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Palladium(II)-Catalyzed Highly Stereoselective Sandwich-Type Triple Cyclization Reaction of 1,5-Bisallenes and 2,3-Allenoic Acids

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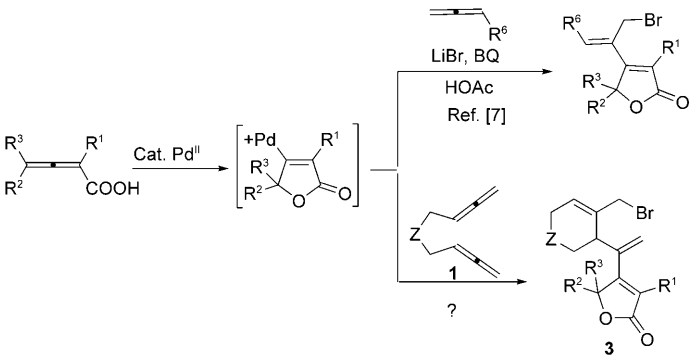
Transition-metal-catalyzed cyclization of functionalized allenes has become one of the most efficient and powerful tools for the synthesis of carbo- and heterocyclic systems.[1,2] In this area, the metal-catalyzed homodimerization reaction of 1,2-allenyl ketones was first reported by Hashmi et al., which led to the formation of furan derivatives.[3] In 2006, Alcaide and co-workers also reported the cross-coupling cyclization reaction of allenols in the presence of 2,3-allenyl carboxylates.[4] Since 2002,[5] we have demonstrated the cyclization of 2,3-allenoic acids in the presence of 1,2-allenyl ketones[5] or 2,3-allenols,[6] affording differently substituted 2(5*H*)-furanones. We also studied the cyclization reaction of 2,3-allenoic acids in the presence of simple monoallenes, which yielded the stereodefined 4-(bromo-2(*E*)-alken-2-yl)-2(5*H*)furanones (Scheme 1).[7] Based on this, we reasoned that the cyclization of 2,3-allenoic acids in the presence of 1,5-bisallenes may involve further cyclization to form **3**-type of products based on the regioselectivity of carbopalladation of allenes.[8] Herein, we wish to disclose our recent unexpected observation of Pd^{II}-catalyzed sandwich-type triple cyclization of 2,3-allenoic acids in the presence of 1,5-bisallenes affording **4**-type tricyclic products (Scheme 2). By applying the optically active 2,3-allenoic acids, an efficient chirality transfer has also been achieved.

At first, we conducted the reaction of 2,4-dimethyl-2,3-pentadienoic acid (**2a**) in the presence of bis(2,3-butadienyl) tosylamide (**1a**) under the conditions described in Ref. [7].



Scheme 1. Palladium-catalyzed cyclizations of 2,3-allenoic acids in the presence of monoallenes or 1,5-bisallenes (BQ = benzoquinone).

The expected product **3a** was not formed, instead, unknown products were formed as an inseparable mixture. Interestingly, when the reaction was conducted in the absence of LiBr by using $[PdCl_2(PhCN)_2]$ as the catalyst in DMSO at 60 °C for 2 h, two tricyclic products *cis*-**4a** (32 %) and **5a** (10 %) were afforded, which were confirmed by spectroscopic analysis: two molecules of allenoic acids formed the two butenolide moieties connected to a central five- or nine-membered ring formed from the cyclization of the bisallene **1a** (Scheme 2).

Optimization of reaction conditions with the purpose of improving the selectivity of *cis*-**4a**/**5a** was then conducted with some of the representative results being listed in Table 1. First, the solvent effect was examined and the reaction in MeCN afforded *cis*-**4a** and **5a** in 45 % (41 % isolated) and 15 % (10 % isolated) yield, respectively (Table 1, entry 5). Fortunately, *cis*-**4a** was afforded exclusively and the yield was improved significantly when the reaction was carried out in MeCN by adding 1,4-bis(diphenylphosphino)-butane (dppb; 5 mol %) as the ligand (Table 1, entry 9). Then some bidentate phosphine ligands were screened and 1,2-bis(diphenylphosphino)ethane (dppe) was found to be the best, affording *cis*-**4a** in 79 % ^{1}H NMR yield (Table 1, entry 10).

