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Pd(OAc)$_2$-Catalyzed Coupling/Cyclization of 2,3-Allenoic Acids and Methyl Propiolate: Observation of Double 1,7-Hydrogen Shifts[**]

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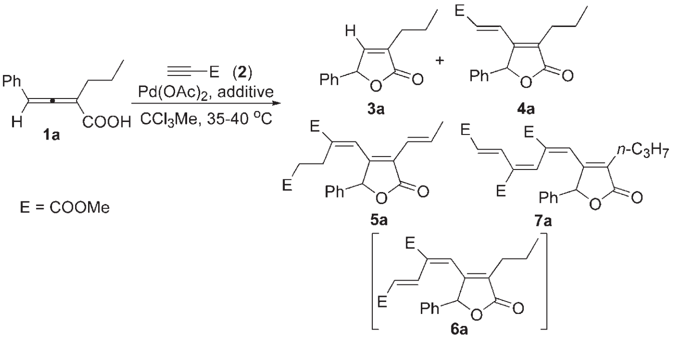
Dedicated to Professor Xikui Jiang
on the occasion of his 80th birthday

Transition-metal-catalyzed reactions of allenes have received much attention from many synthetic organic chemists.[1–2] Both we and Hashmi et al. established the homo- or hetero-dimerization reaction of two functionalized allenes.[3] Recently, we paid attention to the coupling/cyclization reaction between allenes and alkynes.[4] Herein, we report a coupling/cyclization process between 2,3-allenoic acids and methyl propiolate, in which the π bond in some of the 1:2 addition products "migrated" through double 1,7-hydrogen migrations.

A mixture of 2,3-allenoic acid **1a** and methyl propiolate (**2**) in the presence of 5 mol% of Pd(OAc)$_2$ was stirred in CCl_3Me at 35 °C for 12 h to afford (*E*)-**4a** in 10% yield and the cycloisomerization product **3a** in 40% yield (Table 1, entry 1). $MeCCl_3$ is better than other solvents, such as CH_3COOH, benzene, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), $ClCH_2CH_2Cl$, and so forth (see the Supporting Information). When 1.0 equivalent of $BF_3\cdot Et_2O$ was added, the yield of **4a** was improved to 40%. Quite surprisingly, instead of the normal 1:2-product **6a**, we also detected the formation of the unexpected 1:2 adduct **5a** in 15% yield, as confirmed by NMR and IR spectroscopic and mass-spectrometric analysis (Table 1, entry 2). Compound **5a** may be considered to be the "π-bond migration" product of **6a**. $BF_3\cdot Et_2O$ (10 mol%) led to lower yields of **4a** and **5a** (Table 1, entry 3), and to our disappointment, simple increasing of the loading of **2** could not efficiently improve the yield of **5a**. Furthermore, we even observed the formation of the normal 1:3 adduct **7a** when 8.0 equivalents of **2** were applied (Table 1, entry 4). $PdCl_2$ was not an efficient catalyst (Table 1, entry 5), and when 1.0 equivalent of [Sc(OTf)$_3$] (Tf = trifluoromethanesulfonyl) was used as the additive, the reaction could afford **5a** in 37% yield, with a 1:11 ratio of **4a**/**5a**, which was contaminated with **3a** in 51% yield (Table 1, entry 6). Unfortunately, 10 mol% of [Sc(OTf)$_3$] could only afford **4a**

Table 1: The coupling/cyclization reaction of 2,3-allenoic acid **1a** and methyl propiolate (**2**).



Entry	Equivalents of **2**	Additive (mol%)	*t* [h]	Yield [%][a]			
				3a	**4a**	**5a**	**7a**
1[b]	1.0	–	12	40	10	–	–
2	1.0	$BF_3\cdot Et_2O$ (100)	12	28	40	15	–
3	1.0	$BF_3\cdot Et_2O$ (10)	24	43	27	6	–
4	8.0	$BF_3\cdot Et_2O$ (100)	14	20	22	28	3
5[c]	1.0	$BF_3\cdot Et_2O$ (100)	12	8	6	2	–
6	3.0	[Sc(OTf)$_3$] (100)	18	51	3	37	5
7	3.0	[Sc(OTf)$_3$] (10)	12	28	35	20	–
8	5.0	[Sc(OTf)$_3$] + $BF_3\cdot Et_2O$[d]	12	14	4	71	–

[a] Yields were determined by ^1H NMR spectroscopic analysis with CH_2Br_2 as the internal standard. [b] A yield of 14% for starting material **1a**, as determined by ^1H NMR spectroscopic analysis. [c] $PdCl_2$ was used as the catalyst, a yield of 67% for starting material **1a**, as determined by ^1H NMR spectroscopic analysis. [d] [Sc(OTf)$_3$] = 30 mol%, $BF_3\cdot Et_2O$ = 4.0 equiv (for details of the procedure see the Experimental Section).

