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PdI_2-Catalyzed Coupling–Cyclization Reactions Involving Two Different 2,3-Allenols: An Efficient Synthesis of 4-(1′,3′-Dien-2′-yl)-2,5-dihydrofuran Derivatives

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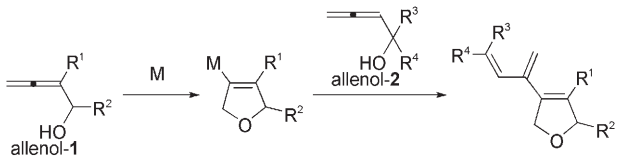
Abstract: Transition-metal-catalyzed dimeric coupling–cyclization reactions of two different 2,3-allenols afforded 4-(1′,3′-dien-2′-yl)-2,5-dihydrofuran derivatives **3**. 2-Substituted 2,3-allenols **1** cyclized to form the 2,5-dihydrofuran ring, whereas the 2-unsubstituted 2,3-allenols **2** provided the 1,3-diene unit at the 4-position. The reaction is proposed to proceed through an oxypalladation, insertion, and β-hydroxide elimination process. The C=C double bond was formed with high *E* stereoselectivity by β-hydroxide elimination.

Keywords: alcohols · allenes · cyclization · elimination · palladium

Introduction

Transition-metal-catalyzed reactions that involve two functionalized allenes have caught the attention of chemists because of the chirality and substituent-loading capability of allenes.[1,2] Hashmi et al. reported the homodimerization reaction of 1,2-allenyl ketones to afford monocyclic 3-(3′-oxo-1′-alkenyl)- and 2-(3′-oxo-1′-alkenyl)-substituted furan derivatives by Pd and $AuCl_3$ catalysis, respectively.[3] We have reported the homodimerization reaction of 2,3-allenoic acids to afford bibutenolides, in which both allenes were cyclized.[4] We have also reported the heterodimeric cyclization of 2,3-allenoic acids or 2,3-allenamides with 1,2-allenyl ketones[5,6] or 2,3-allenols.[7] Alcaide et al. reported a heterocyclization–cross-coupling reaction between an 2,3-allenol and an 2,3-allenyl ester.[8] In the same year, Hashmi et al. reported that the cyclization of tertiary 2,3-allenols under $AuCl_3$ catalysis yielded a mixture of cycloisomerization, double-cyclization, and other products.[9] Recently, we developed a homodimeric coupling–cyclization reaction of 2,3-allenols by using $PdCl_2$/NaI as the catalyst, which provides an efficient route to 4-(1′,3′-dien-2′-yl)-2,5-dihydrofuran derivatives.[10] However, the cyclization of two structurally different molecules from the same class of allenes has never been realized, probably due to molecular recognition difficulties. In this paper, we report the first examples of PdI_2-catalyzed dimeric coupling–cyclization reactions with two different 2,3-allenols to afford 4-(1′,3′-dien-2′-yl)-2,5-dihydrofuran derivatives, in which one 2,3-allenol is used for the construction of the dihydrofuran ring and the second 2,3-allenol for the 1,3-diene unit at the 4-position (Scheme 1).



Scheme 1. Dimeric coupling–cyclization reactions with two different 2,3-allenols.

Results and Discussion

We tried the coupling–cyclization protocol by using **1a** in the presence of buta-2,3-dienol **2a** with PdI_2 as the catalyst. Although the reaction in HOAc, CH_3NO_2, $(CH_2Cl)_2$, CH_3CN, or THF failed to afford the expected product **3a**, the results in *N*,*N*-dimethylacetamide, DMF, and *N*,*N*-dimethylpropylene urea (DMPU) were rather encouraging and gave the expected cross-product **3a** in 27–31% yields. Fur-

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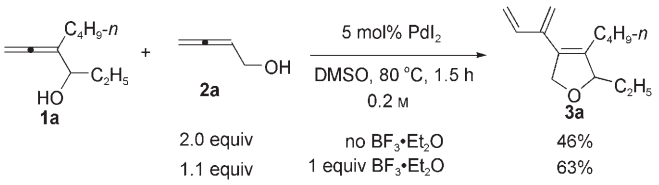
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. It contains detailed experimental procedures for the synthesis of starting materials and products, analytical data of these compounds, and the $^1H/^{13}C$ spectra of all the products.