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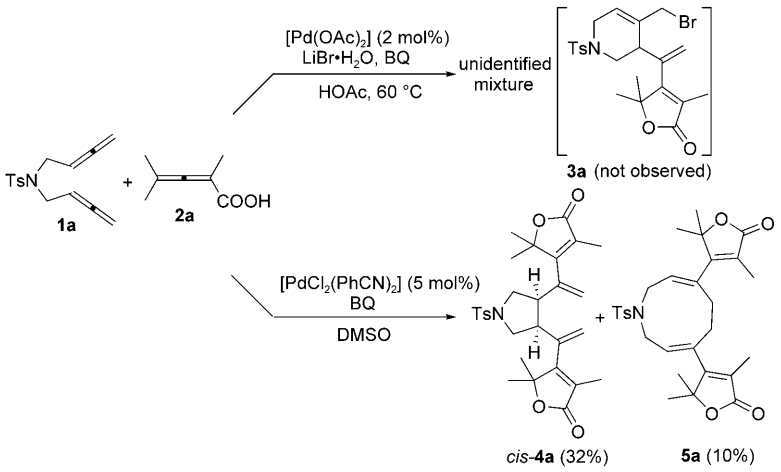
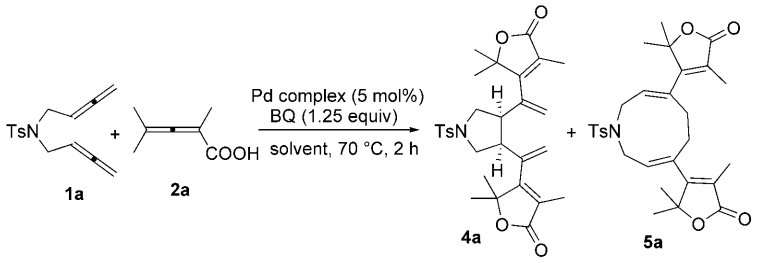


Scheme 2. Pd-catalyzed cyclization reaction of 1,5-bisallene **1a** and 2,3-allenoic acid **2a**.

Table 1. Pd-catalyzed cyclization reaction of 2,3-allenoic acid **2a** in the presence of 1,5-bisallene **1a**: Optimization of reaction conditions.[a]



Entry	Palladium complex/solvent	Yield of *cis*-**4a** [%][b]	Yield of **5a** [%][b]
1	$[PdCl_2(PhCN)_2]$/DMSO	32	10
2	$[PdCl_2(PhCN)_2]$/DMF	35	10
3	$[PdCl_2(PhCN)_2]$/DCE	6	n.d.
4	$[PdCl_2(PhCN)_2]$/toluene	8	n.d.
5	$[PdCl_2(PhCN)_2]$/MeCN	45	15
6	$[PdCl_2(PhCN)_2]$/THF	24	7
7	$[PdCl_2(PhCN)_2]$/MeCN	25	n.d.
8	$[PdCl_2(Sphos)_2]$/MeCN	44	n.d.
9	$[PdCl_2(PhCN)_2]$, dppb/MeCN	69	n.d.
10	$[PdCl_2(PhCN)_2]$, dppe/MeCN	79	n.d.
11	$[PdCl_2(PhCN)_2]$, binap/MeCN	41	21

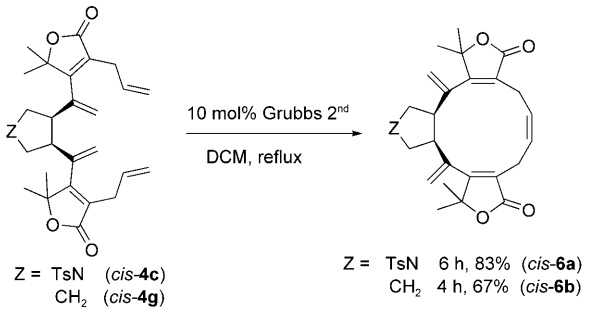
[a] The reaction was carried out under argon in a Schlenk tube by using **1a** (0.2 mmol), **2a** (0.6 mmol), BQ (0.25 mmol), and the palladium complex (5 mol%) in a solvent (3 mL) at 70 °C. [b] Determined by ^{1}H NMR analysis with 1,3,5-trimethyl benzene as the internal standard (n.d. = not determined).

