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$PdCl_2$/NaI-Catalyzed Homodimeric Coupling-Cyclization Reaction of 2,3-Allenols: An Efficient Synthesis of 4-(1′,3′-Dien-2′-yl)-2,5-dihydrofuran Derivatives

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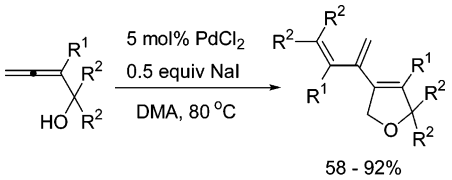

A $PdCl_2$/NaI-catalyzed homodimeric coupling-cyclization reaction of 2,3-allenols was observed to provide an efficient route to 4-(1′,3′-dien-2′-yl)-2,5-dihydrofuran derivatives. By using the easily available optically active starting materials, 2,5-dihydrofurans with high enantiopurity may be prepared. A Pd(II)-catalyzed mechanism was also discussed.

Introduction

The transition metal-catalyzed cyclizative dimerization reaction of two functionalized allenes is attractive for synthetic organic chemists due to the issues of chirality transfer, diversity, and substituent-loading capability of allenes.[1,2] The first palladium-catalyzed homodimerization reaction of 1,2-allenyl ketones has been reported by Hashmi et al., which led to the formation of monocyclic 3-(3′-oxo-1′-alkenyl)-substituted furan derivatives.[3,4] The reaction of 1,2-allenyl ketones would also afford 2-(3′-oxo-1′-alkenyl)-substituted furan derivatives when $AuCl_3$ was used as the catalyst.[5] The palladium-catalyzed macrocyclization reaction of 1,ω-bis(1,2-allenylketone)s was also reported.[6] We have reported the homodimerization reaction of 2,3-allenoic acids affording bibutenolides, in which both allenes were cyclized.[7] Recently, Hashmi et al. reported the $AuCl_3$-catalyzed reaction of 2,3-allenols, which afforded bis-(2,5-dihydrofuran)s as a byproduct in low yield.[8] On the other

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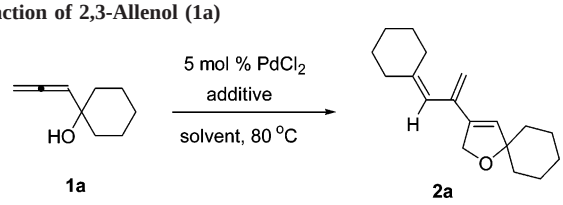
hand, 2,5-dihydrofurans, an important class of heterocyclic compounds, are useful intermediates for organic synthesis[9] and common structural units in many natural products.[10] These compounds are usually prepared via cyclization of 2,3-allenols,[11−16] a RCM reaction,[17] Ag(I)-catalyzed rearrangement-cyclization of 4-hydroxypropargyl esters,[18] dehydration of *cis*-2-alken-1,4-diols,[19] palladium-catalyzed reaction of cyclic alkynyl carbonates with electron-deficient alkenes,[20] Prins reaction of terminal alkene and formaldehyde,[21] reaction of oxazirconacyclopentenes with propynoates,[22] reaction of 1,4-dilithio-1,3-dienes with aldehydes,[23] tungsten-promoted intramolecular annulation of propargyl bromides with ketones and aldehydes,[24] and Au(I)-catalyzed rearrangement of butynediol monobenzoates.[25] In this paper, we wish to report an efficient synthesis of 4-(1′,3′-dien-2′-yl)-2,5-dihydrofuran derivatives via the $PdCl_2$/NaI-catalyzed homodimeric coupling-cyclization reaction of 2,3-allenols, in which one molecule of the 2,3-allenol was cyclized while the other formed the 1,3-diene unit and helped to regenerate the catalytically active Pd(II) species.[26]

TABLE 1. Pd(II)-Catalyzed Homodimeric Coupling-Cyclization Reaction of 2,3-Allenol (1a)



