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Efficient Synthesis of Bibutenolide Derivatives through Oxidative Dimeric Cyclization–Coupling Reaction of 2,3-Allenoic Acids

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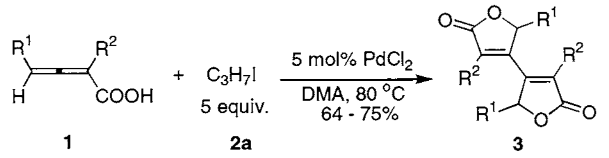
ABSTRACT



An oxidative coupling–dimerization reaction of 2,3-allenoic acids was observed to provide an efficient route to bibutenolide derivatives, which are not readily available. A new system (PdCl$_2$/RI/air) for regeneration of the palladium(II) catalyst was also established.

Allenes are three-carbon functional groups possessing two perpendicular π-orbitals. Their unique reaction behavior, which shows great potential in organic synthesis in terms of chirality transfer and diversity, as a result of the axial chirality as well as the substituent-loading capability, is spread over three carbon atoms.[1,2] We[3,4] and others[5−13] have established the cycloisomerization of functionalized allenes and the coupling−cyclization of functionalized allenes with organic halides for the formation of carbon−carbon bonds as well

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(11) For cyclization of 1,2-allenyl ketones, see: (a) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450 (b) Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169. (c) Marshall, J. A.; Wallace, E. M. *J. Org. Chem.* **1995**, *60*, 796.

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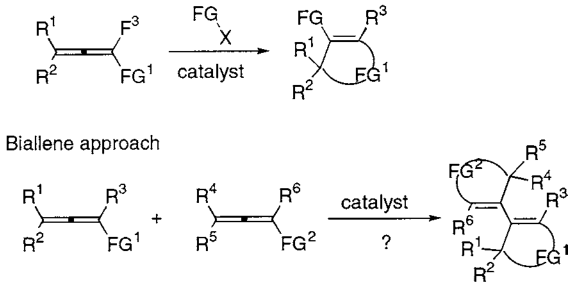
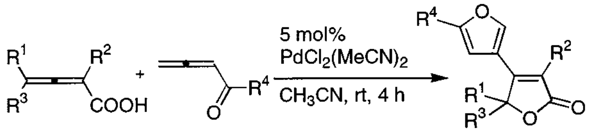
Scheme 1. Cyclization−Dimerization Reaction of Functionalized Allenes to Give Bicyclic Compounds



as carbon−heteroatom bonds. We developed several methods for the synthesis of butenolides with different substitution patterns, which is an area of current interest due to the potential biological activities of butenolides and their existence as a structural unit in many natural products, by using 2,3-allenoic acids.[12] Recently, we devoted ourselves to establishing a new area of oxidative cyclization−dimerization reactions between two different functionalized allenes to give interesting bicyclic compounds in a single step (Scheme 1). The formidable challenges are matching the reactivities of two allenes and regenerating the catalyst, which was reduced after reductive elimination.

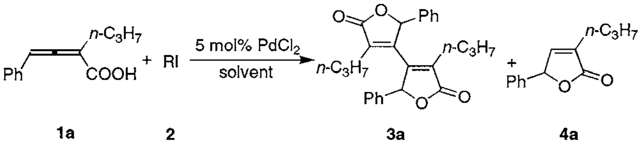
Using the idea in Scheme 1, we have successfully developed a Pd(CH_3CN)$_2$$Cl_2$-catalyzed one-step methodology for the efficient synthesis of 4-(3′-furanyl)butenolides via oxidative cyclization−dimerization reaction of 2,3-allenoic acids and 1,2-allenyl ketones (eq 1).[12d] In this transformation, the Pd(II)-catalyst species was regenerated by the sequential cyclometalation of 1,2-allenyl ketones and protonation. In this paper, we wish to disclose our recent studies on the synthesis of bibutenolides from oxidative cyclization−self-coupling reaction of 2,3-allenoic acids, in which a new system for regeneration of the palladium(II) species was observed.



