Communication

PdCl-Catalyzed Two-Component Cross-Coupling Cyclization of 2,3-Allenoic Acids with 2,3-Allenols. An Efficient Synthesis of 4-(1‘,3‘-Dien-2‘-yl)-2(5*H*)-furanone Derivatives

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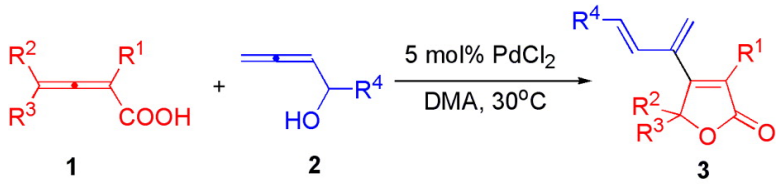

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$PdCl_2$-Catalyzed Two-Component Cross-Coupling Cyclization of 2,3-Allenoic Acids with 2,3-Allenols. An Efficient Synthesis of 4-(1′,3′-Dien-2′-yl)-2(5*H*)-furanone Derivatives

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The transition metal-catalyzed coupling cyclization reaction of functionalized allenes with organic halides has caught the attention of many synthetic chemists due to the great potential of allenes as a result of their unique reactivity, axial chirality, and substituent-loading capability.[1,2] Hashmi *et al.* reported the homodimerization reaction of 1,2-allenyl ketones.[3] We also have shown strong interest in the reactions involving two allenes by reporting the heterodimerization reaction of 2,3-allenoic acids with 1,2-allenyl ketones[4] and homodimerization of 2,3-allenoic acids.[5] It should be noted that in these two reactions (1) the Pd(II) species was regenerated by consuming a large amount of 1,2-allenyl ketones via cyclometalation/protonation or an additional oxidant via direct oxidation and (2) both allenes were cyclized. We wish to report here a coupling cyclization protocol of two different allenes, in which (1) the catalytically active Pd(II) species would be regenerated "automatically" after the reaction and (2) two allenes function differently, that is, 2,3-allenoic acids form the butenolide skeletons while the 2,3-allenols introduce the 1,3-diene substituent to the β-position of the butenolides formed.

After studying numerous combinations of different allenes, fortunately we observed that the reaction of 2,3-allenoic acid **1a** with 1.5 equiv of 2,3-allenol **2a** in the presence of 5 mol % $PdCl_2$ in 2 mL of DMA afforded 4-(1′,3′-dien-2′-yl)butenolide **3aa** in 67% yield. No cycloisomerization and homodimerization products of 2,3-allenoic acid **1a** were detected (Scheme 1).[4]

Solvents, such as $Cl_2CHCHCl_2$ and CH_3CN, are not effective for this reaction. DMA is better than other polar solvents, such as NMP, DMSO, and DMF (see Supporting Information). Palladium acetate and $PdCl_2(PPh_3)_2$ are not effective for the reaction in DMA. Thus, we have established the proposed protocol for the cross-coupling cyclization of 2,3-allenoic acid with 2,3-allenol under the catalysis of 5 mol % $PdCl_2$ in the absence of any oxidant; 2,3-allenoic acid was cyclized to afford the butenolide skeleton, while the 2,3-allenol was incorporated into the 4-position of the 2(5*H*)-furanone skeleton as a 1,3-dien-2-yl moiety. Some typical results are listed in Table 1. Various differently substituted 2,3-allenoic acids that bear an alkyl (entries 2, 5, and 7, Table 1), a benzyl (entries 4 and 8, Table 1), and an aryl group (entries 1, 3, 6, and 9, Table 1) were successfully cross-coupled with 2,3-allenols to afford butenolides in moderate yields. The structures of the products were further established by the X-ray diffraction studies of **3da** (see Supporting Information).

Furthermore, it is important to note that with $R^4 \neq H$ and $R^5 = H$, a very high stereoselectivity was observed affording the products (*E*)-**3** exclusively (Table 2). The stereochemistry was determined by the NOESY study of (*E*)-**3dd** and the *J* value of the related olefinic protons ($J = 15.6$ Hz).