The optimized reaction conditions were then applied to a range of different 1,5-bisallenes and 2,3-allenoic acids (Table 2). For the 2,3-allenoic acids, the fully alkyl-, 2-allyl-, disubstituted, and monosubstituted acids may all react with differently tethered 1,5-bisallenes (Z = CH_2, NTs, O) to afford the tricyclic products *cis*-**4** in moderate to good yields with excellent stereoselectivity. In all these cases, only the *cis* product was formed. The structure of the product *cis*-**4c** was further determined by its X-ray diffraction study (Figure 1a).[9]

Note that the diallyl-substituted *cis* products **4c** and **4g** may be easily converted to fused tetracyclic products **6a** and **6b** with a twelve-membered ring that has three Z–C=C bonds[10] through a ring-closing metathesis (RCM) reaction[11] (Scheme 3). The structure of the product was further determined by the X-ray diffraction study of *cis*-**6a** (Figure 1b).[12]

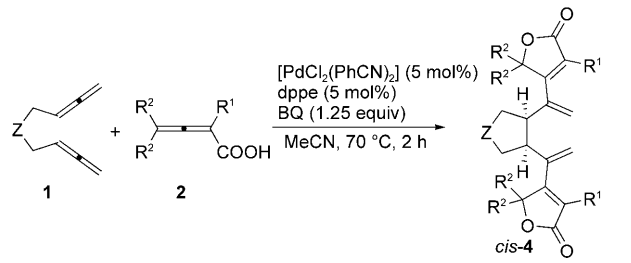
However, the reaction of racemic allenoic acid **2e** with axial chirality gave diastereomeric mixtures.[13] Interestingly, when the corresponding optically active (*R*)-2,3-allenoic acid **2e**[14] was treated with **1a** under the standard reaction conditions, the optically active product (*R*,*S*,*R*,*R*)-**4i** was isolated (Scheme 4a). To determine the absolute configurations in the product, bisallene **1d** with a bromine atom was prepared. (*S*)-2,3-Allenoic acids **2f** and **2g** were able to couple with **1d** under the similar conditions yielding the products (*S*,*R*,*S*,*S*)-**4j** and (*S*,*R*,*S*,*S*)-**4k**, respectively, in acceptable yields (Scheme 4b). The absolute configurations of the products were then unambiguously assigned by the X-ray diffraction study of (*S*,*R*,*S*,*S*)-**4k**, indicating the excellent chirality transfer from the axial chirality of the optically active allenoic acid to the product (Figure 1c).[15]

With the explicit absolute stereochemical information for the starting materials and the products, a possible mechanism for this transformation is shown in Scheme 5 by using the Pd-catalyzed triple cyclization of (*S*)-**2g** with 1,5-bisallene **1d** af-



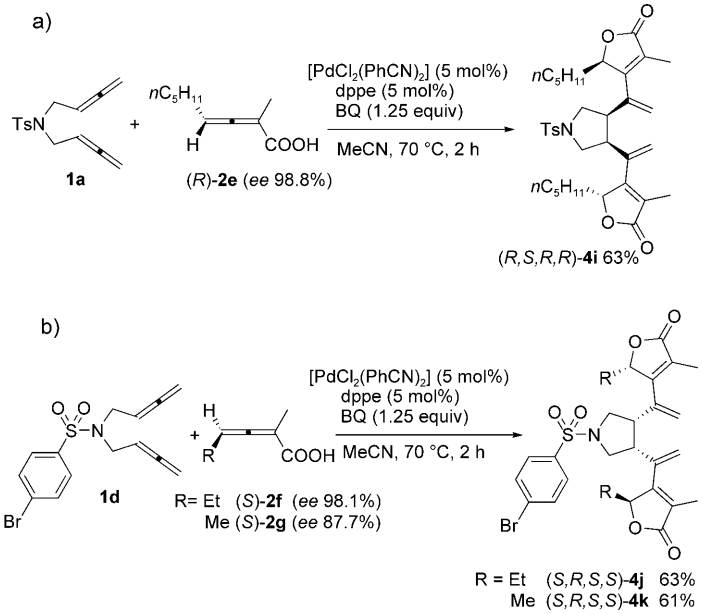
Scheme 3. The RCM reaction to construct the fused twelve-membered rings (Grubbs 2nd = Grubbs second-generation Ru catalyst).