1a **2a**

entry	solvent	additive (equiv)	time (h)	yield of **2a**[a] (%)
1	DMA	none	24	trace
2	DMA	NaCl (0.5)	12	22[b,d]
3	DMA	LiCl (0.5)	12	25[b]
4	DMA	NaI (0.1)	5	42
5	DMA	NaI (0.3)	5	80
6	DMA	NaI (0.5)	5	86
7	DMA	NaI (0.5)	21	75[b,c,e]
8	DMA	NaI (1.0)	5	81
9	DMA	KI (0.5)	5	85
10	DMA	I_2 (0.25)	0.5	66
11	DMA	I_2 (0.05)	3	42
12	DMA	CH_3I (10)	1.5	86
13	THF	NaI (0.5)	17	60[b,f]
14	acetone	NaI (0.5)	17	47[b,g]
15	CH_3CN	NaI (0.5)	17	44[b,h]

[a] Isolated yield. [b] Determined by ^1H NMR analysis using 1,3,5-trimethylbenzene as the internal standard. [c] 2 mol % $PdCl_2$ was used. [d] 10% of **1a** was recovered. [e] 16% of **1a** was recovered. [f] 11% of **1a** was recovered. [g] 40% of **1a** was recovered. [h] 33% of **1a** was recovered.

Results and Discussion

$PdCl_2$/NaI-Catalyzed Homodimeric Coupling-Cyclization Reaction of 2,3-Allenols. The homodimeric coupling-cyclization reaction of 2,3-allenol (**1a**) was chosen to establish the protocol. Some representative results are listed in Table 1. From Table 1, it was observed that under the catalysis of $PdCl_2$, the reaction of **1a** afforded a trace amount of 3-(1-cyclohexylidenemethylvinyl)-1-oxaspiro[4.5]dec-3-ene (**2a**) (Table 1, entry 1). When NaCl or LiCl was applied as the additive, the reaction afforded **2a** in 22% and 25% yields, respectively (Table 1, entries 2 and 3). Surprisingly, when NaI[7b] was applied as the additive, the reaction afforded **2a** in higher yields (Table 1, entries 4−8). Addition of KI[7b] (Table 1, entry 9), I_2[7b](Table 1, entries 10 and 11), or CH_3I[7a] (Table 1, entry 12) is also effective for this reaction. Among the solvents tested, DMA is the best. In THF, acetone, and CH_3CN, the yields were lower and some of **1a** was recovered (Table 1, entries 13−15). In conclusion, the best results were obtained when the reaction was conducted using 5 mol % $PdCl_2$ and 0.5 equiv of NaI in DMA leading to a 86% yield of product **2a** (Table 1, entry 6).

Some typical results are summarized in Tables 2 and 3. Various substituted 2,3-allenols that bear alkyl or aryl groups were successfully used to afford 4-(1′,3′-dien-2′-yl)-2,5-dihydrofuran derivatives in moderate to good yields. Furthermore, it is important to note that a high stereoselectivity for the

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SCHEME 1. Homodimeric Coupling-Cyclization Reaction of Optically Active 2,3-Allenols (1g)

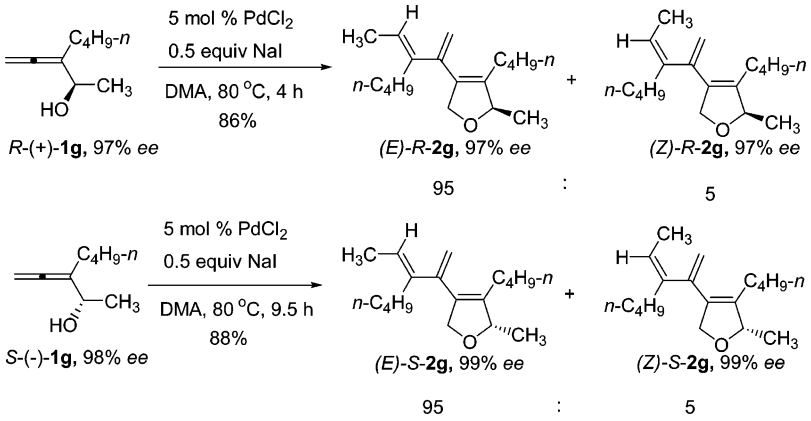
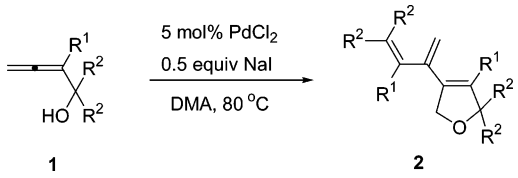
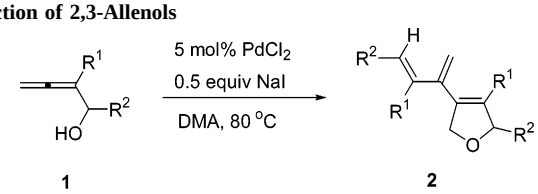