thermore, it is quite interesting to observe that the reaction in dimethyl sulfoxide (DMSO) afforded **3a** in 46% yield (see Table S1 in the Supporting Information). Further studies indicated that the addition of a Lewis acid, such as $Sc(O_3SCF_3)_3$, trifluoroacetic acid, or $BF_3{\cdot}Et_2O$, could further improve the yields. Finally, it was observed that with the addition of 1.0 equivalent of $BF_3{\cdot}Et_2O$, only 1.1 equivalents of buta-2,3-dienol **2a** were required to afford **3a** in 63% yield (Scheme 2). For comparison, the reaction was also carried



Scheme 2. Dimeric coupling–cyclization reaction of 2,3-allenol **1a** with buta-2,3-dienol **2a**. Yields were determined by NMR spectroscopy.

out by using $PdCl_2$ and $PdBr_2$ as catalysts; however, PdI_2 gave the best results.

With this set of optimized reaction conditions in hand, the scope of the heterodimeric coupling–cyclization reactions was demonstrated and some typical results are summarized in Tables 1 and 2. The reactions were usually complete within a couple of hours. Various substituted 2,3-allenols that contained alkyl or aryl groups were successfully used to form the 2,5-dihydrofuran ring and the (1′,3′-dien-2′-yl) unit at the 4-position in moderate to good yields. Furthermore, it is important to note that high stereoselectivities for the formation of the C=C bond were observed and gave products (*E*)-**3** when secondary 2,3-allenols **2** were used (Table 2). The stereochemistry of these products was determined by the NOESY study of (*E*)-**3p**.

With optically active starting 2,3-allenol (*S*)-(−)-**1b** (>99% *ee*; *ee* = enantiomeric excess),[11] 4-(1′,3′-alkadien-2′-yl)-2,5-dihydrofurans (*S*)-**3b** and (*S*)-**3j** were prepared in 58 and 53% yields, respectively (Scheme 3). These results indicated that no racemization took place under the standard reaction conditions.

On the basis of these experiments, it can be noted that the reactivitiy towards cyclization of allenol **1** with a substituent at the 2-position (R^1) is higher than 2-unsubstituted 2,3-allenol **2**. Thus, we propose that allenol **1** forms 2,5-dihydrofuranyl palladium intermediate **M1** by cyclic oxypalladation. Then, regioselective carbopalladation of the allene unit of a second molecule of 2,3-allenol **2** with **M1** forms π-allylic palladium intermediate **M2**. Subsequent *trans*-β-hydroxide elimination[7,10,12–14] affords **3** and PdI(OH). This β elimination process is believed to be mediated by the presence of a Lewis acid. Finally, PdI(OH) is converted to the catalytically active species PdI_2 by reaction with HI generated in the first step (Scheme 4). Interestingly, allenes with R^1 = alkyl, aryl, and even an electron-withdrawing alkoxycarbonyl group all underwent the cyclic oxypalladation reaction.

Table 1. PdI_2-Catalyzed dimeric coupling–cyclization reactions with two different 2,3-allenols.

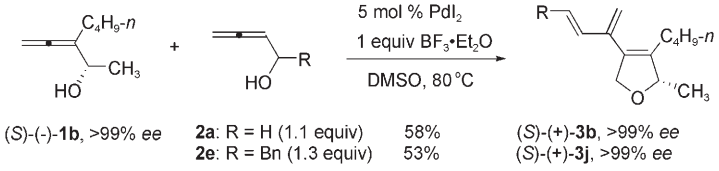
Entry	**1**		**2**		Yield of **3** [%][a]
	R^1	R^2	R^3	R^4	
1[b]	*n*Bu	Et (**1a**)	H	H (**2a**)	57 (**3a**)
2	*n*Bu	Me (**1b**)	H	H (**2a**)	61 (**3b**)
3	*n*Bu	Ph (**1c**)	H	H (**2a**)	78 (**3c**)
4	Ph	*n*Bu (**1d**)	H	H (**2a**)	70 (**3d**)
5	Allyl	Me (**1e**)	H	H (**2a**)	49 (**3e**)
6[c]	CO_2Me	*p*-$CH_3C_6H_4$ (**1f**)	H	H (**2a**)	55 (**3f**)
7	*n*Bu	*p*-$NO_2C_6H_4$ (**1g**)	H	H (**2a**)	70 (**3g**)
8[d]	*n*Bu	*p*-$NO_2C_6H_4$ (**1g**)	Et	Et (**2b**)	50 (**3h**)
9[b,e]	*n*Bu	*p*-$NO_2C_6H_4$ (**1g**)	$(CH_2)_5$ (**2c**)	$(CH_2)_5$ (**2c**)	57 (**3i**)

[a] Isolated yield. [b] Reaction time = 1.5 h. [c] 1.2 equiv of **2a** were used. [d] 1.3 equiv of **2b** were used. [e] 1.3 equiv of **2c** were used.