Table 2. Pd^{II}-catalyzed cyclization reaction of bimolecular 2,3-allenoic acids **2** in the presence of 1,5-bisallene **1**: The substrate scope.[a]



Entry	R^1	R^2	Z	Yield of *cis*-**4** [%][b]
1	Me	Me (**2a**)	TsN (**1a**)	73 (*cis*-**4a**)
2	H	Me (**2b**)	TsN (**1a**)	81 (*cis*-**4b**)
3	allyl	Me (**2c**)	TsN (**1a**)	59 (*cis*-**4c**)
4	H	$-(CH_2)_5-$ (**2d**)	TsN (**1a**)	59 (*cis*-**4d**)
5	Me	Me (**2a**)	CH_2 (**1b**)	68 (*cis*-**4e**)
6	H	Me (**2b**)	CH_2 (**1b**)	79 (*cis*-**4f**)
7	allyl	Me (**2c**)	CH_2 (**1b**)	52 (*cis*-**4g**)
8	H	Me (**2a**)	O (**1c**)	54 (*cis*-**4h**)

[a] The reaction was conducted under an Ar atmosphere with **1** (0.2 mmol), **2** (0.6 mmol), $[PdCl_2(PhCN)_2]$ (5 mol%), dppe (5 mol%), and BQ (0.25 mmol) in MeCN (3 mL) at 70°C. [b] Isolated yield.



Scheme 4. Pd^{II}-catalyzed cyclization reaction of optically active 2,3-allenoic acids **2e**–**g** in the presence of 1,5-bisallenes a) **1a** and b) **1d**.

fording (*S*,*R*,*S*,*S*)-**4k** as the typical example. Firstly, the highly stereoselective cyclic *anti*-oxypalladation[2g] of (*S*)-**2g** would form intermediate **M1** with a center of chirality. Subsequent carbopalladation of one allene moiety in bisallene **1d** with **M1** would form the π-allylic intermediate **M2-a** or **M2-b**.[8] Owing to the steric interaction between the pseudoaxial proton and the 2(5*H*)-furanonyl vinyl group in **M2-b**, the reaction proceeds via the intermediate **M2-a** to generate *cis*-**M3**.[8,16] A second molecule of 2,3-allenoic acid (*S*)-**2g** would undergo sequential coordination and *anti*-oxypalladation[2g] with the vinyl palladium *cis*-**M3** to generate *cis*-**M4**, which upon reductive elimination would release the final tricyclic product (*S*,*R*,*S*,*S*)-**4k** and Pd^0. The Pd^{II} catalyst would finally be regenerated by the reaction of Pd^0 with BQ and H^+.[17]