TABLE 2. Homodimeric Coupling-Cyclization Reaction of 2,3-Allenols



entry	R^1	R^2	R^2	time (h)	isolated yield of **2** (%)
1	H	$(CH_2)_5$ (**1a**)		5	86 (**2a**)
2	H	CH_3	CH_3 (**1b**)	5	66 (**2b**)
3	H	C_2H_5	C_2H_5 (**1c**)	4	85 (**2c**)
4	H	*n*-C_4H_9	*n*-C_4H_9 (**1d**)	10	92 (**2d**)
5	*n*-C_4H_9	H	H (**1e**)	12	84 (**2e**)
6	*n*-C_7H_{15}	H	H (**1f**)	12	87 (**2f**)

TABLE 3. Stereoselective Homodimeric Coupling-Cyclization Reaction of 2,3-Allenols



entry	R^1	R^2	time (h)	yield of **2**[a] (%)	*E*/*Z* ratio of **2**[b]
1	*n*-C_4H_9	CH_3 (**1g**)	13	83 (**2g**)	≥95:5
2	*n*-C_4H_9	C_2H_5 (**1h**)	14	86 (**2h**)	≥96:4
3	Ph	*n*-C_4H_9 (**1i**)	11	75 (**2i**)	>99:1[c]
4	CO_2CH_3	C_2H_5 (**1j**)	17	58 (**2j**)	95:5[c]
5	allyl	CH_3 (**1k**)	1.5	61(**2k**)	>99:1

[a] Isolated yield. [b] *E*/*Z* was determined by ^{1}H NMR analysis. [c] *Z*/*E* ratio.

formation of the C═C bond carrying R^1 and R^2 groups was observed affording the products (*E*)-**2** when secondary 2,3-allenols were applied (Table 3). The stereochemistry of these products was determined by the NOESY study of (*E*)-**2h**.

In addition, by using the optically active 2,3-allenols *R*-(+)-**1g** (97% ee) and *S*-(−)-**1g** (98% ee),[27] the reaction occurred smoothly to give the product *R*-**2g** in 86% yield and 97% ee and *S*-**2g** in 88% yield and 99% ee, respectively (Scheme 1). These results indicated that no racemization was observed under the standard reaction conditions.

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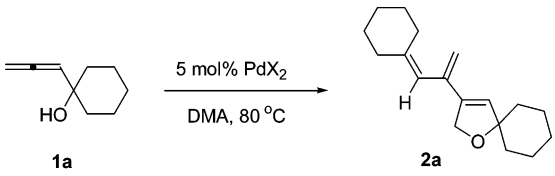
SCHEME 2. PdX_2-Catalyzed Homodimeric Self-Coupling Cyclization Reaction of 2,3-Allenol (1a)



X = Cl, 24 h, trace
X = Br, 16 h, 65%
X = I, 5 h, 90%

To clarify the mechanism of this reaction, three control experiments were conducted (Scheme 2). It should be noted that when 5 mol % $PdBr_2$ or PdI_2 was used, the reaction proceeded even in the absence of NaI affording **2a** in 65% or 90% yields, respectively, indicating the possible in situ formation of PdI_2 under the current reaction conditions.

On the basis of these experimental findings, it was proposed that the interaction of **1g** with PdI_2, which might be produced in situ from $PdCl_2$ and NaI, would form 2,5-dihydrofuranyl palladium intermediate **M1** via cyclic oxypalladation. Then regioselective carbopalladation of a second molecule of **1g** with **M1** would highly regioselectively form the π-allylic palladium intermediate **M2**. Subsequent *trans*-β-hydroxide elimination[28−31] would afford **2g** and $IPd^+[OH^-]$. Finally, $IPd^+[OH^-]$ was converted to the catalytically active species PdI_2 by its reaction with HI generated in the first step (Scheme 3). It should be noted when $R^1 \neq H$, $R^2 \neq H$, and $R^3 = H$, the intermediate **M3** was more favored for its thermodynamic stability over **M4**. **M3** would afford *E*-isomers highly stereoselectively through a *trans*-β-hydroxide elimination (Scheme 4).