(1)

The cyclization−self-coupling reaction of 4-phenyl-2-propyl-2,3-butadienoic acid (**1a**) was chosen to optimize the reaction conditions. Some representative results are listed in Table 1. From Table 1, we could find that without alkyl halide, only the cycloisomerization product **4a** was formed in 76% yield under the catalysis of $PdCl_2$ (Table 1, entry 1).

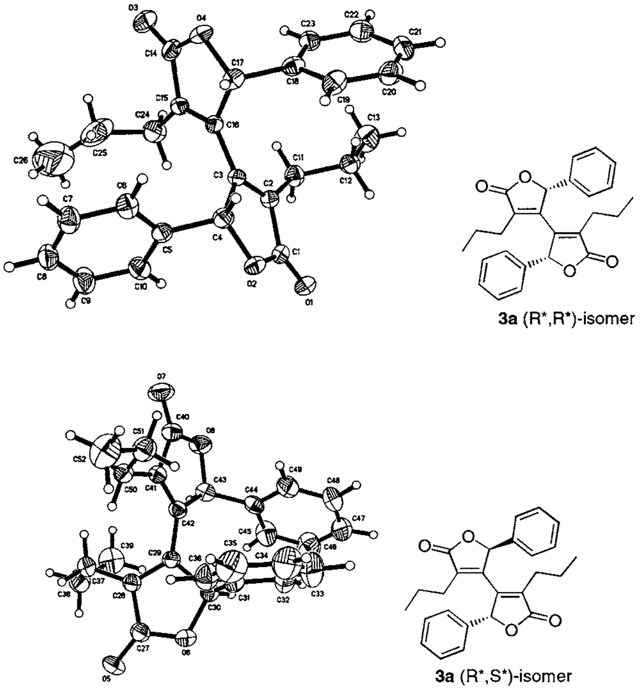
Table 1. Pd(II)-Catalyzed Oxidative Cyclization−Self-Coupling Reaction of 4-Phenyl-2-propyl-2,3-butadienoic Acid (**1a**)



entry	RI (equiv)	solvent	*T* (°C)	time (h)	**3a** (%)	**4a** (%)
1	none	DMA	80	4.5	0	76
2	C_3H_7I (5)	DMA	80	10	74	0
3	C_3H_7I (3)	DMA	80	6.5	62	0
4	CH_3I (5)	DMA	80	4	74	0
5	CH_3I (3)	DMA	80	6	60	20
6	C_3H_7I (5)	THF	reflux	46	trace	0
7	C_3H_7I (5)	MeCN	reflux	16	66	8
8	C_3H_7I (5)	EtOH	80	10	42	14
9	C_3H_7I (5)	CH_2Cl_2	reflux	39	0	trace

However, when 5 equiv of propyl iodide were added, only the oxidative cyclization−self-coupling product **3a** was produced in a 74% yield (Table 1, entry 2). The structure of product **3a** was confirmed by X-ray diffraction analysis (Scheme 2).[14]

Scheme 2. ORTEP Representation of Two Isomers of the Product **3a**


3a (R*,R*)-isomer

3a (R*,S*)-isomer

Iodomethane was also effective (Table 1, entries 4 and 5). The smaller the amount of the iodides, the lower the yields (Table 1, entries 2−5). Among the solvents tested, DMA is the best one. It may help the double oxypalladation and regeneration of the Pd(II)-catalyst. In CH_2Cl_2, CH_3CN, THF,

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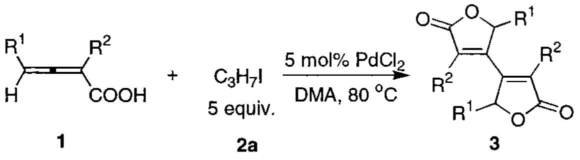
[12] For dimerization of 1,2-allenyl ketones, see: (a) Hashmi, A. S. K.; Choi, J.-H.; Bats, J. W. *J. Prakt. Chem.* **1999**, *341*, 342. (b) Hashmi, A. S. K.; Ruppert, T. L.; Knöfel, T.; Bats, J. W. *J. Org. Chem.* **1997**, *62*, 7295. (c) Hashmi, A. S. K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1581. (d) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285.