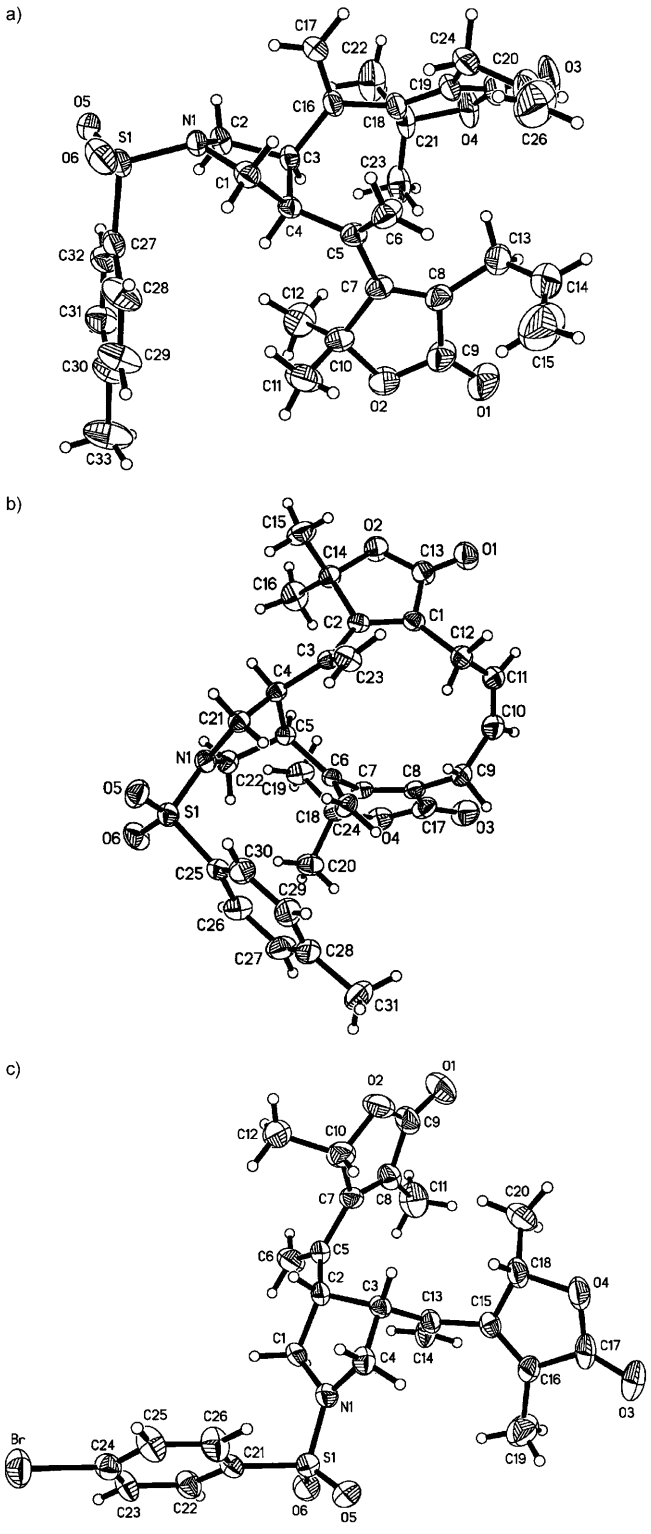
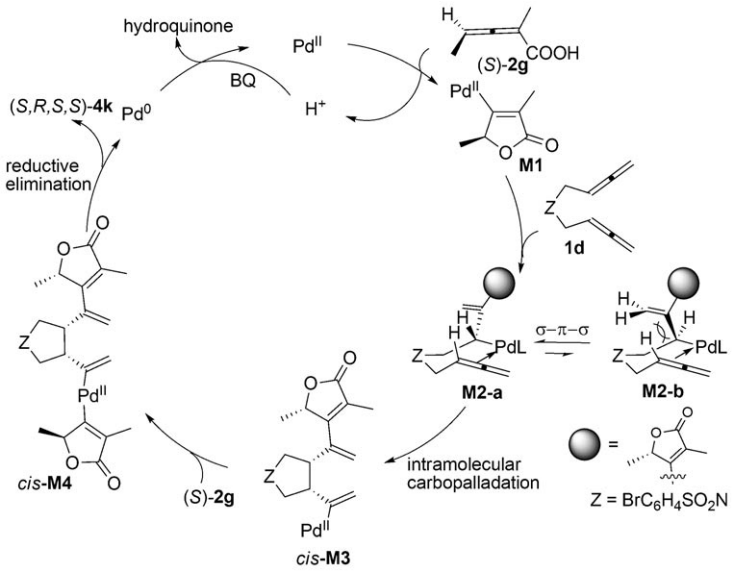


Figure 1. ORTEP representations of a) *cis*-**4c**, b) *cis*-**6a**, and c) (*S*,*R*,*S*,*S*)-**4k** shown with ellipsoids at the 30% probability level.