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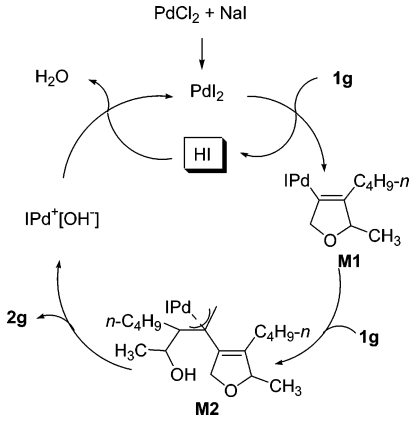
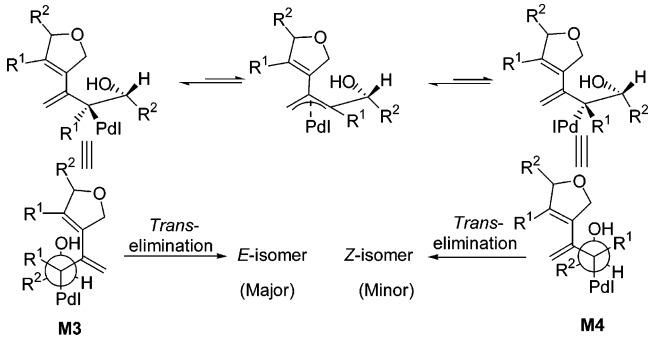
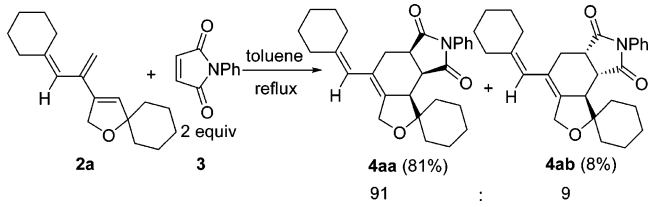
SCHEME 3. Possible Mechanism of the Homodimeric Coupling-Cyclization Reaction of 1g



SCHEME 4. A Rationale for the Stereoselectivity Observed



SCHEME 5. The Diels−Alder Reaction of 2a with 3



Furthermore, the Diels−Alder reaction of **2a** with maleamide **3** afforded diastereoisomeric polycyclic compounds **4aa** and **4ab** in 81% and 8% yields, respectively (Scheme 5). The structure of the major product **4aa** was further established by the X-ray diffraction study (Figure 1).

In conclusion, we have developed a homodimeric coupling-cyclization reaction of 2,3-allenols using $PdCl_2$/NaI as the catalyst, which provides an efficient route to 4-(1′,3′-dien-2′-yl)-2,5-dihydrofuran derivatives. By using the optically active 2,3-allenols, no racemization was observed under the standard reaction conditions, affording optically active products in good yields. On the basis of control experiment, it was found that the addition of NaI is very important for this transformation. Due to the easy availability of the starting allenols and usefulness of 2,5-dihydrofuran, this method will be useful in organic synthesis. Further studies on the scope, mechanism, and synthetic applications of this reaction are being carried out in our laboratory.

Experimental Section

Synthesis of 3-(1-Cyclohexylidenemethylvinyl)-1-oxaspiro[4.5]-dec-3-ene (2a): Typical Procedure. To a mixture of $PdCl_2$ (8.8 mg, 5 mol %, 0.050 mmol) and NaI (75.1 mg, 0.50 mmol) were added **1a** (136.8 mg, 0.99 mmol) and DMA (2 mL). After being stirred at 80 °C for 5 h the reaction was complete as monitored by TLC and the resulting mixture was cooled to room temperature and quenched by 10 mL of water. The mixture was extracted with Et_2O (3 × 25 mL). The combined organic layer was 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 (petroleum ether/diethyl ether = 20:1) afforded **2a** (109.3 mg, 86%): liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.74 (s, 1H), 4.89 (s, 1H), 4.86 (s, 1H), 4.73 (d, J = 2.0 Hz, 2H), 2.20 (t, J = 5.6 Hz, 2H), 2.16 (t, J = 5.6 Hz, 2H), 1.72−1.28 (m, 16H).

