Highly Enantioselective Palladium(II)-Catalyzed Cyclization of (*Z*)-4′-Acetoxy-2′-butenyl 2-Alkynoates: An Efficient Synthesis of Optically Active γ-Butyrolactones

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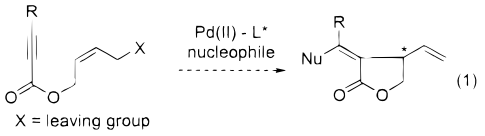
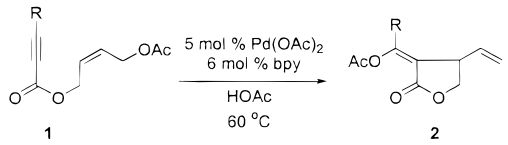
The use of transition metal catalysts in the carbocyclization of alkenes and alkynes offers the unique means to construct a variety of synthetically important carbo- and heterocycles with high efficiency not normally accessible by traditional methods.[1] Despite the development of numerous catalytic carbocyclization protocols, highly enantioselective reactions remain limited.[1c,2] On the other hand, compared to the impressive development of asymmetric reactions with chiral Pd(0) catalyst,[3] asymmetric reactions with Pd(II) species have received scant attention.[4] Herein, we wish to report a new type of Pd(II)-catalyzed cyclization of enyne esters utilizing bidentate nitrogen-containing ligands for the synthesis of γ-butyrolactones initiated by acetoxypalladation with high efficiency as well as its catalytic asymmetric version.

A Pd(II)-catalyzed cyclization of 4′-X-2′-butenyl 2-alkynoates (X = leaving groups) initiated by halopalladation has been developed in this group,[5] our long-standing goal is to make it an enantioselective process. Our previous work shows that excess amounts of halide ions are required to inhibit the β-hydride elimination reaction[6] and make the reaction highly reactive and selective.[5] However, there exist problems in the way of developing the corresponding catalytic asymmetric process. A major one lies in the inevitable disturbance of the excess of requisite halide ions to the coordination of chiral ligands with palladium species. In fact, the reaction dose not occur in the presence of the commonly used phosphine ligands.[5a] To solve these problems, a new type of reaction should be developed where a ligand and a nucleophile are utilized to act the both roles of halide ions (eq 1).



(1)

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

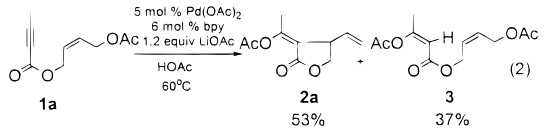


entry	**1**	R	time (h)	**2**	yield(%)[b,c]
1	**1a**	CH_3	10	**2a**	87
2	**1b**	*n*-Pr	10.5	**2b**	90
3	**1c**	Ph	34	**2c**	90
4	**1d**	*i*-C_7H_{15}	18	**2d**	83
5	**1e**	CH_3OCH_2	10.5	**2e**	83

[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.

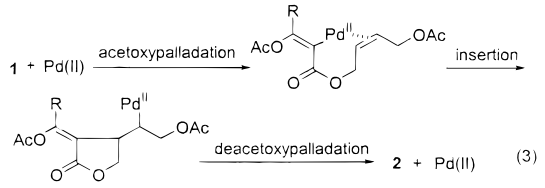
In hydroacetoxylation of alkynoates, acetate attacks the triple bond under palladium catalyst via *trans*-acetoxypalladation followed by protonolysis.[7] It occurs to us that acetate may be a good nucleophile to replace halide ions in the Pd(II)-catalyzed cyclization of enyne esters.

We initially examined the reaction of (*Z*)-4′-acetoxy-2′-butenyl 2-butynoates (**1a**).[8] The cycloisomerization of **1a** under the action of 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 the hydroacetoxylation byproduct **3** (eq 2).[9] 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 reactions proceeded smoothly to afford the γ-butyrolactones in high yields with high stereoselectivity regarding the exocyclic double bonds (*Z*:*E* > 95:5).[10]



(2)

The plausible mechanism of the reaction involves *trans*-acetoxypalladation of the triple bond, followed by intramolecular olefinic insertion and finally the carbon−palladium bond is quenched by deacetoxypalladation instead of the common β-hydride elimination (eq 3). Here, the nitrogen-containing ligand was of critical importance in the reaction. It not only played the same role as the halide ions to inhibit the β-hydride elimination but also made the intramolecular olefinic insertion into the vinyl−palladium bond more preferable to its protonolysis, thus avoiding the formation of protonolysis product **3**.



(3)

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(9) With the catalyst systems such as $Pd(OAc)_2/PPh_3$, $Pd(OAc)_2/AsPh_3$, $Pd(OAc)_2$/PhSMe, $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$, no desired cyclization product **2a** was obtained.