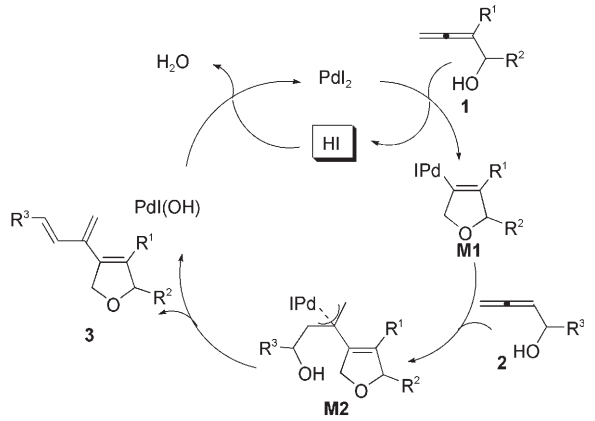
Table 2. PdI_2-catalyzed stereoselective dimeric coupling–cyclization reactions with two different 2,3-allenols.[a]

Entry	**1**	**2**		Yield of (*E*)-**3** [%][b]
	R^1	R^2	R^3	
1[c]	*n*Bu	Me (**1b**)	Bn (**2e**)	55 (**3j**)
2	*n*Bu	Ph (**1c**)	Bn (**2e**)	62 (**3k**)
3	*n*Bu	*p*-$NO_2C_6H_4$ (**1g**)	*n*Hex (**2d**)	69 (**3l**)
4	*n*Bu	*p*-$NO_2C_6H_4$ (**1g**)	Bn (**2e**)	81 (**3m**)
5	*n*Bu	*p*-$NO_2C_6H_4$ (**1g**)	Ph (**2f**)	38 (**3n**)
6	*n*Bu	*o*-ClC_6H_4 (**1h**)	Bn (**2e**)	65 (**3o**)
7	CO_2Me	Et (**1i**)	*n*Hex (**2d**)	52 (**3p**)
8	CO_2Me	Et (**1i**)	Bn (**2e**)	52 (**3q**)
9	CO_2Me	nC_5H_{11} (**1j**)	Bn (**2e**)	53 (**3r**)
10	Ph	*n*Bu (**1d**)	Bn (**2e**)	48 (**3s**)

[a] Reaction time = 0.5–1.2 h. [b] Isolated yield. [c] 1.3 equiv of **2e** were used.



Scheme 3. Dimeric coupling–cyclization reactions of optically active 2,3-allenols.



Scheme 4. Possible mechanism for the dimeric coupling–cyclization reaction of **1** with **2**.

Conclusion

We have developed the first example of a transition-metal-catalyzed dimeric coupling–cyclization reaction with two different 2,3-allenols by using PdI_2 as the catalyst in the presence of BF_3•Et_2O. This reaction provides an efficient route to 4-(1′,3′-dien-2′-yl)-2,5-dihydrofuran derivatives, in which the 2-substituted 2,3-allenols construct the 2,5-dihydrofuran ring, whereas the 2-unsubstituted 2,3-allenols provide the 1,3-diene unit at the 4-position. Due to the easy availability of the 2,3-allenol starting materials[15] and the catalyst, and its wide scope, this reaction may prove very useful in organic synthesis. Further studies in this area and synthetic applications of this reaction are being carried out in our laboratory.

Experimental Section

Synthesis of starting materials 1 and 2: Starting materials **1** and **2** were prepared according to previously published procedures. The starting allenols **1a–e** and **1g–h** were prepared by the reaction of a propargylic bromide and an aldehyde in the presence of NaI and $SnCl_2$ in DMF.[10a,15c] Allenols **1f**, **1i**, and **1j** were prepared by the reaction of 3-(methoxycarbonyl)propargyl bromide and an aldehyde in the presence of NaI and $SnCl_2$ in DMPU.[15d,e] For the preparation of allenols **2a–e** see references [15a,b].