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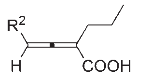
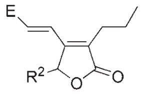
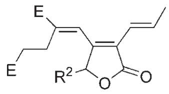
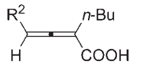
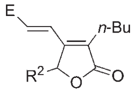
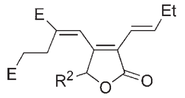
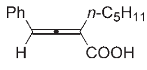
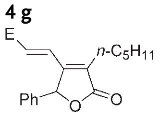
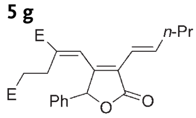
and **5a** in 35 and 20% yield, respectively (Table 1, entry 7). It was reported that the Lewis acid coordinates preferentially with the methyl acrylate derivatives rather than **2**;[5] thus, an excess amount of $BF_3 \cdot Et_2O$ was added to release [Sc(OTf)$_3$] from the products. Further studies showed that when a mixture of **1a** and 2.0 equivalents of **2** was added by a syringe pump to a mixture of 3.0 equivalents of **2**, 30 mol% of [Sc(OTf)$_3$], 4.0 equivalents of $BF_3 \cdot Et_2O$, and 5 mol% Pd(OAc)$_2$ in 1.0 mL of Cl_3CMe, **5a** was formed in 71% yield, as shown by NMR spectroscopic analysis with **5a**/**4a** = 16:1 (Table 1, entry 8).

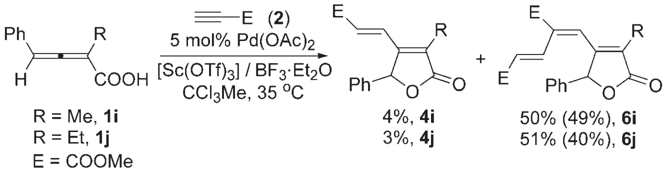
We next tested the generality of this type of "π-bond migration" reaction: This transformation is general when the α-substituent of 2,3-allenoic acids is either an *n*-propyl, *n*-butyl, or *n*-pentyl group (Table 2, entries 1–3, 4–7, and 8, respectively). The reaction afforded **5** in moderate yields with **4**/**5** = 1:9–1:16 when the R^2 function is either a phenyl, 4-halophenyl, 1′-naphthyl, or methyl group. It should be noted that the two noncyclic C=C double bonds are exclusively in the *E* form.

There are three significant issues within this transformation: 1) Is **6a** the precursor of **5a**? If yes, is the metal necessary for this transformation? 2) Where did the two hydrogen atoms of the propyl group of **1a** go? 3) Where did the three hydrogen atoms in **5a** (two at the 4′-position and one at the 3′-position) come from? In fact, when R = Me, we obtained the normal 1:2 adduct **6i** as expected. It is noteworthy that the normal adduct **6j** was formed as the major product even when R = Et; the "π-bond migration" adduct, if any, was formed in less than 5% yield (Scheme 1). The structures of **4** and **5** were further established by X-ray diffraction studies of **4i** and **5c**.[6]

Table 2: The coupling/cyclization reaction of **1** with methyl propiolate (**2**).[a]

Entry	Substrate 1	Products 4	Products 5	4/5	Yield of 5 [%][b]
					
1	R^2 = Ph **1a**	**4a**	**5a**	1:16	71 (54)
2	R^2 = 4-Br-C_6H_4 **1b**	**4b**	**5b**	1:11	75 (53)
3[c]	R^2 = 1′-naphthyl **1c**	**4c**	**5c**	1:9	52 (45)
					
