of isolated product.

Internal propargylic carbonates with various substituents in the α and γ positions worked equally well under the standard conditions (entries 1, 4, and 5, Table 3). Moreover, with differently tethered bisallenes as the substrates, bicyclic compounds with a five-membered carbo- or azacyclic ring with conjugate trienes were obtained in good yields (Table 3).

Table 3: The coupling–cyclization reaction of various propargylic carbonates **1**, phenyl boronic acid **2a**, and bisallenes **3**.[a]

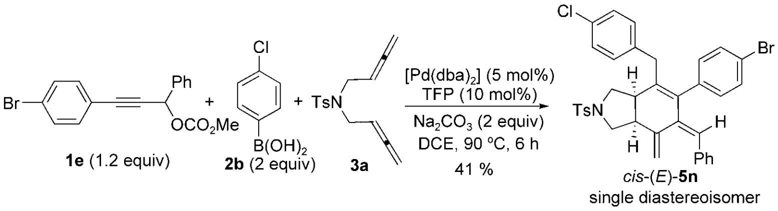


Entry	**1**		**3**	t [h]	Yield of **5** [%][b]
	R^1	R^2	X		
1	Me	*n*Bu	NTs	3	73 (**5i**)
2	Me	*n*Bu	$C(E^1)_2$[c]	4	67 (**5j**)
3	Me	*n*Bu	$C(E^2)_2$[c]	4	61 (**5k**)
4	Me	4-BrC_6H_4	NTs	5	68 (**5l**)
5	$-(CH_2)_4-$	Ph	NTs	3	67 (**5m**)

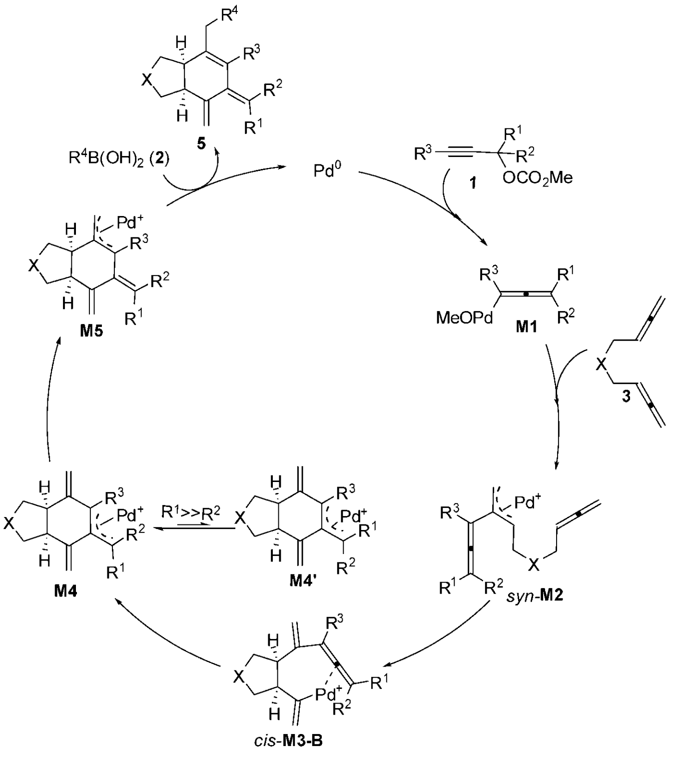
[a] The reaction was carried out with 0.2 mmol **3**, 0.24 mmol **1**, and 0.4 mmol **2a**. [b] Yield of isolated product. [c] $E^1 = CO_2Bn$, $E^2 = SO_2Ph$.

The most notable feature is that when secondary propargylic carbonate **1e** was used as the substrate, only the *cis*-*E* diastereoisomer referring to the substituted *exo* C=C bond, that is, *cis*-(*E*)-**5n**, was formed (Scheme 2), which was confirmed by ^1H NMR spectroscopy of the crude reaction mixture and a NOE study of this product.

A rationale that accounts for the observed results is shown in Scheme 3. First, the oxidative addition of palladium(0) with the propargylic carbonate **1** would generate the 1,2-allenyl



Scheme 2. The reaction of **3a** with **2b** and **1e**.



