Palladium(II)-Catalyzed Asymmetric Cyclization of (*Z*)-4′-Acetoxy-2′-butenyl 2-Alkynoates. Role of Nitrogen-Containing Ligands in Palladium(II)-Mediated Reactions

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$Pd(OAc)_2$ combined with nitrogen-containing ligands (e.g., 2,2′-bipyridine) catalyzed the cyclization of (*Z*)-4′-acetoxy-2′-butenyl 2-alkynoates (**1**) in acetic acid to afford the α-(*Z*)-acetoxyalkylidene-*β*-vinyl-*γ*-butyrolactones (**2**) with high efficiency and high stereoselectivity. The nitrogen-containing ligands, like halides, served to favor *β*-heteroatom elimination over *β*-hydride elimination in Pd(II)-mediated reactions. The generality of this ligand effect was probed in both stoichiometric and catalytic reactions. With these results in hand, the catalytic asymmetric protocol was achieved with high enantioselectivity (up to 92% ee) when pymox (pyridyl monooxazoline) or bisoxazoline was used. The absolute configuration of the products and the synthetic utility of this asymmetric transformation were established through the convenient synthesis of (3*S*)-(+)-A-factor.

Introduction

Carbon−carbon bond formation reaction is fundamentally important in organic chemistry. Recent years witnessed tremendous growth in a number of reactions and reagents for carbon−carbon bond formation. Among them, carbocyclizations of alkenes and alkynes catalyzed by transition metals and their complexes are emerging as one of the most important and useful reactions.[1] The method offers the unique tool to construct a variety of synthetically important carbo- and heterocycles with high efficiency not normally accessible with traditional methods. Due to the existence of the wealth of biologically active and naturally occurring chiral cyclic compounds, development of catalytic asymmetric annulation protocols is of great interest in organic synthesis.[2] However, highly enantioselective transition metal-catalyzed cyclizations are rare in contrast with the extensively studied racemic variants.[3] A powerful and well-studied reaction is the transition metal-catalyzed cycloisomerization of 1,6-enynes.[4] The early contribution of Pd-catalyzed asymmetric cyclization with chiral carboxylic acids gave fairly low induction,[5] which was improved moderately by the use of chiral amide-diphosphine ligands (about 50% ee).[6] When a derivative of *trans*-coordinating (*S*,*S*)-(*R*,*R*)-TRAP ligand was utilized for cyclization of a series of substituted sulfonamido enynes, good to excellent (95% ee, one example) enantioselectivity was obtained.[7] More recently, Rh−diphosphine complexes catalyzed cycloisomerization of enyne ethers and amines generated the five-membered heterocycles with high enantioselectivity.[8,9] For other types of enyne cyclizations, Ti,[10] Co,[11] Rh,[12] and Ir[13] catalyzed cyclocarbonylation of enynes were reported.

A Pd(II)-catalyzed cyclization of 4′-X (X = leaving groups)-2′-butenyl 2-alkynoates has been developed for the synthesis of *γ*-butyrolactones in this group.[14] Different from the known methods for the cyclization of enynes,[15] the current system employs halide ions as

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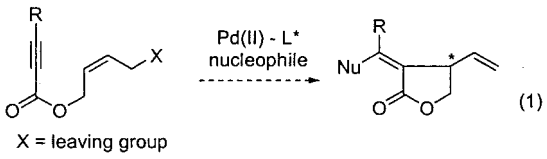
nuclephile to attack the Pd(II)-coordinated alkynes as the initial step and β-heteroatom elimination as the final step. It should be noted here that halide ions acts not only as a nucleophile but also as a ligand which plays the key role in inhibiting the usual β-hydride elimination and promoting the β-heteroatom elimination, making the catalytic cycle of the Pd(II) species possible.[16,17] Thus, halide ion is necessary in the halopalladation initiated reaction as a ligand.

Our long-standing goal is to develop the enantioselective process of this Pd(II)-catalyzed reaction. Compared to the impressive development of the asymmetric reactions with chiral Pd(0) catalyst,[18] asymmetric reactions with Pd(II) species have received much less attention.[19,20] Moreover, most of the Pd(II)-catalyzed asymmetric reactions quench the carbon−palladium bond using excess amounts of oxidants to recycle the Pd(II) species from Pd(0) species produced by β-hydride abstraction,[20] while our reaction system employs β-heteroatom elimination to regenerate the Pd(II) species instead of using an oxidant.

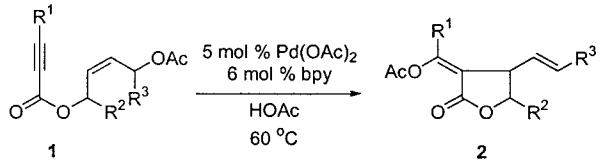
However, much effort devoted toward realizing the halopalladation-initiated asymmetric cyclization failed.[21] The reaction rate decreased dramatically in the presence of the commonly used chiral nitrogen or phosphine ligands, and no chiral induction was observed. These results indicated that the extra chiral ligand drastically altered the reactivity of the catalyst; hence, it affected the reaction significantly. On the other hand, the inevitable disturbance of the excess of requisite halide ions to the coordination of chiral ligands with palladium species might also contribute to the difficulty of developing the catalytic asymmetric cyclizations.

To solve the problems, it seems that the halide ions must be excluded from the reaction. A new type of reaction should be developed where a weakly coordinated nucleophile will replace halide ions to act as the nucleophile (eq 1).



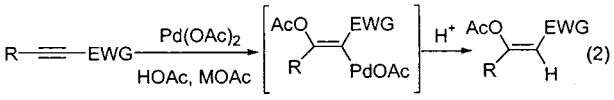
Hydroacetoxylation of alkynoates was developed in early work where acetate attacked the triple bond under palladium catalyst via *trans*-acetoxypalladation followed by protonolysis (eq 2),[22] which implied that acetate might be a good nucleophile to replace halide ion in the Pd(II)-catalyzed cyclization of enyne esters. From our previous work, however, it was shown that acetate as the ligand, unlike halides, could not inhibit the usual β-hydride elimination.[16] Thus, we would have to find another ligand to play this role of halides. Herein we report a highly efficient Pd(II)-catalyzed cyclization of enyne esters initiated by acetoxypalladation as well as its asymmetric version employing nitrogen-containing ligands.[23]

Table 1. Pd(II)-Catalyzed Cyclization of (*Z*)-4′-Acetoxy-2′-butenyl 2-Alkynoates (1)[a]



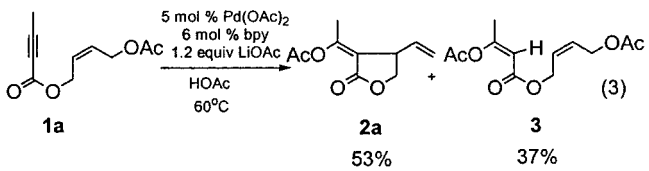
entry	**1**	R^1	R^2	R^2	time (h)	**2**	yield (%)[b,c]
1	**1a**	CH_3	H	H	10	**2a**	87
2	**1b**	*n*-Pr	H	H	10.5	**2b**	90
3	**1c**	Ph	H	H	34	**2c**	90
4	**1d**	*i*-C_7H_{15}	H	H	18	**2d**	83
5	**1e**	CH_3OCH_2	H	H	10.5	**2e**	83
6	**1f**	CH_3	H	Ph	24	**2f**	76
7	**1g**	CH_3	*i*-Pr	H	12	**2g**	89[d]
8	**1h**	CH_3	*n*-C_5H_{11}	H	11	**2h**	92[d]

[a] Reaction conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (0.027 mmol), and bpy (0.032 mmol) in HOAc (2.0 mL) at 60 °C. [b] Isolated yield. [c] *Z*:*E* > 95:5. [d] β,γ-Relative stereochemistry is cis, determined by NOE experiments.