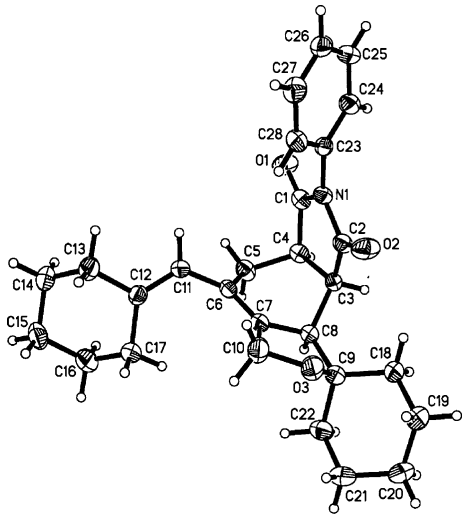


FIGURE 1. ORTEP structure of **4aa**.

Synthesis of Polycyclic Compound 4aa. To maleamide **3** (519.3 mg, 3.0 mmol) were added **2a** (387.8 mg, 1.5 mmol) and toluene (15 mL). The mixture was refluxed at 130 °C for 5 h. After the reaction was complete as monitored by TLC, it was cooled to room temperature, evaporated, and analyzed by 300 MHz ^{1}H NMR spectroscopic analysis with CH_2Br_2 (105 μL, 1.5 mmol) as the internal standard, which showed that the diastereomeric ratio of **4aa**/**4ab** is 91/9. Column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1) afforded 54.1 mg (8%) of **4ab** and 524.0 mg (81%) of **4aa**. **4ab**: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.43 (m, 2H), 7.43−7.34 (m, 1H), 7.30 (d, J = 7.5 Hz, 2H), 5.55 (s, 1H), 4.26 (dd, J_1 = 27.9 Hz, J_2 = 13.8 Hz, 2H), 3.08−2.95 (m, 2H), 2.80−2.69 (m, 1H), 2.50−2.40 (m, 1H), 2.25−1.90 (m, 6H), 1.80−1.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.00, 177.95, 143.5, 137.3, 131.7, 129.1, 128.5, 126.3, 124.8, 119.7, 83.7, 66.4, 48.9, 40.6, 40.3, 37.0, 36.4, 30.7, 30.1, 29.1, 28.5, 27.7, 26.4, 25.6, 22.8, 21.7; MS (m/z) 431 (M^+, 3.21), 333 (100); IR (neat, cm^{-1}) 2929, 2853, 1779, 1716, 1599, 1500, 1447, 1380, 1178; HRMS calcd for $C_{28}H_{33}NO_3$ (M^+) 431.2460, found 431.2450. **4aa**: solid, mp 178−179 °C (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.27 (m, 3H), 7.13 (d, J = 8.1 Hz, 2H), 5.44 (s, 1H), 4.21 (s, 2H), 3.54−3.44 (m, 1H), 3.27 (t, J = 8.1 Hz, 1H), 2.78 (d, J = 14.7 Hz, 1H), 2.55−2.38 (m, 2H), 2.40−2.30 (m, 1H), 2.20−2.00 (m, 4H), 2.08−1.30 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 175.5, 143.7, 139.7, 131.9, 128.8, 128.3, 126.4, 125.1, 119.7, 82.9, 66.1, 49.9, 41.7, 41.1, 36.8, 36.1, 32.1, 31.7, 30.5, 28.3, 27.5, 26.3, 25.6, 23.0; MS (m/z) 431 (M^+, 7.89), 333 (100); IR (neat, cm^{-1}) 2928, 2853, 1775, 1713, 1598, 1500, 1446, 1382. Elemental analysis calcd for $C_{28}H_{33}NO_3$: C, 77.93; H, 7.71; N, 3.25. Found: C, 77.74; H, 7.81; N, 2.99. Crystal data for **4aa**: $C_{28}H_{33}NO_3$, MW = 431.55, monoclinic, space group $P2(1)/c$, final R indices [$I > 2\sigma(I)$], $R1$ = 0.0688, w$R2$ = 0.1807, a = 16.051(6) Å, b = 13.024(5) Å, c = 11.211(4) Å, α = 90°, β = 97.815(8)°, γ = 90°, V = 2322.0(15) Å^3, crystal size 0.490 × 0.362 × 0.178 mm^3, T = 293(2) K, Z = 4, reflections collected/unique 13674/5282 (R_{int} = 0.0967), 5282

data, 1 restraint, 302 parameters. Supplementary crystallographic dada have been deposited at the Cambridge Crystallographic Data Center as CCDC 651148.

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Supporting Information Available: Experimental procedures, copies of ^{1}H and ^{13}C NMR spectra of all compounds, and the CIF file of compound **4aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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