Scheme 3. A plausible mechanism for the formation of **5**.

palladium species **M1**. Subsequent carbopalladation of 1,5-bisallene **3** with **M1** would form the delocalized π-allylic species *syn*-**M2**,[8] which intramolecularly undergoes carbometallation to afford the vinyl palladium species *cis*-**M3-B** highly stereoselectively.[9] The *cis* stereoselectivity may be explained by the coordination of the palladium center with the allene moiety in *cis*-**M3-B**. Intramolecular carbopalladation of *cis*-**M3-B** involving the in situ formed allene moiety yields again π-allylic species **M4** or **M4′**. The stereoselectivity observed for the formation of *cis*-(*E*)-**5n** may be explained by the fact that π-allylic intermediate **M4′** would easily isomerize to the more stable **M4** to avoid the steric repulsion between the Pd center and the R^1 group (R$^1 \gg$ R^2) by a π–σ–π process.[11] **M4** would further isomerize to **M5** because of the presence of the "upper" *exo* C=C bond. The final product **5** is subsequently formed by the Suzuki-type coupling of **M5** with the organoboronic acid **2**. It should be noted that the direct coupling product of propargylic carbonate and arylboronic acid is not serious (less than 5%), which may be explained by the rapid reaction between the bisallene and 1,2-allenylpalladium.

In conclusion, we have developed an efficient palladium(0)-catalyzed three-component coupling cyclization reaction of 1,5-bisallene with propargylic carbonate in the presence of organoboronic acid. This reaction may involve three carbopalladation reactions to form sequentially a π-allylic palladium, a vinylic palladium, and a π-allylic palladium intermediate. The interesting *cis*-bicyclo[4.3.0]nonene skeleton in the final product exists in some bioactive molecules, such as the analogue of asparvenone.[12] Further studies in this area are continuing in our laboratory.

Experimental Section

Typical procedure for the preparation of *cis*-**5a**: To a Schlenk tube containing Na_2CO_3 (42 mg, 0.40 mmol), $[Pd(dba)_2]$ (6 mg, 0.01 mmol, 5 mol%), and tri(2′-furyl)phosphine (5 mg, 0.02 mmol, 10 mol%) were added sequentially **3a** (56 mg, 0.20 mmol), **2a** (49 mg, 0.4 mmol), **1a** (52 mg, 0.24 mmol), and dichloroethane (2 mL). Then, the resulting mixture was stirred at 90°C. When the reaction was complete, as monitored by TLC, the solvent was evaporated under reduced pressure. Flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) afforded *cis*-**5a** (71 mg, 70%) as a colorless solid: m.p. 126–127°C (ethyl acetate/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.63$ (d, $J = 7.8$ Hz, 2H), 7.32–7.14 (m, 10H), 7.00 (d, $J = 7.8$ Hz, 2H), 4.91 (s, 1H), 4.76 (s, 1H), 3.69–3.61 (m, 2H), 3.50 (t, $J = 8.7$ Hz, 1H), 3.29 (d, $J = 15.0$ Hz, 1H), 3.06–2.97 (m, 1H), 2.77–2.63 (m, 2H), 2.52 (t, $J = 9.6$ Hz, 1H), 2.41 (s, 3H), 1.52 (s, 3H), 1.02 ppm (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 148.8$, 143.4, 141.4, 140.1, 139.5, 134.9, 133.2, 132.0, 131.1, 129.3, 128.9, 128.6, 128.4, 128.0, 127.9, 126.4, 126.2, 110.0, 54.6, 52.8, 45.0, 42.9, 38.6, 22.0, 21.44, 21.42 ppm; MS(EI): *m*/*z* (%) 495 (M^+, 3.24), 91 (100); IR (neat): $\tilde{\nu} = 1640$, 1598, 1492, 1473, 1452, 1348, 1304, 1163, 1094, 1029 cm^{-1}; elemental analysis calcd (%) for $C_{32}H_{33}NO_2S$: C 77.54, H 6.71, N 2.83; found: C 77.34, H 6.80, N 2.99.

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Keywords: allenes · cyclization · multicomponent reactions · palladium · tandem reactions

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