Results and Discussion

Developing of Reaction Conditions and Synthetic Scope. We initially examined the reaction of (*Z*)-4′-acetoxy-2′-butenyl 2-butynoate (**1a**) in the presence of LiOAc with HOAc as solvent under different catalyst systems. The reaction of **1a** catalyzed by $Pd(OAc)_2$ with no extra ligand afforded only the hydroacetoxylation product **3** in 82% yield. Other catalyst systems such as $Pd(OAc)_2/PPh_3$, $Pd(OAc)_2/AsPh_3$, $Pd(OAc)_2$/PhSMe, $PdCl_2(PPh_3)_2$, and $Pd_2(dba)_3{\cdot}CHCl_3$ as well as common solvents such as DMF, CH_3CN, THF, benzene, and dioxane were also tested, but no desired cyclization product was produced. Finally, subjecting **1a** to 5 mol % $Pd(OAc)_2$, 6 mol % bpy (2,2′-bipyridine), and 1.2 equiv of LiOAc at 60 °C led to a 53% yield of the cyclization product α-(*Z*)-acetoxymethylidene-β-vinyl-γ-butyrolactone (**2a**) and a 37% yield of **3** (eq 3). Further experiments revealed that LiOAc could be omitted, and the yield was raised to 87% without the detection of **3** (Table 1, entry 1). The stereochemistry of the exocyclic double bond in **2a** was assigned (*Z*)-configuration based on ^1H NMR and NOESY analysis.



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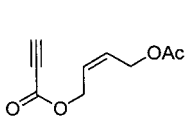
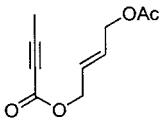
(21) Chiral ligands such as bisoxazolines, (*S*)-MOP, [(3,2,10-η^3-pinene)$PdCl]_2$, and BINOL have been tested.

Other substituted alkynyl esters, e.g., phenyl, *n*-alkyl, or methoxymethyl, reacted smoothly to furnish the γ-butyrolactones in high yields (Table 1, entries 2−5). The substrate containing the 4′-phenyl group (**1f**) produced the cyclization product in 76% yield (Table 1, entry 6). The enyne esters possessing the 1′-substitent, e.g., *i*-Pr or *n*-C_5H_{11}, afforded the β,γ-*cis*-disubstituted γ-butyrolactones in high yields (Table 1, entries 7 and 8).[24] It is noteworthy that all the reactions are stereoselective to afford the γ-butyrolactones with the exocyclic double bond in (*Z*)-configuration.

However, attempts to cyclize the (*Z*)-4′-acetoxy-2′-butenyl propiolate (**1i**) failed, which was in accord with $Pd(OAc)_2$-catalyzed hydroacetoxylation of 2-alkynoates[22a] and might be attributed to the possible formation of (alkynyl)palladium species.[25] Additionally, the reaction of (*E*)-4′-acetoxy-2′-butenyl 2-butynoate (**1j**)[26] was in-



1i

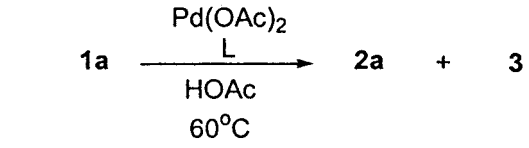


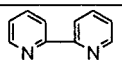
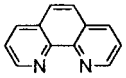
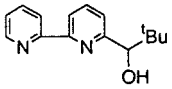
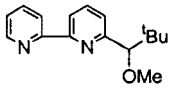
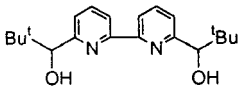
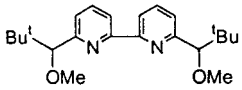
1j

effective under the same reaction condition, and the starting material remained intact after 24 h even at elevated temperature. The stronger coordinating ability of (*Z*)-olefins compared to (*E*)-olefins may account for the discrepancy.[27]

Influence of Bipyridyl/Pyridyl Substituent. As shown above, bpy ligand is crucial for the success of the cycloisomerization of the enyne esters. Employment of 1,10-phenanthroline (phen) as the ligand gave similar result with that of bpy (Table 2, entries 1 and 2). For further insight into the scope of the reaction, we also examined the influence of pyridyl/bipyridyl substituent with different electronic or steric character on the model reaction of **1a** in the presence of 5 mol % $Pd(OAc)_2$ in HOAc at 60 °C (Table 2). Generally, increasing steric hindrance adjacent to the nitrogen atom of the bipyridine decreases its coordinating ability to palladium,[28] and its effect on the reaction is significant. Employment of the 6-substituted bipyridine as the ligands led to a lower yield of **2a** than bpy or phen did and gave predominately **3** (Table 2, entries 3 and 4). While the use of the 6,6′-disubstituted bipyridine as the ligands totally suppressed the cyclization of **1a** and only hydroacetoxylation occurred (Table 2, entries 5 and 6). These results indicated that excessive steric crowding of the coordinating plane

Table 2. Effect of Bipyridyl/Pyridyl Substituent on the Cyclization[a]



		Yield (%)[b]	
entry	L	**2a**	**3**
1		87	
2		86	
3		24	41
4		26	43
5			80
6			81
7[c]		36	30
8[c]		13	55
9[c]			75
10[c]			70
11[c]			77

[a] Reaction conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (0.027 mmol), and L (0.032 mmol) in HOAc (2.0 mL) at 60 °C. [b] Isolated yield. [c] L/Pd = 2/1.

around palladium was detrimental to the efficiency of cyclization. Pyridine could also serve as the ligand in the reaction to furnish a 36% yield of **2a** as well as a 30% yield of **3** (Table 2, entry 7). The effect of the electronic and steric factor of the pyridyl substituent on the reaction was also evident. For example, employment of the electron-donating group substituted 2-isopropyloxy pyridine as the ligand afforded a 13% yield of **2a** in addition to a 55% yield of **3** (Table 2, entry 8), while utilizing 2-methyl or 2-chloro pyridine as the ligands, **3** was isolated as the sole product in 75% and 70% yield, respectively (Table 2, entries 9 and 10). Only **3** was obtained in 77% yield with DMAP as the ligand (Table 2, entry 11), which might be due to the protonation of

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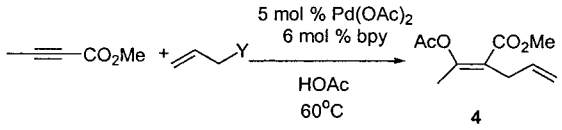
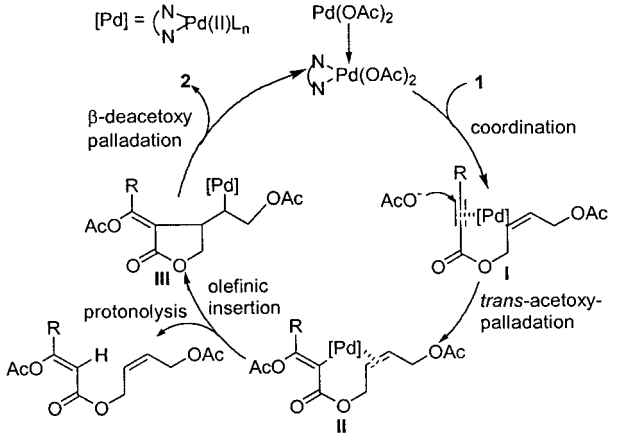
Table 3. Intermolecular Coupling of Methyl 2-Butynoate with Allyl Compounds[a]



entry	Y	**4**, yield (%)[b]
1	OAc	57 (55)[c]
2	Cl	9[d]
3	OEt	<2[d]
4	OH	<2[d]

[a] Reaction conditions: methyl 2-butynoate (1 mmol), allyl compounds (4 mmol), $Pd(OAc)_2$ (0.049 mmol), and bpy (0.058 mmol) in HOAc (5.0 mL) at 60 °C. [b] ^1H NMR yield with CH_2Br_2 as internal standard. [c] Isolated yield in parentheses. [d] Most of the starting materials remained intact.