[13] For a recent highlight, see: Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590.

Table 2. Oxidative Dimeric Cyclization−Coupling Reaction of 2,3-Allenoic Acids



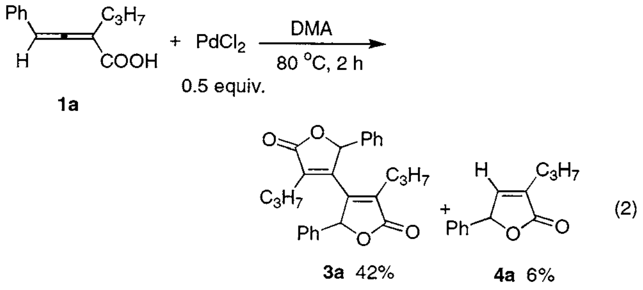
entry	substrate **1**		time (h)	product **3**	yield (%)	$(R^*,R^*)/R^*,S^*)$[a]
	R^1	R^2				
1	Ph	n-C_3H_7 (**1a**)	10	**3a**	74	1/1.87
2	Ph	CH_3 (**1b**)	4	**3b**	64	1/1.62 [b]
3	Ph	$PhCH_2$ (**1c**)	11.5	**3c**	75	1/1.53 [b]
4	α-Naphthyl	CH_3 (**1d**)	4	**3d**	71	1/1.28
5	α-Naphthyl	n-C_3H_7 (**1e**)	4.5	**3e**	64	1/1.43
6	CH_3	$PhCH_2$ (**1f**)	3.5	**3f**	72[c]	1.04/1

[a] Relative configurations of other products were tentatively assigned by comparing the chemical shifts of the γ-protons according to the results of **3a**. The ratio was determined by the ^1H NMR spectrum, unless otherwise stated. [b] Determined by isolation. [c] Cycloisomerization product was formed in a 21% yield.

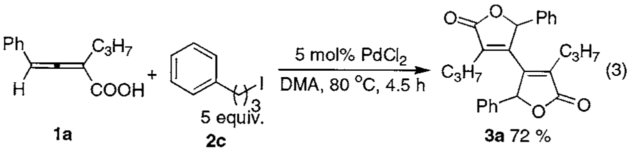
and ethanol, the yields were lower and cycloisomerization product **4** was formed (Table 1, entries 6−9). The best results were obtained when we used 5 mol % $PdCl_2$ and 5 equiv of propyl iodide in DMA leading to a 74% yield of product **3a** (Table 1, entry 2).[15]

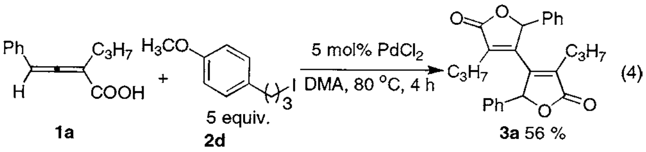
Some typical results are summarized in Table 2. It should be noted that (1) a new system for regeneration of the palladium species was established. (2) This is the first example of synthesis of bibutenolides by using the oxidative cyclization−self-coupling of 2,3-allenoic acids.[16] (3) Various 2,3-allenoic acids that bear alkyl, benzyl, aryl, or alkyl groups are successfully used to afford bibutenolides in decent yields.

To clarify the mechanism of this reaction, several control experiments were conducted. At first, the reaction of **1a** with 0.5 equiv of $PdCl_2$ occurred smoothly to afford **3a** in 42% together with 6% **4a** (eq 2).

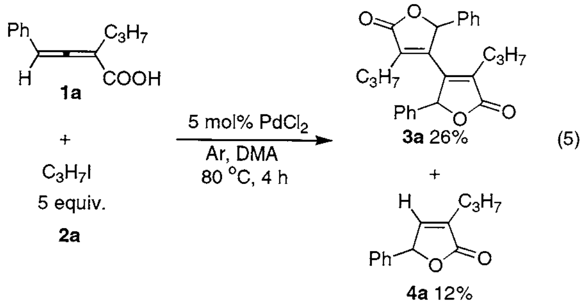


When we used two alkyl iodides with high boiling points (**2c** and **2d**), we found that the alkyl iodides were recovered in 94 or 95% yields, respectively (eqs 3 and 4).