To clarify the mechanism of this reaction, two controlled experiments were conducted. Under a N_2 atmosphere, the reaction occurred smoothly to afford **3aa** in 52% yield, indicating that air does not participate in the catalytic cycle. However, the reaction did not yield **3aa** in the presence of 1.0 equiv of K_2CO_3, which indicates the importance of the proton to the catalytic reaction.

Scheme 1. Cross-Coupling Cyclization Reaction of **1a** and **2a**

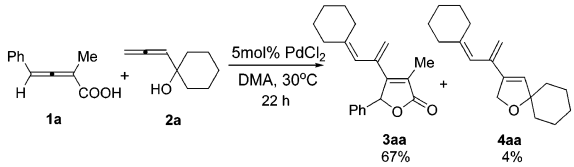
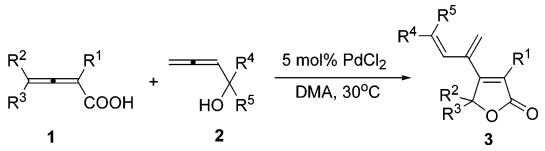


Table 1. $PdCl_2$-Catalyzed Cross-Coupling Reaction of 2,3-Allenoic Acids and 2,3-Allenols[a]



	1			2		
entry	R^1	R^2	R^3	R^4	R^5	yield of **3** (%)
1	Me	Ph	H (**1a**)	$(CH_2)_5$ (**2a**)		67 (**3aa**)
2	Me	Me	H (**1b**)	$(CH_2)_5$ (**2a**)		61 (**3ba**)
3[b]	Me	Ph	H (**1a**)	Me	Me (**2b**)	59 (**3ab**)
4	Bn	Me	H (**1c**)	Me	Me (**2b**)	52 (**3cb**)
5	Me	$(CH_2)_5$ (**1d**)		$(CH_2)_5$ (**2a**)		75 (**3da**)
6[c]	Me	Ph	H (**1a**)	H	H (**2c**)	59 (**3ac**)
7[b]	H	*n*-C_7H_{15}	H (**1e**)	$(CH_2)_5$ (**2a**)		52 (**3ea**)
8	Bn	H	H (**1f**)	$(CH_2)_5$ (**2a**)		62 (**3fa**)
9	Me	1-Nap	H (**1g**)	$(CH_2)_5$ (**2a**)		56 (**3ga**)

[a] A solution of **1** (0.25 mmol), **2** (0.375 mmol), and $PdCl_2$ (5 mol %) in 2−3 mL of DMA was stirred at 30 °C for 8−28 h. [b] A quantity of 0.50 mmol of **2** was used. [c] A quantity of 0.625 mmol of **2** was used.

In addition, when optically active allenoic acid (*R*)-(−)-2-methyl-4-phenyl-2,3-allenoic acid [**(*R*)-(−)-1a**] was used as the mechanistic probe to react with **2b** in the presence of 5 mol % $PdCl_2$ in 2 mL of DMA,[4] the product **3ab** was formed with partial racemization. We have observed that a base may induce the racemization of optically active butenolides.[6] Thus, to neutralize any in situ generated basic species, TFA (CF_3COOH) was added to the reaction mixture, and as a result, the racemization was indeed mostly inhibited. Best results were obtained with addition of 0.8 equiv of TFA (Scheme 2). Thus, it was concluded that [OH^-] species may be formed during the reaction, which may induce the partial racemization of the product.[6]

On the basis of these experimental findings, it was proposed that the interaction of PdX_2 with **(*R*)-(−)-1a** would form 4-furanonyl palladium intermediate **M1** via cyclic oxypalladation, which is responsible for the high efficiency of chirality transfer observed.[4]

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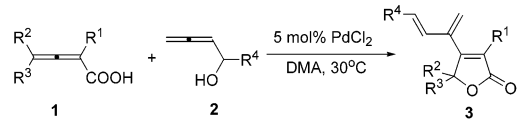
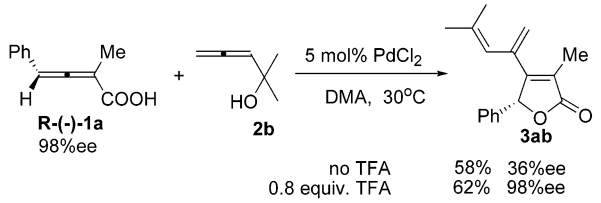
Table 2. Table 2. $PdCl_2$-Catalyzed Stereoselective Cross-Coupling Reaction of 2,3-Allenoic Acids and 2,3-Allenols[a]



