Palladium-Catalyzed Regio- and Stereoselective Cyclized Coupling of Lithium Alkynoates with Allyl Halides

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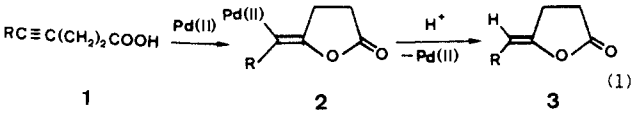
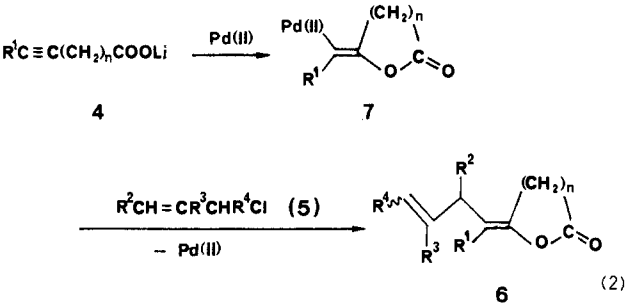
Stereoselective synthesis of olefins utilizing alkenylmetals as key intermediates has received considerable attention in the past decade.[1] Hydrometalation[2] and carbometalation[3] are effective for producing alkenylmetals of defined stereochemistry from alkynes. We have reported stereoselective synthesis of γ-alkylidenebutyrolactones **3** from 4-alkynoic acids **1** by palladium-catalyzed intramolecular cyclization.[4-6] Regio- and stereoselective formation of alkenylpalladium intermediate **2** is postulated as the key step of the above lactone formation (eq 1). Trapping of the



1 2 3 (1)

organopalladium intermediate **2** with electrophiles is expected to afford γ-butyrolactones bearing stereodefined alkylidene group on γ position. We report herein (a) that the alkenylpalladium intermediate prepared from lithium 4-pentynoate by the action of $PdCl_2(MeCN)_2$ couples with allyl or vinyl halides to afford allyl- or vinyl-substituted 4-buten-4-olides stereoselectively[7,8] and (b) that lithium 5-hexynoate gives substituted 5-hexen-5-olides by the same sequence of reactions. Preparation of 3-allyl-3-decen-4-olide from lithium 3-decynoate is added last.

In a typical procedure, lithium 4-pentynoate (**4**, R^1 = H, n = 2; 2 mmol), allyl chloride (**5**, R^2-R^4 = H; 40 mmol, 20 equiv), and $PdCl_2(MeCN)_2$ (0.1 mmol) were dissolved in 5 mL of THF and the whole was stirred for 5 h at room temperature. Concentration of the reaction mixture and column chromatography of the residue afforded (*E*)-4,7-octadien-4-olide (**6**, R^1-R^4 = H) in 94% yield[9,10] (eq 2).



4 7 6 (2)

Stereoselective formation of the *Z* isomer (**3**, R = CH_2=$CHCH_2$)[11,12] from 7-octen-4-ynoic acid by palladium-catalyzed cyclization supports the above described reaction mechanism. Regioselective attack at γ position of allyl chlorides was clarified by the reactions with various types of allyl chlorides. Results are summarized in Table I.

Though yield of the allylated product diminished markedly with the reduced amount of allyl chloride, ultrasonic irradiation improved the results (Table I). Bromoethene could react with the organopalladium intermediate to give (*E*)-4,6-heptadien-4-olide exclusively.[13]

Lithium 5-alkynoates (**4**, n = 3) gave δ-alkylidenevalerolactones (**6**, n = 3) in good yields by the same sequence of reactions as shown in Table I, and lithium 6-heptynoate also afforded the allylated product **6** (n = 4, R^1-R^4 = H, in 34%).