4	R^2 = Ph **1d**	**4d**	**5d**	1:10	65 (47)
5	R^2 = 4-Br-C_6H_4 **1e**	**4e**	**5e**	1:12	71 (51)
6	R^2 = 4-Cl-C_6H_4 **1f**	**4f**	**5f**	1:14	70 (60)
7[d]	R^2 = Me **1g**	**4g**	**5g**	1:9	58 (44)
					
8	**1h**	**4h**	**5h**	1:11	64

[a] The reaction was carried out using 0.25 mmol of **1**, 5.0 equivalents of **2**, 5 mol% of Pd(OAc)$_2$, 30 mol% of [Sc(OTf)$_3$], and 4.0 equivalents of $BF_3 \cdot Et_2O$ in Cl_3CMe (2.2 mL) (see the Experimental Section for details of the procedure). [b] Yields were determined by ^1H NMR spectroscopic analysis with CH_2Br_2 as the internal standard; yields of the isolated products are given in parenthesis. [c] An approximate 9% yield of 1:3 adduct **7c** was detected by ^1H NMR spectroscopic analysis. [d] [**2**] = 7.0 equiv.



Scheme 1. The reaction of **1i** and **1j** with propiolate. The yields were determined by ^1H NMR spectroscopic analysis with CH_2Br_2 as the internal standard. The yields of the isolated products are given in parenthesis.

Although we failed to obtain the pure product **6a**, we isolated a mixture of **5a** and **6a** in a ratio of 1:1.27 when the reaction was conducted at 12 °C for 5 h. Quite interestingly, it was observed that **6a** can be converted into **5a** in $CDCl_3$ at 25 °C in the absence of any metallic catalyst. Nevertheless, complete conversion could not be achieved even at a higher temperature or over a longer reaction time (Figure 1). These results indicate that **6** may be the precursor of **5**.

The deuterium incorporation in [D$_1$]**4a** and [D$_1$]**5a** was approximately 72 and 68%, respectively, when [D$_1$]**1a** was used as the substrate to react with **2** in Cl_3CMe/CD_3CO_2D (10:1). It should be noted that the deuterium atom in [D$_1$]**5a** is at the 4′-position (Scheme 2). On the contrary, when [D$_2$]**1a** was treated with **2**, one of the deuterium atoms was completely transferred to the 3′-position in product [D$_2$]**5a**. These experimental findings reveal that one of the hydrogen atoms at the 4′-position comes from the acidic environment whereas one of the two hydrogen atoms at the 3′-position comes from the 2-position of the propyl group (Scheme 3).

In addition, it should be noted that under similar conditions with **1k** 8% of the normal 1:2 adduct **6k** remained even after stirring at 35 °C for 69 h (Scheme 4).

Based on these experimental results, we proposed the following mechanism: the cyclic oxypalladation of PdX_2 with [D$_2$]**1a** would form the intermediate **8**.[7] The subsequent stereoselective *cis* carbopalladation of **8** with the C–C triple bond of **2** would form intermediate **9**, which may afford [D$_2$]**4a** through protonolysis, while regenerating the Pd^{II} catalyst.[4a,8] The *cis* carbopalladation of **9** with the second molecule of **2** would form intermediate **10**. The subsequent protonolysis of **10** may form *Z*,*E*,*E*-triene [D$_2$]**6a**. The thermal antarafacial 1,7-hydrogen migration of *Z*,*E*,*E*-triene [D$_2$]**6a** would form the intermediate *E*,*E*,*E*-triene **11**, which may afford [D$_2$]**5a** through the second 1,7-hydrogen migration (Scheme 5).[9–11]