Scheme 1



the pyridyl nitrogen in acetic acid making its coordination ability decreased.

Apparently, there existed competency between the cyclization and hydroacetoxylation in the reaction. The current results indicated that the strong coordinating ability of bipyridine/pyridine ligand with palladium was beneficial to the cycloisomerization of the enyne esters.

Effect of Leaving Groups. In the above reactions, acetate played the roles as a nucleophile as well as a leaving group. We have demonstrated previously in the Pd(II)-catalyzed cyclization of 4′-heteroatom-2′-butenyl 2-alkynoates initiated by halopalladation that the leaving ability of β-elimination follows the order $Cl^- > OAc > OMe > OH \sim H$ in HOAc.[29] To investigate the possibility of other leaving groups in the enyne couplings initiated by acetoxypalladation, we examined the reaction of methyl 2-butynoate and allyl compounds in the presence of 5 mol % $Pd(OAc)_2$, 6 mol % bpy in HOAc at 60 °C (Table 3). Similar to the intramolecular cylizations, the intermolecular coupling with allyl acetate gave a 57% yield of the coupling product **4** (Table 3, entry 1). However, with allyl chloride as a partner only 9% of **4** was obtained according to the NMR analysis (Table 3, entry 2). It was proposed that the chloride dissociated at the beginning of the reaction would replace the acetate around the palladium coordination sphere, and then the chloride ion coordinated palladium complex deactivated the coupling. Additionally, only trace amounts of **4** were observed with OEt or OH as the leaving group, and most of the starting materials remained intact (Table 3, entries 3 and 4). Thus, acetate is still the most appropriate leaving group of those tested.

Mechanism. The mechanism for this transformation is believed to be analogous to that of the halopalladation initiated cyclization of enyne esters.[14b] This will involve insertion of the pendant olefin into the vinyl-palladium intermediate **II** formed by *trans*-acetoxypalladation of the carbon−carbon triple bond, followed by β-deacetoxy-palladation to give the γ-butyrolactone and the catalytically active Pd(II) species (Scheme 1). Additionally, the intermediate **II** may also be intercepted by acid to produce the hydroacetoxylation product. Which route (cyclization or protonolysis) predominates depends on the kinetics of the reaction. As shown above, no detectable **3** was formed with bpy as ligand (Table 1, entry1), which means that the intermediate **II** is stable enough in acetic acid and the rate of intramolecular olefinic insertion is much faster than that of protonolysis.

The stereospecific (*Z*)-configuration of the exocyclic double bond in the γ-butyrolactones supports the mechanism of the *trans*-acetoxypalladation of alkynes. This point is different from the halopalladation of alkynes where *cis*-halopalladation is manifested especially in the event of low concentration of halide ions.[14b,30]

Role of Nitrogen-Containing Ligands. β-Hydride elimination usually occurs with an alkyl palladium species with a β-hydrogen atom to carbon−palladium bond (Heck-type reaction). Our previous work has shown that excess of halide ions can block the usual β-hydride elimination.[16,17] In the above catalytic cycle, the normal β-hydride elimination is also inhibited and β-acetoxy elimination takes place instead for the alkylpalladium intermediate **III** (Scheme 1). Evidently, nitrogen-containing ligands play a key role here.

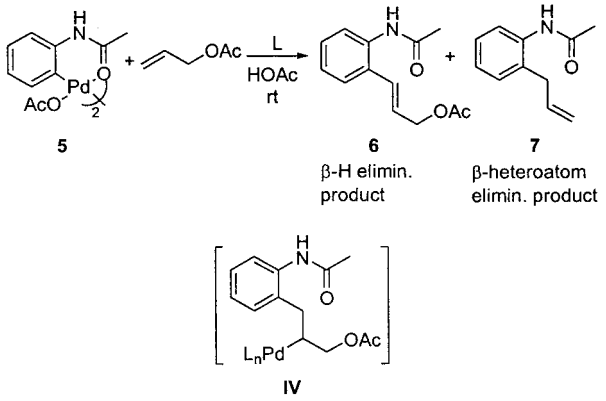
To probe the role of nitrogen-containing ligands, we investigated the stoichiometric reaction of the palladium complex **5** with allyl acetate by providing different coordinating ligands in HOAc at room temperature (Table 4). We postulate an intermediate **IV** formed by intermolecular olefinic insertion into the aromatic carbon−palladium bond. From the intermediate, β-hydride elimination leads to **6**, while β-acetoxy elimination gives **7**. As shown in Table 4, reaction with no extra ligand gave **6** as the only product in 66% yield together with precipitated palladium black (Table 4, entry 1), while reaction in the presence of Cl^- afforded **7** in 75% yield (Table 4, entry 2). Significantly, all the reactions with pyridine, bpy, or phen as the ligands also produced exclusively **7** in 69%, 81%, and 77% yield, respectively (Table 4, entries 3−5).

The generality of this ligand effect was further examined in a catalytic process incorporating Pd(II)-mediated transmetalation.[18d] The reaction of phenylmercuric acetate with allyl acetate in the presence of 5 mol % $Pd(OAc)_2$ in HOAc was conducted with different ligands.[17] As shown in Table 5, reaction with no extra ligand gave,

(29) Zhu, G.; Lu, X. *Organometallics* **1995**, *14*, 4899.

(30) (a) Dietl, H.; Reinheimer, H.; Moffat, J.; Maitlis, P. M. *J. Am. Chem. Soc.* **1970**, *92*, 2276. (b) Mann, B. E.; Bailey, P. M.; Maitlis, P. M. *J. Am. Chem. Soc.* **1975**, *97*, 1275. (c) Maitlis, P. M. *Acc. Chem. Res.* **1976**, *9*, 93. (d) Kaneda, K.; Uchiyama, T.; Kobayashi, H.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *Tetrahedron Lett.* **1977**, *23*, 2008. (e) Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55. (f) Imanaka, T.; Kimura, T.; Kaneda, K.; Teranishi, S. *J. Mol. Catal.* **1980**, *9*, 103. (g) Bäckvall, J. E.; Nilsson, Y. I. M.; Gatti, R. G. P. *Organometallics* **1995**, *14*, 4242.

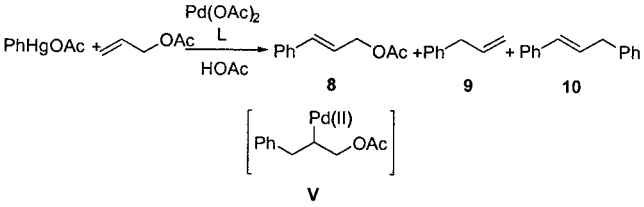
Table 4. Stoichiometric Reactions of Palladium Complex (5) with Allyl Acetate[a]



entry	L	L/Pd	observation	yield (%)[b] 6	7
1	none		Pd↓	66	
2	Cl^{-}[c]	10/1	clear solution		75
3	py	2/1	clear solution		69
4	bpy	1/1	clear solution		81
5	phen	1/1	clear solution		77

[a] Reaction conditions: complex **5** (0.13 mmol) and allyl acetate (1.3 mmol) in HOAc (2.0 mL) at room temperature. [b] Isolated yield based on Pd. [c] LiCl.

Table 5. Catalytic Reactions of Phenylpalladium Complexes with Allyl Acetate through Transmetalation[a]



entry	L	observation	**8:9:10**[b]	yield (%)[c]
1	none	Pd↓	-	3[d]
2	Cl^{-}[e]	clear solution	trace:5:2	76
3[f]	bpy	clear solution	trace:6:1	65

[a] Reaction conditions: PhHgOAc (3 mmol), allyl acetate (9 mmol), and $Pd(OAc)_2$ (5 mol %) in HOAc (15 mL) at room temperature. [b] ^{1}H NMR ratio. [c] Isolated yield. [d] Only **8** was obtained. [e] LiCl/Pd = 200/1. [f] 80 °C and bpy/Pd = 1/1.