Scheme 5. Plausible catalytic cycle for the formation of (*S*,*R*,*S*,*S*)-**4k** from (*S*)-**2g** and **1d**.

In summary, we have observed an unexpected sandwich-type triple cyclization of two molecules of 2,3-allenoic acid in the presence of one molecule of 1,5-bisallene with excellent stereoselectivity. The axial chiralities of the optically active 2,3-allenoic acids can be transferred to the products efficiently. Based on the careful X-ray diffraction studies of some of the products, a possible mechanism involving sequential highly stereoselective *anti*-oxypalladation, intermolecular carbopalladation, cyclic *cis*-carbopalladation, *anti*-oxypalladation, and reductive elimination to afford the tricyclic products have been proposed. Further study in this area is being carried out in our laboratory.

Experimental Section

Typical procedure: 1,5-Bisallene **1a** (55 mg, 0.20 mmol), 2,3-allenoic acid **2a** (74 mg, 0.59 mmol), [$PdCl_2(PhCN)_2$] (4 mg, 0.010 mmol), dppe (5 mg, 0.013 mmol), BQ (29 mg, 0.27 mmol), and MeCN (3 mL) were sequentially added to a dried Schlenk tube under an Ar atmosphere. The resulting mixture was stirred at 70 °C under an Ar atmosphere and after completion of the reaction (monitored by TLC), the resulting mixture was diluted with CH_2Cl_2 (50 mL) and was washed sequentially with aqueous K_2CO_3 (10 %, 30 mL) and water (30 mL). Drying over Na_2SO_4, filtration, evaporation, and purification by column chromatography on silica gel (eluent: CH_2Cl_2/diethyl ether = 10:1) afforded the product *cis*-**4a** as a white solid (76 mg, 73 % yield). M.p. 197–199 °C (acetone/ethyl ether = 1:10); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, J = 7.8 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 5.45 (s, 2H), 5.22 (s, 2H), 3.64–3.54 (m, 2H), 3.50–3.40 (m, 2H), 3.05–2.94 (m, 2H), 2.45 (s, 3H), 1.76 (s, 6H), 1.40 (s, 6H), 1.38 ppm (s, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 172.1, 165.1, 144.0, 137.5, 133.5, 129.8, 127.1, 124.9, 120.7, 85.4, 51.2, 43.7, 25.9, 25.8, 21.3, 10.0 ppm; IR (neat): $\tilde{\nu}$ = 1749, 1667, 1621, 1596, 1487, 1465, 1367, 1331, 1279, 1220, 1198, 1163, 1132, 1091, 1046, 1015, 972, 955, 926, 903, 810, 763, 723, 705, 661, 623 cm^{-1}; EIMS: *m*/*z* (%): 525 [M^+] (4.38), 480 [$M^+ - 3CH_3$] (6.24), 370 [M^+–Ts] (68.99), 91 [$CH_3C_6H_4^+$] (100); elemental analysis calcd (%) for $C_{29}H_{35}NO_6S$: C 66.26, H 6.71, N 2.66; found: C 66.29, H 6.68, N 2.58.

Acknowledgements

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Keywords: allenes · chirality · cyclization · palladium · ring-closing metathesis reaction

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[15] Crystal data for (*S*,*R*,*S*,*S*)-**4k**: Recrystallization from acetone/diethyl ether (1:10); $C_{26}H_{28}BrNO_6S$; $M_W=562.46$; monoclinic; $P21/c$; $a=9.893(4)$, $b=7.771(3)$, $c=17.251(7)$ Å; $\alpha=90$, $\beta=98.223(7)$, $\gamma=90°$; $V=1312.5(9)$ Å^3; $Z=2$; $T=293(2)$ K; $Mo_{K\alpha}$; $\lambda=0.71073$ Å; final R indices $[I>2\sigma(I)]$, $R1=0.0631$, $wR2=0.1425$; R indices (all data): $R1=0.1083$, $wR2=0.1582$; reflections collected/unique = 6708/4596 ($R_{int}=0.1090$); number of observation $[I>2\sigma(I)]=2439$; parameters 320. CCDC-763153 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.

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