Furthermore, under an argon atmosphere, the reaction occurred with difficulty to afford **3a** only in 26% yield along with **4a** in a 12% yield (eq 5),[15] which indicates that oxygen may participate in the catalytic cycle. In fact, it is observed that the reaction is much faster with bubbling of pure O_2.



On the basis of these experimental findings, it is proposed that the Pd(II) species first coordinated with the double bond

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(14) Crystal data for compound **3a**. (R^*,R^*)-Isomer: $C_{26}H_{26}O_4$, MW = 402.47, monoclinic, space group Cc, Mo Kα, final R indices [$I > 2\sigma(I)$], $R_1 = 0.0658$, $wR_2 = 0.1761$, $a = 12.2918(14)$ Å, $b = 14.5009(17)$ Å, $c = 12.6441(15)$ Å, $\alpha = 90°$, $\beta = 96.671(2)°$, $\gamma = 90°$, $V = 2238.5(5)$ Å^3, $T = 293$ K, $Z = 4$, reflections collected/unique 5798/3431 ($R_{int} = 0.0554$), no observation [$I > 2\sigma(I)$] 2299, parameters 281. (R^*,S^*)-Isomer: $C_{26}H_{26}O_4$, MW = 402.47, orthorhombic, space group $P2$ (1) 2 (1) 2 (1), Mo Kα, final R indices [$I > 2\sigma(I)$], $R_1 = 0.0433$, $wR_2 = 0.0774$, $a = 17.3667(12)$ Å, $b = 29.873(2)$ Å, $c = 8.5210(6)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 4420.6(5)$ Å^3, $T = 293$ K, $Z = 8$, reflections collected/unique 26942/10052 ($R_{int} = 0.0484$), no observation [$I > 2\sigma(I)$] 6027, parameters 750.

(15) Typical procedure: A solution of 4-phenyl-2-propyl-2,3-butadienoic acids (**1a**) (50 mg, 0.248 mmol), propyl iodide (**2a**) (0.13 mL, 224 mg, 1.32 mmol), and $PdCl_2$ (2 mg, 0.011 mmol) in DMA (N,N-dimethylacetamide, 2 mL) was stirred at 80 °C for 10 h. Then, the mixture was diluted with ether (50 mL), washed with water (2 × 10 mL), and dried by $MgSO_4$. After evaporation, the residues were purified via flash chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as the eluent to afford 37 mg (74%) of **3a** (R^*,R^*:R^*,S^* = 1:1.87). The two isomers could be separated via flash chromatography on silica gel with CH_2Cl_2 as the eluent. Mp: (R^*,R^*)-isomer, 143−145 °C; (R^*,S^*)-isomer, 186−187 °C (ethyl acetate and petroleum ether).

in the allene moiety to form a coordination complex. Subsequent double cyclic oxypalladation and reductive−elimination yielded the bibutenolides **3** and the palladium(0) species. Then, the Pd(0) species was oxidized by the oxygen in the presence of alkyl iodide to regenerate the Pd(II) species.

In conclusion, we developed an oxidative dimeric cyclization−coupling reaction of 2,3-allenoic acids, which provides an efficient route to nonreadily available bibutenolides. A new system ($PdCl_2$/RI/air) for regeneration of palladium(II) species was also established. Further studies into the scope, mechanism, and synthetic applications of this reaction are being carried out in our laboratory.

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Supporting Information Available: Typical experimental procedure and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For reports on the synthesis of bibutenolide, see: (a) Padwa, A.; Kinder, F. R. *J. Org. Chem.* **1993**, *58*, 21. (b) Kinder, F. R.; Padwa, A. *Tetrahedron Lett.* **1990**, 6835.