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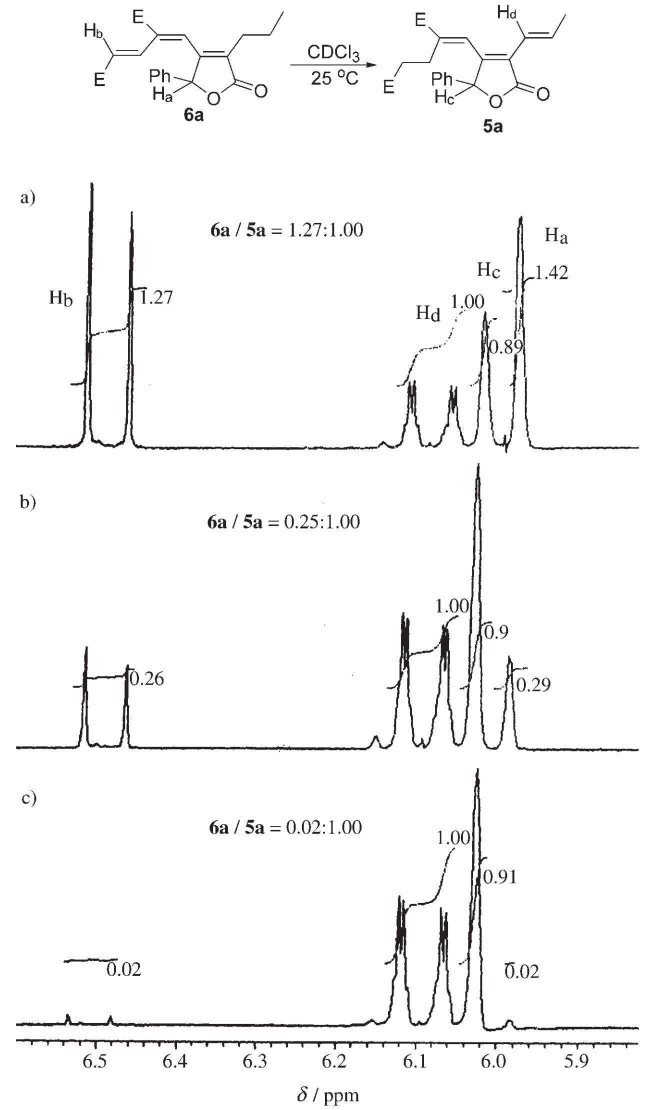
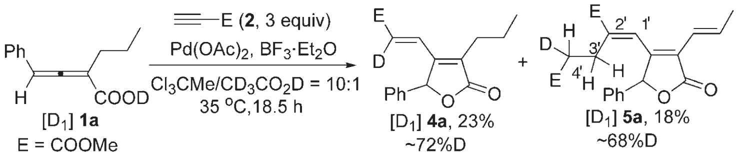
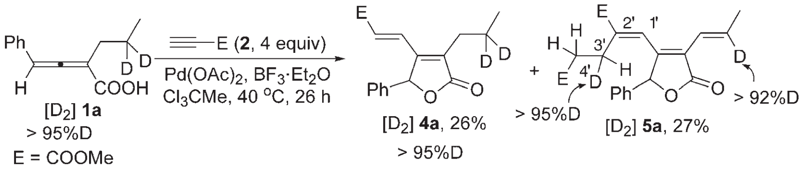


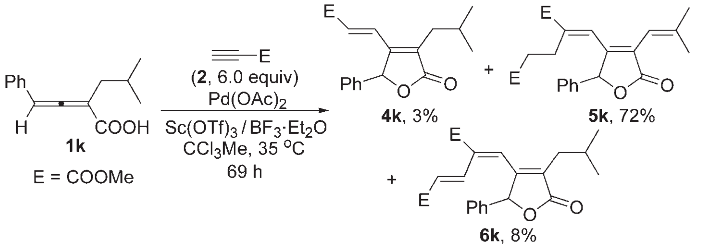
Figure 1. The ^{1}H NMR (300 MHz) spectra of the mixture of **5a** and **6a** in $CDCl_3$ at 25 °C. ^{1}H NMR spectra of the reaction mixture obtained a) immediately after isolation, b) after 6 h, and c) after 27 h.



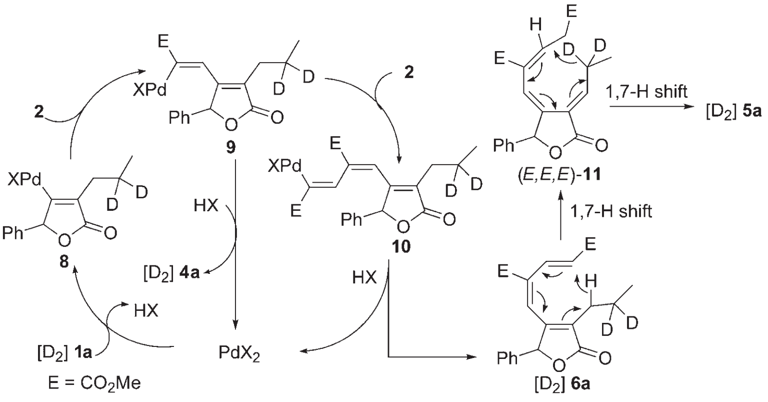
Scheme 2. The reaction of [D$_1$]**1a** with **2**.