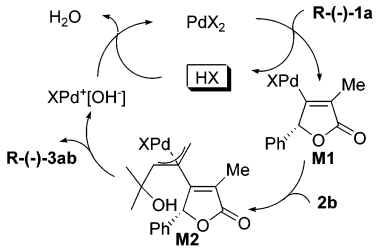
	1			2	
entry	R^1	R^2	R^3	R^4	yield of **3** (%)
1[b]	Me	Me	H (**1b**)	*n*-C_5H_{11} (**2d**)	52 [(*E*)-**3bd**]
2	Me	$(CH_2)_5$ (**1d**)		*n*-C_5H_{11} (**2d**)	55 [(*E*)-**3dd**]
3	Me	$(CH_2)_5$ (**1d**)		Ph (**2e**)	63 [(*E*)-**3de**]
4	Me	$(CH_2)_5$ (**1d**)		Bn (**2f**)	74 [(*E*)-**3df**]
5	Me	Ph	Et (**1h**)	Ph (**2e**)	66 [(*E*)-**3he**]
6	Me	Ph	Et (**1h**)	Bn (**2f**)	82 [(*E*)-**3hf**]
7	Me	Me	Me (**1i**)	Bn (**2f**)	71 [(*E*)-**3if**]

[a] A solution of **1** (0.25 mmol), **2** (0.375 mmol), and $PdCl_2$ (5 mol %) in 2−3 mL of DMA was stirred at 30 °C for 8−28 h. [b] A quantity of 0.625 mmol of **2** was used.

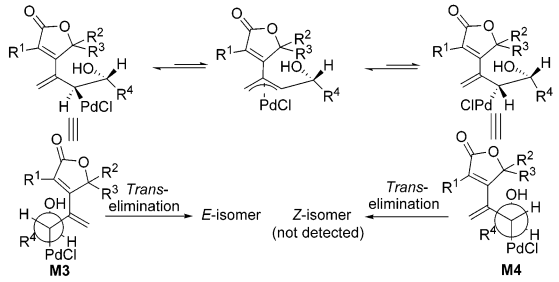
Scheme 2. Using **(*R*)-(−)-1a** as the Mechanistic Probe to React with **2b**



Scheme 3. Possible Mechanism of the Cross-Coupling Cyclization Reaction of **(*R*)-(−)-1a** and **2b**



Scheme 4. A Rationale for the Stereoselectivity Observed



Then, regioselective carbopalladation of 2,3-allenol **2b** with **M1** would highly regioselectively form the π-allylic palladium intermediate **M2**. Subsequent β-hydroxide elimination would afford **(*R*)-(−)-3ab** and $XPd^+[OH^-]$,[7−9] the $[OH^-]$ of which may induce the partial racemization of the product when this reaction was conducted in the absence of TFA.[7] Then, $XPd^+[OH^-]$ was converted to the catalytically active species, PdX_2, by the reaction with H^+ (Scheme 3). It should be noted when $R^4 \neq H$ and $R^5 = H$, the intermediate **M3** was more favored for its thermodynamic stability over **M4**, which can easily transform to **M3** through a $\sigma-\pi-\sigma$ process.[9a] **M3** would afford *E*-isomers highly stereoselectively through a trans-β-hydroxide elimination (Scheme 4).[9]

In conclusion, we have established the first coupling cyclization protocol of two different allenes, that is, 2,3-allenoic acids with 2,3-allenols, affording 4-(1′,3′-dien-2′-yl)-2-furanone derivatives. On the basis of some brief mechanistic studies, it was concluded that the reaction may proceed via cyclic oxypalladation, carbopalladation, and β-hydroxide elimination to afford the products by releasing $XPd^+[OH^-]$, which may react with H^+ to regenerate PdX_2. Further studies in this area are being pursued in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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