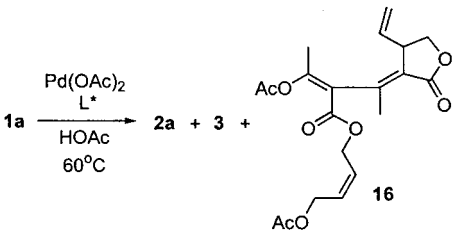
via β-hydride elimination of the intermediate **V**, cinnamyl acetate (**8**) in 3% yield (60% based on Pd) (Table 5, entry 1). Reactions with bpy and excess amounts of Cl^- as the ligands gave very similar results where allylbenzene (**9**) and 1,3-diphenylpropene (**10**) were isolated as the main products (Table 5, entries 2 and 3). Allybenzene was produced via β-acetoxy elimination from the intermediate **V**. Presumably, 1,3-diphenylpropene was formed by the consecutive reaction of allylbenzene with phenylmercuric acetate in the presence of Pd(II) complexes while the Hg(II) salts formed through transmetalation served as reoxidant.[31]

The above two experiments strongly demonstrate that the nitrogen-containing ligands, like halides, serve to favor β-heteroatom elimination over β-hydride elimination.

Henry et al. ever reported that when adding pyridine to the $PdCl_2$−$CuCl_2$ Wacker oxidation system chlorohydrine was formed effectively at [Cl^-] as low as 0.2 M. While at this low [Cl^-] in the absence of pyridine, $PdCl_4^-$ gave only acetaldehyde at any [$CuCl_2$].[32] The work implied that there existed some relationship between the catalysts with pyridine or chloride as ligand.[33]

(31) Heck, F. R. *J. Am. Chem. Soc.* **1968**, *90*, 5526.

Table 6. Asymmetric Cyclization of 1a Employing Oxazoline Ligands[a]



entry	L*	T (°C)	yield (%)[b] **2a**	**3**	**16**	ee % of **2a**[c]
1[d]	(*S*,*S*)-**11a**	60		24		
2	(*S*,*S*)-**11b**	60	29	34	18	0
3[e]	(*R*,*R*)-**11c**	60	36		40	91
4[f]	(*R*,*R*)-**11c**	60	50		33	88
5	(*R*,*R*)-**11c**	60	67			89
6[g]	(*R*,*R*)-**11c**	60	78			92
7[e]	(*R*,*R*)-**12**	60	15	44		68
8	(*S*)-**13a**	60	82			34[h]
9	(*R*)-**13b**	60	88			81
10	(*R*)-**13b**	40	89			83
11	**13c**	60	82			64[h]

[a] Unless otherwise noted, the reaction was carried out under the following conditions. **1a** (0.5 mmol), $Pd(OAc)_2$ (0.027 mmol), and L* (0.054 mmol) in HOAc (5 mL). [b] Isolated yield. [c] Determined by chiral HPLC using the chiralcel OJ column eluting with hexane:2-propanol (8:2, v:v) (λ = 214 nm). [d] 43% of **1a** was recovered. [e] HOAc (0.5 mL). [f] HOAc (2.0 mL). [g] **1a** (0.5 mmmol), $Pd(OAc)_2$ (0.049 mmol), and (*R*,*R*)-**11c** (0.099 mmol). [h] Reversed configuration compared with other ligands.

Asymmetric Cyclization. The racemic variant of the acetoxypalladation initiated cyclization of enyne esters has been realized under the catalysis of nitrogen-coordintated Pd(II) complexes. With these results in hand, further effort to the development of an asymmetric catalysis was made using the homochiral nitrogen-containing ligands. We initially employed oxazoline ligands[34] due to their availability and the wealth of asymmetric transformations which utilized these ligands.[35] Generally the reaction of **1a** was carried out with 5 mol % $Pd(OAc)_2$ and 10 mol % chiral ligand in HOAc at 60 °C (Table 6). First we targeted the C_2-symmetric bis-oxazoline ligands **11** and found that the different substituent on the oxazoline ring significantly affected the

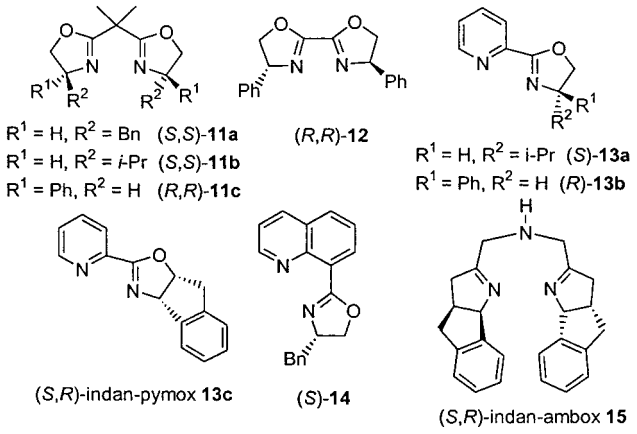
(32) Francis, J. W.; Henry, P. M. *J. Mol. Catal. A*: *Chem.* **1995**, *99*, 77.

(33) This phenomenon may be explained from our suggestion that pyridine, like chlorides, can inhibit the β-H abstraction, and the oxidative cleavage occurs in the presence of $CuCl_2$.

(34) Employing 4,5-dihydro-2-phenyloxazole as the extra ligand in the stoichiometric reaction similar to that shown in Table 4, a 18% yield of **7** was formed and no detectable **6** was observed by NMR spectra after 1 h. However, further reaction occurred affording *N*-acetoxy-2-methylindole as a major product on lengthening the reaction time (24 h: 21% yield of **7** and 67% yield of *N*-acetoxy-2-methylindole). **7** was reported to be converted to *N*-acetoxy-2-methylindole with palladium dichloride: Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800. These results shows that the reaction did favor β-heteroatom elimination in the presence of the oxazoline ligand.

(35) For reviews, see: (a) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (c) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497. (d) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159.

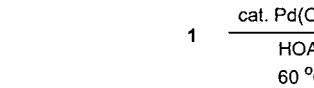
reactivity and enantioselectivity of the reaction. For example, no cyclization product **2a** was obtained with the benzyl-substituted bisoxazoline ligand (*S*,*S*)-**11a** (Table 6, entry 1) and only a 29% yield of **2a** with disappointing zero enantiomeric excess employing the isopropyl substituted bisoxazoline (*S*,*S*)-**11b** as the ligand (Table 6, entry 2). Luckily, employment of the phenyl-substituted bisoxazoline (*R*,*R*)-**11c** as the ligand led to remarkable improvement in enantioselectivity (91% ee). However, a two-component adduct **16** emerged as a major byproduct at high substrate concentration (1.0 M) (Table 6, entry 3). It was expected that the intermolecular reaction should be suppressed by diluting the reaction system. As expected, when the concentration of **1a** was reduced to 0.1 M, no detectable **16** was formed and the yield of **2a** was raised to 67% and without great loss of enantioselectivity (89% ee) (Table 6, entry 5). Increasing the catalyst loading to 10 mol % $Pd(OAc)_2$ and 20 mol % (*R*,*R*)-**11c** gave **2a** in 78% yield (92% ee) (Table 6, entry 6). While the use of another kind of bisoxazoline ligand (*R*,*R*)-**12** afforded lower yield and enantioselectivity than did (*R*,*R*)-**11c** (15% yield and 68% ee) (Table 6, entry 7). Palladium−pymox (pyridyl monooxazoline) complexes are relatively uncrowded in comparison with those of bisoxazoline ligands. As a result, these complexes catalyzed the cyclization more efficiently and led to higher cyclization yield (Table 6, entries 8−11). Again, employment of the phenyl-substituted ligand (*R*)-**13b** gave the highest enantioselectivity (81% ee) of the kind (Table 6, entry 9). Lowing the temperature (40 °C) only raised the enantioselectivity slightly (Table 6, entry 10). Other types of ligands such as the quinolinyl-oxazoline (*S*)-**14** and the tridentate ligand (*S*,*R*)-Indan-Ambox **15** were also tested, but no detectable cyclization product was formed.