3-Butyl-2-ethyl-4-(1′,3′-butadien-2′-yl)-2,5-dihydrofuran (3a). A general procedure for the synthesis of compounds 3: BF_3•Et_2O (127 μL, ρ = 1.12 g mL^{-1}, 142.2 mg, 1 mmol), **1a** (154.7 mg, 1.00 mmol), and DMSO (2.5 mL) were added sequentially to a mixture of PdI_2 (18.5 mg, 5 mol %, 0.051 mmol) and buta-2,3-dienol **2a** (77.9 mg, 1.11 mmol) in DMSO (2.5 mL). Then, the mixture was stirred at 80 °C for 1.5 h. After the reaction had gone to completion, as determined by TLC, it was cooled to room temperature and quenched with water (10 mL). The mixture was extracted with Et_2O (3×25 mL). The combined organic layers were washed with a saturated aqueous solution of $Na_2S_2O_3$ and brine. The product solution was dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 100:1) afforded **3a** (118.6 mg, 57 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.37 (dd, J_1 = 17.6, J_2 = 10.4 Hz, 1H), 5.23 (s, 1H), 5.17 (d, J = 17.6 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 4.98 (s, 1H), 4.92–4.84 (m, 1H), 4.67–4.55 (m, 2H), 2.24–2.12 (m, 1H), 1.88–1.70 (m, 2H), 1.59–1.46 (m, 1H), 1.44–1.16 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H), 0.85 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.2, 137.6, 137.2, 131.0, 117.8, 116.1, 88.3, 77.6, 29.9, 26.8, 25.3, 22.6, 13.8, 8.5 ppm; IR (neat): $\tilde{\nu}$ = 3089, 2960, 2932, 2873, 2859, 1825, 1585, 1456, 1379, 1355, 1030, 899 cm^{-1}; MS m/z (%): 206 (2.85) $[M]^+$, 177 (27.81) $[M-C_2H_5]^+$, 57 (100); HRMS: m/z calcd for $C_{14}H_{22}O$: 206.1671 $[M]^+$; found: 206.1666.

Synthesis of optically active (*S*)-(+)-3b and (*E*,*S*)-(+)-3j

(*S*)-(+)-3-Butyl-2-methyl-4-(1′,3′-butadien-2′-yl)-2,5-dihydrofuran ((*S*)-3b): The reaction of PdI_2 (18.1 mg, 5 mol %, 0.050 mmol), **2a** (79.9 mg, 1.14 mmol), BF_3•Et_2O (127 μL, 1.0 mmol), and (*S*)-(−)-**1b** (137.3 mg, 0.98 mmol, >99 % *ee*) in DMSO (5 mL) afforded (*S*)-(+)-**3b** (108.4 mg, 58 %, >99 % *ee*) as an oil. $[\alpha]_D^{20}$ = +26.4 (c = 1.09 in $CHCl_3$); HPLC conditions: ReGIS (S,S)-whelk-01 column; flow rate = 0.7 mL min^{-1}, eluent = hexane/*i*PrOH 100:0.1, λ = 214 nm.

(*S*)-(+)-3-Butyl-2-methyl-4-(5′-phenyl-1′,3′-pentadien-(3′*E*)-2′-yl)-2,5-dihydrofuran ((*E*,*S*)-(+)-(3j)): The reaction of PdI_2 (7.2 mg, 5 mol %, 0.020 mmol), **2e** (86.8 mg, 0.54 mmol), BF_3•Et_2O (51 μL, 0.40 mmol), and (*S*)-(−)-**1b** (56.0 mg, 1.00 mmol, >99 % *ee*) in DMSO (2 mL) afforded (*E*,*S*)-(+)-**3j** (60.1 mg, 53 %, >99 % *ee*) as an oil. $[\alpha]_D^{20}$ = +10.1 (c = 0.64 in $CHCl_3$); HPLC conditions: ReGIS (S,S)-whelk-01 column; flow rate = 0.6 mL min^{-1}, eluent = hexane/*i*PrOH 100:0.1, λ = 214 nm..

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