Scheme 3. The reaction of [D$_2$]**1a** with **2**.



Scheme 4. The reaction of **1k** with **2**. The yields were determined by ^{1}H NMR spectroscopic analysis with CH_2Br_2 as the internal standard.



Scheme 5. A plausible catalytic cycle.

In conclusion, we have developed a $Pd(OAc)_2$-catalyzed coupling/cyclization reaction of 2,3-allenoic acids with methyl propiolate in the presence of $[Sc(OTf)_3]/BF_3{\cdot}Et_2O$. In this transformation, we observed the "π-bond migration" in some of the products, which may proceed through double 1,7-hydrogen migrations. Further studies in this area are being pursued in our laboratory.

Experimental Section

Typical experimental procedure for the coupling cyclization of 2,3-allenoic acids **1** with methyl propiolate (**2**): A solution of **1a** (50 mg, 0.248 mmol) and **2** (42 mg, 0.50 mmol) in Cl_3CMe (1.2 mL) was added by a syringe pump (0.06 mL h^{-1}) to a mixture of **2** (63 mg, 0.75 mmol), $[Sc(OTf)_3]$ (37 mg, 0.075 mmol), $BF_3{\cdot}Et_2O$ (124 μL, 1.00 mmol, 4.0 equiv), and $Pd(OAc)_2$ (3 mg, 0.0134 mmol) in Cl_3CMe (1.0 mL) at 40 °C with stirring. After the addition, the reaction mixture was stirred at 40 °C for 13 h. After complete consumption of the starting material, as determined by TLC, the reaction mixture was filtered through a short column of silica gel, evaporated, and analyzed by ^{1}H NMR spectroscopic analysis with CH_2Br_2 (9 μL, 0.129 mmol) as the internal standard. The ratio of **4a**/**5a** = 1:16, the yield of **5a** as determined by NMR spectroscopy was 71 %. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate (10:1)) to afford **5a** as a liquid (49 mg, 54 %) and **4a** as a solid. **4a**: M.p. 97–99 °C (ethyl acetate/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (d, J = 15.9 Hz, 1 H), 7.43–7.33 (m, 3 H), 7.30–7.18 (m, 2 H), 5.93 (s, 1 H), 5.82 (d, J = 15.9 Hz, 1 H), 3.72 (s, 3 H), 2.55 (t, J = 7.5 Hz, 2 H), 1.78–1.62 (m, 2 H), 1.02 ppm (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.9, 21.9, 26.0, 52.1, 82.4, 125.6, 127.7, 129.2, 129.8, 131.9, 134.8, 135.9, 151.7, 165.8,

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172.7; MS(EI): m/z 286 (M^+, 5.20), 181 (100); IR (KBr): $\tilde{\nu}=1759$, 1724, 1614, 1313, 1204, 1169, 1003 cm^{-1}; elemental analysis (%) calcd for $C_{17}H_{18}O_4$: C 71.31, H 6.34; found: C 71.24, H 6.36. **5a**: oil; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta=7.45$–7.33 (m, 3H), 7.28–7.10 (m, 4H), 6.11 (d, $J=15.6$ Hz, 1H), 6.05 (s, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 2.51 (t, $J=7.5$ Hz, 2H), 2.09 (t, $J=7.5$ Hz, 2H), 1.93 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75.4 MHz, CDCl$_3$): $\delta=19.6$, 24.4, 32.3, 51.6, 52.4, 82.7, 118.9, 126.3, 127.2, 129.06, 129.10, 129.6, 134.6, 136.6, 136.9, 151.1, 166.5, 171.0, 172.5 ppm; MS(EI): m/z 370 (M^+, 10.61), 105 (100); IR (neat): $\tilde{\nu}=1761$, 1736, 1718, 1437, 1257, 1197, 1103 cm^{-1}; HRMS (MALDI/DHB) calcd for $C_{21}H_{22}O_6Na$: [M^++Na] 393.1309; found: 393.1312.

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