On the basis of these results, (*R*,*R*)-**11c** and (*R*)-**13b** were selected as the preferred ligands for the Pd(II)-catalyzed cyclization of the enyne esters. Some representative results employing the two ligands were summarized in Table 7. High enantioseclectivity (79−92% ee) was achieved. In general, the catalyst system with (*R*,*R*)-**11c** as the ligand showed relatively lower reactivity but higher enantioselectivity than that with (*R*)-**13b** (Table 7, compare entries 1 with 2 and 9 with 10). But in some cases, the two catalyst systems showed similar enantioselectivity (Table 7, compare entries 3 with 4 and 7 with 8).

Absolute Configuration. To establish the absolute configuration of the optically active γ-butyrolactones obtained above and demonstrate the synthetic utility of the asymmetric protocol, we chose A-factor as our target molecule.[36] A-factor is an inducer of the biosynthesis of Streptomycin in inactive mutants of *Streptomycis griseus*.[37] Mori et al. determined the absolute configuration of its two enantiomers by synthesizing them from chiral paraconic acid.[36b,38] The retrosynthetic analysis of A-factor could easily identify γ-butyrolactone **2d** as the key intermediate. Thus, selective cleavage of the terminal alkene of (+)-**2d** was performed with potassium osmate-(VI) (1 mol %) and NMO (1.1 equiv) followed by sodium periodate cleavage of the resulting diol. The aldehyde was used without purification in a subsequent reduction with sodium borohydride in methanol at −2 °C to give (+)-**17** in 82% overall yield from (+)-**2d**. Finally, transformation of the vinyl acetate in (+)-**17** to ketone (either existing as enol form) under the catalysis of DMAP in methanol at 9 °C furnished the enantiomerically enriched (3*S*)-(+)-A-factor (86% ee[39]) in 70% yield (Scheme 2). Hence, the starting material (+)-**2d** was assigned 3*R* configuration. Thus, by comparing the signs of the specific rotation of the other γ-butyrolactones with (+)-**2d** and based on their

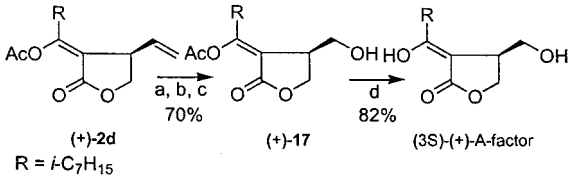
Table 7. Asymmetric Cyclization of 1 Employing (*R*,*R*)-11c or (*R*)-13b as Ligand



entry	1	conditions[a] (time)	2	yield (%)[b]	% ee[c] (config)
1	**1a**	A (18 h)	**2a**	88	81 ((+)-*R*)
2	**1a**	B (35 h)	**2a**	78	92 ((+)-*R*)
3	**1b**	A (34 h)	**2b**	83	81 ((+)-*R*)
4	**1b**	B (42 h)	**2b**	80	80 ((+)-*R*)
5	**1c**	A (48 h)	**2c**	70	81 ((+)-*R*)
6	**1c**	B (72 h)	**2c**	58	79 ((+)-*R*)
7	**1d**	A (23 h)	**2d**	86	84 ((+)-*R*)
8	**1d**	B (48 h)	**2d**	77	85 ((+)-*R*)
9	**1e**	A (41 h)	**2e**	72	79 ((+)-*R*)
10	**1e**	B (48 h)	**2e**	67	87 ((+)-*R*)

[a] Conditions A: **1** (0.5 mmol), $Pd(OAc)_2$ (0.027 mmol), and (*R*)-**13b** (0.054 mmol) in HOAc (5 mL) at 60 °C. Conditions B: **1** (0.5 mmol), $Pd(OAc)_2$ (0.049 mmol), and (*R*,*R*)-**11c** (0.099 mmol) in HOAc (5 mL) at 60 °C. [b] Isolated yield. [c] Determined by chiral HPLC using the chiralcel OJ column eluting with hexane:2-propanol (8:2, v:v) (λ = 214 nm).

Scheme 2[a]



[a] Reagents and conditions: (a) cat. K_2OsO_4, NMO, acetone−H_2O, rt; (b) $NaIO_4/SiO_2$, CH_2Cl_2, rt; (c) $NaBH_4$, MeOH, −2 °C; (d) cat. 4-(dimethylamino)pyridine, MeOH, 9 °C.

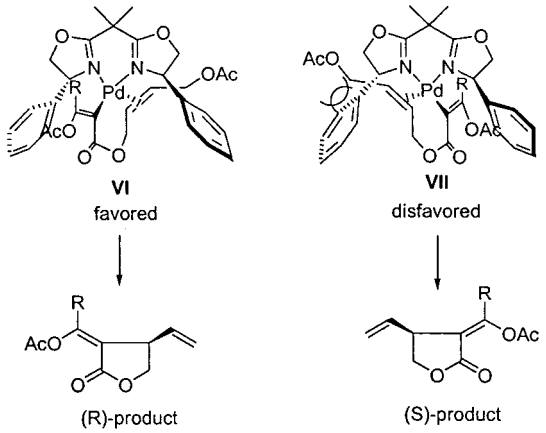
(36) (a) Kleiner, E. M.; Onoprienko, V. V.; Pliner, S. A.; Soifer, V. S.; Khokhlov, A. S. *Bioorg. Khim.* **1977**, *3*, 424. (b) Mori, K.; Yamane, K. *Tetrahedron* **1982**, *38*, 2919. (c) Mori, K.; Chiba, N. *Liebigs Ann. Chem.* **1990**, 31. (d) Kinoshita, T.; Hirano, M. *J. Heterocycl. Chem.* **1992**, *29*, 1025. (e) Ji, J.; Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1160.

(37) (a) Khokhlov, A. S.; Anisova, L. N.; Tovarova, I. I.; Kleiner, E. M.; Kovalenko, I. V.; Krasilnikova, O. I.; Kornitskaya, E. Y.; Pliner, S. A. *Z. Allg. Mikrobiol.* **1973**, *13*, 67. (b) Kleiner, E. M.; Pliner, S. A.; Soifer, V. S.; Onoprienko, V. V.; Balasheva, T. A.; Rozynov, B. V.; Khokhlov, A. S. *Bioorg. Khim.* **1976**, *2*, 1142.

(38) Mori, K. *Tetrahedron* **1983**, *39*, 3107.

(39) The 86% ee of our synthesized (3S)-(+)-A-factor is calculated according to the specific rotation ($[\alpha]^{22}_D$ +10.9°, lit.[36b] $[\alpha]^{22}_D$ +12.7°).

Scheme 3



similarity in the order of retention time in the HPLC analysis (Table 6), all other γ-butyrolactones in Table 6 were identified to be in 3*R* configuration.

Mechanism of Asymmetric Induction. It has been noted that distortion of the normal square planar structure of Pd(II) complexes toward a tetrahedral arrangement due to steric interactions, especially in the event that bulky substitution occurred in adjacent to coordination atoms, such as the nitrogen of bipyridine and phenanthroline ligands.[28b,c] In the above asymmetric cyclizations, the large steric effect around the Pd(II) sphere may be significant in determining the preference for a rarely precedented tetrahedral species. According to this tetrahedral model, we speculated that the steric interaction between the allylic ester and the proximal phenyl substituent of oxazoline (with (*R*,*R*)-**11c** as example) would prefer the intermediate **VI** (with the Pd atom situated in front of the olefinic double bond) to **VII** (Scheme 3). From the favored transition state, the cyclization would give the γ-butyrolactones in 3*R* configuration. This speculation is in accord with those observed experimentally.