In contrast to the above described Exo-Dig cyclization, palladium-catalyzed reaction of lithium 3-octynoate (**8**) with allyl

Table I. Alkylidenelactones **6** from Lithium Alkynoates **4** and Allyl Halides **5** under Catalytic Action of $PdCl_2(MeCN)_2$

	lithium alkynoate **4**		allyl halide **5**			product **6** yield, %[a]	
entry	n	R^1	R^2	R^3	R^4		
1	2	H	H	H	H	94[b]	(80)
2	2	n-C_6H_{13}	H	H	H	85	(73)
3	2	Ph	H	H	H	73	(71)
4	2	Me_3Si	H	H	H	76	(64)
5	2	H	Me	H	H	82	(59)
6	2	H	H	Me	H	70	(63)
7	2	H	H	H	Me	78[c]	(66)[c]
8	2	H	H	H	Et	63[c]	(47)[c]
9	3	H	H	H	H	81	(73)
10	3	n-C_6H_{13}	H	H	H	85	(70)
11	3	Ph	H	H	H	79	(66)
12	3	H	Me	H	H	71	(58)
13	3	H	H	Me	H	76	(61)
14	3	H	H	H	Me	74[c]	(58)[c]
15	4	H	H	H	H	34	
16	2	H	(H_2C=CHBr)			65[d]	
17	2	H	(H_2C=CMeBr)			37[e]	
18	3	H	(H_2C=CHBr)			68[f]	

[a] Obtained by standard procedure, **4**:**5**:$PdCl_2(MeCN)_2$ = 1:20:0.05, stirring at room temperature for 5 h. Yield shown in parentheses was obtained by the use of 1.5-2.5 equiv of **5** under ultrasound irradiation. [b] Use of 5 and 1.5 equiv of **5** diminished the yields to 54% and 26%, respectively. [c] About 1:1 mixture of two stereoisomers. [d] Product is (*E*)-4,6-heptadien-4-olide. [e] (*E*)-6-Methyl-4,6-heptadien-4-olide was obtained. [f] (*E*)-5,7-Octadien-5-olide.

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(4) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323.

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(6) Stereoselective γ-alkylidenebutyrolactone synthesis utilizing Si as key element was reported: Luo, F.-T.; Negishi, E. *J. Org. Chem.* **1983**, *48*, 5144.

(7) Palladium-catalyzed reaction of 4-pentynoic acid with allyl chloride afforded 4-penten-4-olide as the sole product and addition of 2,2-dimethyloxirane as proton scavenger did not give any coupling product.

(8) Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655.

(9) ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.63-2.93 (6 H, m), 5.00-5.18 (2 H, m), 5.28 (1 H, tt, J = 2.2, 7.9 Hz), 5.87 (1 H, m).

(10) Sodium and potassium 4-pentynoate, in place of the lithium salt, afforded the same product in 80% and 78%, respectively. On the other hand, tetrabutylammonium 4-pentynoate gave allyl (*Z*)-4-chloro-4,7-octadienoate exclusively.

(11) ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.54-2.74 (2 H, m), 2.76-2.97 (4 H, m), 4.64 (1 H, tt, J = 1.6, 7.4 Hz), 4.95-5.25 (2 H, m), 5.83 (1 H, m).

(12) Comparison of the observed olefinic proton NMR of the *E* isomer and that of the Z isomer with those of calculated ones[13] shows the validity of the structural assignment.

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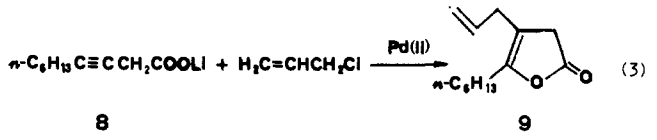
chloride afforded 3-allyl-3-decen-4-olide (**9**) in 85% yield by the cyclization of Endo-Dig manner (eq 3). Lithium 3-butynoate, however, did not give any allylated product.



8 **9**

The above described unsaturated lactones are useful intermediates for organic synthesis. Alkaline hydrolysis of (*E*)-4,7-octadien-4-olide gave 4-oxo-7-octenoic acid in 94% yield and other lactones shown in Table I afforded the corresponding keto acids in excellent yields. Diketones and heterocyclic compounds can be derived from the above lactones.

In summary we have shown unprecedented regio- and stereoselective synthesis of unsaturated lactones from lithium alkynoates by intramolecular oxypalladation affording alkenylpalladiums which couple with allyl or vinyl chloride stereospecifically.