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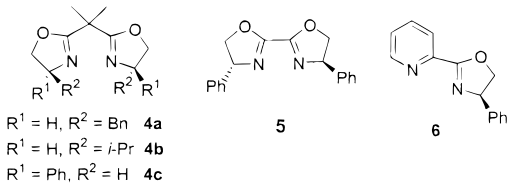
Table 2. Asymmetric Cyclization of **1a** Employing Pymox and Bisoxazoline Ligands[a]

entry	ligand	yield (%)[b] **2a**	yield (%)[b] **3**	% ee of **2a**[c]
1[d]	**4a**		24	
2	**4b**	29	34	0
3[e]	**5**	15	44	68
4	**6**	88		81
5[f]	**4c**	78		92

[a] Unless otherwise noted, the reaction was carried out under the following conditions. **1a** (0.5 mmol), $Pd(OAc)_2$ (0.027 mmol) and ligand (0.054 mmol) in HOAc (5 mL) at 60 °C. [b] Isolated yield. [c] Determined by chiral HPLC using the chiralcel OJ column eluting with 8:2 hexane: 2-propanol (λ = 214 nm). [d] 43% of **1a** was recovered. [e] HOAc (0.5 mL). [f] **1a** (0.5 mmmol), $Pd(OAc)_2$ (0.049 mmol) and **4c** (0.099 mmol).

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 the easily available monooxazoline (pymox) and bisoxazoline ligands.[11] Generally the reaction of **1a** was carried out with 5 mol % $Pd(OAc)_2$ and 10 mol % chiral ligand in HOAc at 60 °C. We found that the different substituent on the oxazoline ring significantly affected the reactivity and enantioselectivity of the reaction (Table 2). For example, no cyclization product **2a** was obtained with the benzyl-substituted bisoxazoline ligand **4a** (Table 2, entry 1) and only a 29% yield of **2a** with disappointing zero enantiomeric excess employing the isopropyl-substituted bisoxazoline **4b** as the ligand (Table 2, entry 2). Limited improvement was made utilizing the bisoxazoline ligand **5** to give modest levels of stereoinduction (68% ee) despite the lower yield (15%) (Table 3, entry 3). Luckily, the employment of (*R*)-pymox-Ph (**6**) or phenyl-substituted bisoxazoline **4c** as the ligands led to remarkable improvement in both yield and enantioselectivity (Table 2, entries 4 and 5).



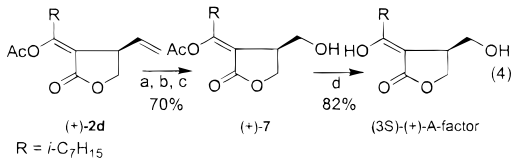
Some representative results employing **4c** or **6** as the ligands were summarized in Table 3. High enantioseclectivity (79% - 92% ee) was achieved. In general, the catalyst system employing **4c** as the ligand showed relatively lower reactivity but higher enantioselectivity than that emloying **6** (Table 3, compare entries 1 with 2 and 9 with 10). But in some cases, the two catalyst systems showed similar enantioselectivity (Table 3, compare entries 3 with 4 and 7 with 8).

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.[12] The retrosynthetic analysis of A-factor could easily identify γ-butyrolactone **2d** as the key intermediate. Conveniently, (+)-**2d** (84% ee) (Table 3, entry 7) was converted in four steps (57% total yield) to enantiomerically enriched (3*S*)-(+)-A-factor (86% ee[13]) (eq 4). Thus, comparing the signs of the specific rotation of the other γ-butyrolactones with (+)-**2d** (Table 3), all other γ-butyrolactones in Table 3 were identified to be in 3*R* configuration.

Table 3. Asymmetric Cyclization of **1** Employing **4c** or **6** as Ligand

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

[a] Conditions A: **1** (0.5 mmol), $Pd(OAc)_2$ (0.027 mmol) and **6** (0.054 mmol) in HOAc (5 mL) at 60 °C. Conditions B: **1** (0.5 mmol), $Pd(OAc)_2$ (0.049 mmol) and **4c** (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 8:2 hexane:2-propanol (λ = 214 nm).



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.

In summary, we first 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 played an important role in the reaction. Employing pymox or bisoxazoline 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,[2d,14] 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.

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Supporting Information Available: Spectroscopic and analytical data for new compounds and (3*S*)-(+)-A-factor, ^{1}HMR spectra of compounds **3** and **7**, and the specific rotation of the optically active γ-butyrolactones **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) It should be noted that the corresponding reactions of propiolate ester and (*E*)-4′-acetoxy-2′-butenyl 2-alkynoates did not occur.

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(13) The 86% ee of our synthesized (3*S*)-(+)-A-factor is calculated according to the specific rotation ($[\alpha]^{22}_D$ +10.9°, lit.[12b] $[\alpha]^{22}_D$ +12.7°).

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