Conclusion

We developed a new type of carbocyclization of enyne esters for the synthesis of γ-butyrolactones initiated by acetoxypalladation under Pd(II) catalysis with high efficiency and stereoselectivity. The nitrogen-containing ligands, e.g., bpy and phen, are crucial to realize the cyclization and like halides, serve to favor β-heteroatom elimination over β-hydride elimination. This important finding is expected to have a broad impact on the studies of Pd(II)-catalyzed reactions and lead to rational design of efficient catalytic systems. In addition, employing bisoxazoline (*R*,*R*)-**11c** or pymox (*R*)-**13b** as the ligands, the catalytic asymmetric protocol was established with high enantioselectivity (up to 92% ee). While the asymmetric cyclization of enyne is usually catalyzed with Pd(0) catalyst,[5−7] this work is the first example of realizing the efficient asymmetric synthesis of the optically active γ-butyrolactones from the cyclization of enyne esters catalyzed by Pd(II) species.

Experimental Section

General Methods. ^{1}H NMR spectra were obtained at 300 MHz. Optical rotations were measured with a Perkin-Elmer model 341 polarimeter. HPLC was conducted on a Waters 515 pump/2487 instrument. Flash chromatography was performed employing 300−400 mesh silica gel. ^{1}H NMR yield was determined with CH_2Br_2 as internal standard. Acetic acid was purified by heating with acetic acid and CrO_3 and then fractionally distilling.[40]

The substituted 2,2′-bipyridines were prepared according to the literature methods.[41] The oxazoline ligands **11a-c**,[42a−b] **12**,[42c] and **13a-c**[42d−e] were pepared by known methods. Palladium complex **5** was prepared by the literature procedure.[43]

Typical Procedure for the Synthesis of (*Z*)-4′-Acetoxy-2′-butenyl 2-Alkynoates (1). Synthesis of (*Z*)-4′-Acetoxy-2′-butenyl 2-Butynoate (1a). To a solution of 2-butynoic acid (1.68 g, 20 mmol) and (*Z*)-1-acetoxy-2-buten-4-ol (2.86 g, 22 mmol) in CH_2Cl_2 (20 mL) was added dropwise at −20 °C a solution of 1,3-dicyclohexylcarbodiimide (4.13 g, 20 mmol) and 4-(dimethylamino)pyridine (224 mg, 2 mmol) in CH_2Cl_2 (20 mL) with stirring. Then the reaction mixture was stirred at room temperature for 10 h. After the reaction was complete, the white solid was filtered off and the solvent was removed in vacuo. The residue was then submitted to column chromatography on silica gel (petroleum ether:ethyl acetate 5:1), affording **1a** as an oil: yield 91%. IR (neat) 2960, 2243, 1741, 1712, 1442, 1377, 1253 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80−5.76 (m, 2H), 4.76 (d, J = 5.4 Hz, 2H), 4.68 (d, J = 5.3 Hz, 2H), 2.08 (s, 3H), 2.00 (s, 3H). MS (*m*/*z*) 197 ($M^+ + 1$), 163, 137, 113, 67 (100), 43. Anal. Calcd for $C_{10}H_{12}O_4$ C, 61.22; H, 6.16. Found C, 60.98; H, 6.33.

(*Z*)-4′-Acetoxy-2′-butenyl 2-Hexynoate (1b). Oil: yield 89%. IR (neat) 2965, 2235, 1743, 1714. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88−5.70 (m, 2H), 4.77 (d, J = 5.3 Hz, 2H), 4.68 (d, J = 5.1 Hz, 2H), 2.32 (t, J = 7.1 Hz, 2H), 2.07 (s, 3H), 1.62 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H). MS (*m*/*z*) 225 ($M^+ + 1$), 165, 113, 95 (100), 43. Anal. Calcd for $C_{12}H_{16}O_4$ C, 64.27; H, 7.19. Found C, 64.42; H, 7.16.

(*Z*)-4′-Acetoxy-2′-butenyl 3-Phenyl-2-propynoate (1c). White solid: mp 27−28 °C. yield 87%. IR (neat) 2225, 1741, 1711, 1286, 1232. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57−7.54 (m, 2H), 7.43−7.32 (m, 3H), 5.84−5.74 (m, 2H), 4.82 (d, J = 4.5 Hz, 2H), 4.68 (d, J = 4.5 Hz, 2H), 2.05 (s, 3H). MS (*m*/*z*) 259 ($M^+ + 1$), 149, 57 (100), 43. Anal. Calcd for $C_{15}H_{14}O_4$ C, 69.76; H, 5.46. Found C, 69.51; H, 5.60.

(*Z*)-4′-Acetoxy-2′-butenyl 5-Methyl-2-nonynoate (1d). Oil: yield 93%. IR (neat) 2956, 2236, 1744, 1714, 1232. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80−5.76 (m, 2H), 4.76 (d, J = 5.2 Hz, 2H), 4.68 (d, J = 5.1 Hz, 2H), 2.33 (t, J = 7.1 Hz, 2H), 2.07 (s, 3H), 1.59−1.37 (m, 5H), 1.21−1.16 (m, 2H), 0.88 (d, J = 6.6 Hz, 6H). MS (*m*/*z*) 281 ($M^+ + 1$), 221, 197, 113 (100), 43. Anal. Calcd for $C_{16}H_{24}O_4$ C, 68.55; H, 8.63. Found C, 68.62; H, 8.77.

(*Z*)-4′-Acetoxy-2′-butenyl 4-Methoxy-2-butynoate (1e). Oil: yield 90%. IR (neat) 2940, 2237, 1741, 1416, 1452, 1248, 1230. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85−5.72 (m, 2H), 4.80 (d, J = 5.6 Hz, 2H), 4.68 (d, J = 5.5 Hz, 2H), 4.24 (s, 2H), 3.42 (s, 3H), 2.07 (s, 3H). MS (*m*/*z*) 227 ($M^+ + 1$), 167, 113 (100), 97, 43. Anal. Calcd for $C_{11}H_{14}O_5$ C, 58.40; H, 6.24. Found C, 58.61; H, 6.32.

(*Z*)-4′-Acetoxy-4′-phenyl-2′-butenyl 2-Butynoate (1f). Oil: yield 62%. IR (neat) 3035, 2243, 1739, 1712, 1495, 1454, 1371, 1257, 1233 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 6.52 (d, J = 8.3 Hz, 1H), 5.86−5.72 (m, 2H), 4.98−4.85 (m, 2H), 2.10 (s, 3H), 1.98 (s, 3H). MS (*m*/*z*) 230 ($M^+ - CH_2CO$), 213, 146 (100), 128, 117, 67. Anal. Calcd for $C_{16}H_{16}O_4$ C, 70.57; H, 5.92. Found C, 70.78; H, 6.20.

(*Z*)-4′-Acetoxy-1′-isopropyl-2′-butenyl 2-Butynoate (1g).[26] Oil: yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81−5.72 (m,

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1H), 5.57−5.49 (m, 1H), 5.29 (dd, J = 9.5, 7.0 Hz, 1H), 4.77−4.71 (m, 2H), 2.06 (s, 3H), 1.99 (s, 3H), 1.95−1.81 (m, 1H), 0.96 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H).

(*Z*)-4′-Acetoxy-1′-pentyl-2′-butenyl 2-Butynoate (1h). Oil: yield 70%. IR (neat) 3030, 2958, 2935, 2243, 1743, 1710, 1255, 1232 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75−5.64 (m, 1H), 5.58−5.45 (m, 2H), 4.84−4.65 (m, 2H), 2.06 (s, 3H), 1.98 (s, 3H), 1.80−1.45 (m, 2H), 1.32−1.28 (m, 6H), 0.89 (t, J = 6.7 Hz, 3H). MS (m/z) 223 ($M^+ - CH_3CO$), 207, 183, 140, 67 (100), 43. Anal. Calcd for $C_{15}H_{22}O_4$ C, 67.64; H, 8.33. Found C, 67.84; H, 8.42.