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Steric Models for Stereoselectivity of Nitrile Oxide Cycloadditions to Chiral Alkenes

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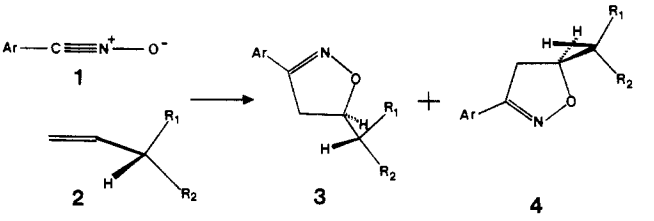
We have studied the cycloadditions of nitrile oxides to chiral alkenes, where the groups attached to the stereogenic center differ only in size. These cycloadditions occur preferentially on the face of the alkene that is more sterically shielded in the ground state. We propose a new transition-state model to account for stereoselectivities in this and related electrophilic cycloadditions and additions.[1]

The reactions of *p*-nitrobenzonitrile oxide, **1**, with various 3-substituted-1-butenes, **2**, give mixtures of diastereomers **3** and **4**.

Table I. Ratios of Isoxazoline Diastereomers from *p*-Nitrobenzonitrile Oxide Cycloadditions (25 °C, CH_2Cl_2)



3-R-1-butene		total	3:4	
R_1	R_2	yield (%)	exptl (±3%)	calcd[c]
a. Et	Me	72	50:50	50:50[d]
b. Ph	Me	70	59:41[a]	53:47[d]
c. *i*-Pr	Me	50	65:35[b]	72:28
d. $C(OMe)Me_2$	Me	93	80:20[a]	87:13[e]
e. *t*-Bu	Me	82	77:23[a]	97:3
f. Me	OMe	63	64:36[a]	68:32
g. Me	OPh-*p*-MeO	89	66:34[b]	
h. Me	OPh	93	60:40[b]	
i. Me	OPh-*p*-NO_2	91	60:40[b]	
j. *t*-Bu	OMe	64	>97:3[a]	96:4

[a] Structural assignments by X-ray crystallographic analysis carried out by Frank R. Fronczek at Louisiana State University or Jaime Abola and J. Mandel at the University of Pittsburgh. [b] Structural assignment based on vicinal coupling constants in the 300-MHz NMR spectrum. [c] From MM2 model calculations.[4] Ratios are obtained from Boltzmann distribution over the six staggered transition-state conformations. [d] Conformations with one group anti and one inside are essentially the same in energy as conformations with one group anti and one outside. [e] No lone pairs were included on the ether oxygen. With lone pairs included, a 96:4 ratio is predicted.

Product ratios were determined by NMR spectroscopy or HPLC analysis. Diastereomeric products were separated by column chromatography, and the structures were proven by X-ray crystallography or by NMR spectroscopy. Table I summarizes these and two previously reported results, entries f and j.[1i] These reactions were also studied by an MM2 transition-state model,[2,3] the predictions of which are given in the last column of Table I.

In every case, the major product is that which would arise from attack of the nitrile oxide on the more hindered face of the preferred conformation of the isolated alkene,[4] and stereoselectivity increases as the size of R increases. We believe that the major product arises from the staggered[5] transition state, A, which has the largest group anti and the medium-sized group inside. The minor product arises from B. This model also rationalizes the stereoselectivities of nitrile oxide cycloadditions of allylic ethers, reported earlier, when M = alkoxy and L = alkyl.[1g-i] Entries f–i in Table I involve different alkoxy groups but give essentially identical product ratios. Previous studies by Jäger showed that similar stereoselectivities are observed for reactions of allylic ethers in which OR = OMe, OTHP, OAc, or $OSiR_3$.[1h,i] Thus, the "inside alkoxy effect", described earlier,[1i] reinforces, rather than reverses, the purely steric effect which we have now found to favor A. An allylic oxygen avoids the anti position in order to minimize electron

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(2) The positions of the five atoms involved in isoxazoline formation were fixed at ab initio transition-state distances (Brown, F. K.; Houk, K. N., in press). The normal bond angles of groups attached to ethylene carbons were set at transition-state values, but these angles were optimized. Both ethylenic carbons were assigned as sp^3 carbons. Force constants for bending of bonds to H or C attached to C_5 were set at 0.15 and 0.25, respectively. All other parameters are normal MM2 values.[3]

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