(*Z*)-4′-Acetoxy-2′-butenyl Propiolate (1i). Oil: yield 82%. IR (neat) 3261, 2956, 2122, 1739, 1718, 1450, 1378, 1222 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87−5.73 (m, 2H), 4.81 (d, J = 6.0 Hz, 2H), 4.68 (d, J = 5.6 Hz, 2H), 2.96 (s, 1H), 2.08 (s, 3H). MS (m/z) 183 (M^+ + 1), 123, 113, 70, 53, 43 (100). Anal. Calcd for $C_9H_{10}O_4$ C, 59.74; H, 5.53. Found C, 59.35; H, 5.69.

Typical Procedure for the Cyclization of (*Z*)-4′-Acetoxy-2′-butenyl 2-Alkynoates (1). Synthesis of α-(*Z*)-(1′-Acetoxyethylidene)-*β*-vinyl-*γ*-butyrolactone (2a). To a solution of $Pd(OAc)_2$ (6 mg, 0.027 mmol) and 2,2′-bipyridine (5 mg, 0.032 mmol) in HOAc (2 mL) at 60 °C was added **1a** (98 mg, 0.5 mmol) with stirring. The reaction mixture was monitored by TLC. After the reaction was complete, ethyl ether (80 mL) was added. The mixture was washed with saturated $NaHCO_3$ solution (2 × 20 mL) and brine (20 mL). The ether layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was submitted to column chromatography on silica gel (petroleum ether:ethyl acetate 4:1), affording pure **2a** as an oil: yield 87%. IR (neat) 1756, 1684, 1638, 1212, 1162. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90−5.79 (m, 1H), 5.30−5.21 (m, 2H), 4.42 (dd, J = 9.0, 8.3 Hz, 1H), 4.04 (dd, J = 9.0, 3.5 Hz, 1H), 3.80−3.74 (m, 1H), 2.25 (s, 3H), 2.02 (d, J = 1.2 Hz, 3H). MS (m/z) 196 (M^+), 155, 136, 111, 43 (100). Anal. Calcd for $C_{10}H_{12}O_4$ C, 61.22; H, 6.16. Found C, 61.19; H, 6.11.

α-(*Z*)-(1′-Acetoxybutylidene)-*β*-vinyl-*γ*-butyrolactone (2b). Oil: yield 90%. IR (neat) 2967, 1759, 1675, 1637, 1368, 1208, 1156. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89−5.81 (m, 1H), 5.28 (dt, J = 17.0, 1.0 Hz, 1H), 5.22 (dt, J = 10.0, 0.9 Hz, 1H), 4.42 (dd, J = 9.0, 8.1 Hz, 1H), 4.05 (dd, J = 9.0, 3.4 Hz, 1H), 3.82−3.75 (m, 1H), 2.31−2.26 (m, 5H), 1.60 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H). MS (m/z) 225 (M^+ + 1), 183 (100), 164, 136. Anal. Calcd for $C_{12}H_{16}O_4$ C, 64.27; H, 7.19. Found C, 64.36; H, 7.33.

α-(*Z*)-(1′-Acetoxy-1′-phenylmethylidene)-*β*-vinyl-*γ*-butyrolactone (2c). White solid: mp 77−79 °C. IR (KBr) 1763, 1741, 1654, 1218, 1199. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.55 (m, 2H), 7.43−7.30 (m, 3H), 5.93−5.81 (m, 1H), 5.27 (dt, J = 17.2, 0.7 Hz, 1H), 5.21 (dt, J = 10.1, 1.0 Hz, 1H), 4.38 (dd, J = 8.7, 7.3 Hz, 1H), 4.10 (dd, J = 8.7, 2.6 Hz, 1H), 3.96−3.90 (m, 1H), 2.35 (s, 3H). MS (m/z) 258 (M^+), 216, 198, 111, 105 (100), 77, 43. Anal. Calcd for $C_{15}H_{14}O_4$ C, 69.76; H, 5.46. Found C, 69.42; H, 5.17.

α-(*Z*)-(1′-Acetoxy-6′-methylheptylidene)-*β*-vinyl-*γ*-butyrolactone (2d). Oil: yield 83%. IR (neat) 2957, 1761, 1723, 1675, 1368, 1226, 1209, 1157. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93−5.81 (m, 1H), 5.28 (dt, J = 17.0, 0.9 Hz, 1H), 5.22 (dd, J = 10.0, 0.9 Hz, 1H), 4.42 (dd, J = 9.0, 8.2 Hz, 1H), 4.04 (dd, J = 9.0, 3.4 Hz, 1H), 3.81−3.75 (m, 1H), 2.30 (t, J = 8.6 Hz, 2H), 2.27 (s, 3H), 1.55−1.47 (m, 3H), 1.34−1.14 (m, 4H), 0.87 (d, J = 6.6 Hz, 6H). MS (m/z) 281 (M^+ + 1), 239 (100), 220, 113, 43. Anal. Calcd for $C_{16}H_{24}O_4$ C, 68.55; H, 8.63. Found C, 68.09, H, 8.66.

α-(*Z*)-(1′-Acetoxy-2′-methoxyethylidene)-*β*-vinyl-*γ*-butyrolactone (2e). Oil: yield 83%. IR (neat) 1762, 1683, 1370, 1205, 1161, 1116. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94−5.83 (m, 1H), 5.28 (dd, J = 17.0, 1.0 Hz, 1H), 5.25 (dd, J = 10.0, 1.0 Hz, 1H), 4.44 (td, J = 8.4, 0.3 Hz, 1H), 4.14−4.01 (m, 3H), 3.95−3.89 (m, 1H), 3.37 (s, 3H), 2.30 (s, 3H). MS (m/z) 227 (M^+ + 1), 185, 152, 139, 121, 43 (100). Anal. Calcd for $C_{11}H_{14}O_5$ C, 58.40; H, 6.24. Found C, 58.36; H, 6.32.

α-(*Z*)-(1′-Acetoxyethylidene)-*β*-(*E*)-styryl-*γ*-butyrolactone (2f). Oil: IR(neat) 3028, 2974, 1756, 1682, 1600, 1578, 1494, 1479, 1450, 1370, 1210, 1162 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.25 (m, 5H), 6.58 (d, J = 15.8 Hz, 1H), 6.17 (dd, J = 15.8, 7.9 Hz, 1H), 4.45 (dd, J = 9.1, 8.4 Hz, 1H), 4.08 (dd, J = 9.1, 3.7 Hz, 1H), 3.95−3.89 (m, 1H), 2.26 (s, 3H), 2.03 (s, 3H). MS (m/z) 272 (M^+), 230, 212 (100), 184, 141, 128, 43. HRMS Calcd for $C_{16}H_{16}O_4$ 272.1049, Found 272.1041.

α-(*Z*)-(1′-Acetoxyethylidene)-*cis*-*β*-vinyl-*γ*-isopropyl-*γ*-butyrolactone (2 g). Oil: IR (neat) 2965, 1759, 1687, 1369, 1213, 1191, 1168, 1142, 1001 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84−5.72 (m, 1H), 5.28−5.22 (m, 2H), 3.95 (dd, J = 10.3, 5.9 Hz, 1H), 3.63−3.59 (m, 1H), 2.24 (s, 3H), 1.99 (s, 3H), 1.98−1.78 (m, 1H), 1.07 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H). MS (m/z) 239 (M^+ + 1), 197, 179, 155, 124, 95, 43(100). Anal. Calcd for $C_{13}H_{18}O_4$ C, 65.53; H, 7.61. Found C, 65.25; H, 7.71.

α-(*Z*)-(1′-Acetoxyethylidene)-*cis*-*β*-vinyl-*γ*-pentyl-*γ*-butyrolactone (2h). Oil: IR (neat) 3084, 2956, 2935, 1760, 1688, 1637, 1213, 1170 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83−5.69 (m, 1H), 5.28−5.22 (m, 2H), 4.47−4.39 (m, 1H), 3.63 (t, J = 7.4 Hz, 1H), 2.25 (s, 3H), 1.99 (s, 3H), 1.57−1.29 (m, 8H), 0.89 (t, J = 6.7 Hz, 3H). MS (m/z) 266 (M^+), 225 (100), 206, 181, 124, 43. Anal. Calcd for $C_{15}H_{22}O_4$ C, 67.64; H, 8.33. Found C, 67.99; H, 8.38.

The Procedure for the Cyclization of (Z)-4′-Acetoxy-2′-butenyl 2-Butynoate (1a) Employing Substituted Pyridine or 2,2′-Bipyridine as the Ligands Was Similar as Above in the Preparation of 2a.

(*Z*)-4′-Acetoxy-2′-butenyl (*Z*)-3-Acetoxy-2-butenoate (3). Oil: IR (neat) 2958, 1768, 1743, 1729, 1674, 1441, 1370, 1276, 1231, 1175, 1140 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75−5.71 (m, 2H), 5.60 (s,1H), 4.68−4.64 (m, 4H), 2.22 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H). MS (m/z) 257 (M^+ + 1), 215, 155, 139, 113, 85, 43 (100). HRMS Calcd for $C_{12}H_{16}O_6$ 256.0947, Found 256.0940.

General Procedure for the Coupling Reactions of Methyl 2-Butynoate with Allyl Compounds. To a solution of $Pd(OAc)_2$ (11 mg, 0.049 mmol) and 2,2′-bipyridine (9 mg, 0.058 mmol) in HOAc (5 mL) at room temperature was added allyl compounds (4 mmol) and methyl 2-butynoate (98 mg, 1 mmol) with stirring. The reaction mixture was heated at 60 °C and monitored by TLC. After the reaction was complete, ethyl ether (80 mL) was added. The mixture was washed with saturated $NaHCO_3$ solution (2 × 20 mL) and brine (20 mL). The ether layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was submitted to column chromatography on silica gel (petroleum ether:ethyl acetate 10:1), affording **4** as the product as shown in Table 3.

Methyl (*Z*)-3-Acetoxy-2-allyl-2-butenoate (4). Oil: IR (neat) 3082, 3009, 1763, 1723, 1657, 1641, 1230, 1175 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80−5.69 (m, 1H), 5.04 (dd, J = 17.2, 1.6 Hz, 1H), 4.97 (dd, J = 10.2, 1.6 Hz, 1H), 3.63 (s, 3H), 3.00 (d, J = 6.2 Hz, 2H), 2.11 (s, 3H), 1.93 (s, 3H). MS (m/z) 198 (M^+), 156, 141, 124, 109, 96, 43 (100). HRMS Calcd for $C_{10}H_{14}O_4$ 198.0892, Found 198.0887.

General Procedure for the Reactions of Di-*μ*-acetato-bis(2-acetaminophenyl-2C,O)dipalladium(II) (5) with Allyl Acetate. To a suspension of complex **5** (80 mg, 0.13 mmol) and ligand in HOAc (1 mL) was added allyl acetate (135 mg, 1.35 mmol). The mixture was stirred at room temperature for 1.5 h. After separation of the palladium by filtration through a short column of silica gel with the aid of ethyl acetate, the filtrate was concentrated under vacuum and the residue was submitted to column chromatography on silica gel (petroleum ether:ethyl acetate 2:1) to afford products **6** and **7** as shown in Table 4.

***N*-[2-(3-Acetoxy-1-propenyl)phenyl]acetamide (6).** White solid: mp 97−98 °C. IR (KBr) 3240, 1736, 1652, 1579, 1542, 1455, 1301, 1239, 1025 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64−7.07 (m, 5H), 6.66 (dd, J = 15.8, 1.4 Hz, 1H), 6.11 (dt, J = 15.8, 6.3 Hz, 1H), 4.65 (dd, J = 6.3, 1.4 Hz, 2H), 2.11 (s, 3H), 2.03 (s, 3H). MS (m/z) 233 (M^+), 191, 173, 130(100), 118, 77, 43. Anal. Calcd for $C_{13}H_{15}NO_3$ C, 66.94; H, 6.48; N, 6.00. Found C, 66.73; H, 6.45; N, 5.82.

***N*-[2-(2-Propenyl)phenyl]acetamide (7).**[44] White solid: mp 87−89 °C. IR (KBr): 3286, 1657, 1587, 1536, 1482, 1371, 1298, 994, 970, 916, 753 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ

7.75 (d, J = 8.0 Hz, 1H), 7.22−7.02 (m, 4H), 5.95−5.84 (m, 1H), 5.11 (dd, J = 10.1, 1.4 Hz, 1H), 5.03 (dd, J = 17.1, 1.6 Hz, 1H), 3.31 (dt, J = 6.1, 1.6 Hz, 2H), 2.21 (s, 3H). MS (m/z) 176 ($M^+ + 1$), 175 (M^+), 160, 132 (100), 118, 91, 77.

General Procedure for the Palladium Catalyzed Reactions of Phenylmercuric Acetate with Allyl Acetate. To a mixture of phenylmercuric acetate (1.14 g, 3 mmol) and ligand in HOAc (15 mL) was added allyl acetate (9 mmol) and $Pd(OAc)_2$ (34 mg, 5 mol %). After stirring at room temperature (80 °C in the case of bpy as the ligand) for 24 h, the mixture was poured into water (50 mL) and extracted with pentane (200 mL). The organic layer was washed with saturated $NaHCO_3$ solution and brine and dried (Na_2SO_4). After removing the solvent, the residue was purified by column chromatography on silica gel (pentane) to obtain products **8**, **9**, and **10** (pentane:ethyl acetate 19:1) as shown in Table 5.

Cinnamyl Acetate (8). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.28 (m, 5H), 6.67 (d, J = 15.8 Hz, 1H), 6.31 (dt, J = 15.8, 6.4 Hz, 1H), 4.75 (d, J = 6.4 Hz, 2H), 2.12 (s, 3H).

Allylbenzene (9). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.33 (m, 2H), 7.29−7.24 (m, 3H), 6.10−5.97 (m, 1H), 5.17−5.11 (m, 2H), 3.45 (d, J = 6.6 Hz, 2H).

(*E*)-1,3-Diphenylpropene (10). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.26 (m, 10 H), 6.54 (d, J = 15.8 Hz, 1H), 6.41 (dt, J = 15.8, 6.4 Hz, 1H), 3.60 (d, J = 6.4 Hz, 2H).

The Procedure for the Asymmetric Cyclization of (Z)-4′-Acetoxy-2′-butenyl 2-Alkynoates (1) Was Similar as Above in the Preparation of 2a. Enantiomers were separated by HPLC using the chiralcel OJ column eluting with hexane:2-propanol (8:2, v:v) (λ = 214 nm).

16. Oil: IR(neat) 2916, 1752, 1724, 1660, 1644, 1433, 1373, 1226, 1193, 1170 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68−5.56 (m, 3H), 5.05 (dt, J = 17.0, 1.0 Hz, 1H), 4.96 (d, J = 10.4 Hz, 1H), 4.66−4.53 (m, 4H), 4.28 (dd, J = 9.1, 7.5 Hz, 1H), 4.00 (dd, J = 9.1, 2.8 Hz, 1H), 3.58 (m, 1H), 2.33 (s, 3H), 2.16 (s, 3H), 2.00 (s, 3H), 1.87 (s, 3H). MS (m/z) 393 ($M^+ + 1$), 351, 291, 221, 113, 43(100). HRMS Calcd for $C_{20}H_{24}O_8$ 392.1472, Found 392.1494.

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Supporting Information Available: ^{1}HMR spectra for **2f**, **3**, **4**, **16**, and **17**, and the NOE spectra for **4**, **2a**, **2g**, and **2h**. Spectroscopic and analytical data for 6-(1-methoxy-2,2′-dimethylpropyl)-2,2′-bipyridine (entry 4 in Table 2). The specific rotation of the optically active γ-butyrolactones **2**. Retention time for **2** in the HPLC analysis. Experimental details for the synthesis of (3*S*)-(+)-A-factor. This material is available free of charge via the Internet at http://pubs.acs.org.

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