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Highly enantioselective ene-type spiro-cyclization of allyl propargyl ethers catalyzed by cationic palladium(II) complexes with a new type of PN-ligand bearing achiral *gem*-dimethyl oxazoline

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Abstract

The first examples of the asymmetric ene-type spiro-cyclization catalyzed by cationic palladium(II) complexes with a new PN-ligand bearing achiral *gem*-dimethyl oxazoline unit were demonstrated. Spiro-products were synthesized from ether substrates with common, medium and large membered rings with high enantiomeric excesses in almost quantitative yields.

Keywords: Asymmetric catalysis; Cyclizations; Enynes; PN-ligands; Palladium; Spiro

1. Introduction

The enantioselective spiro ring construction is an important issue because many natural compounds have chiral spiro centers [1,2]. Some examples of catalytic spiro-cyclizations have been reported by asymmetric intramolecular Mizoroki–Heck reactions [3–7]. In spite of a similar but higher potential, transition metal-catalyzed ene-type carbocyclization has never been applied to asymmetric spiro-cyclizations [8–19].[1] We have already reported that palladium(II)-catalyzed ene-type cyclization proceeds quantitatively with excellent enantioselectivity generating a new quarternary carbon center [20]. Herein, we wish to report a highly enantioselective spiro ethers formation catalyzed by our cationic chiral palladium(II) complexes with a new PN-ligand bearing achiral oxazoline unit substituted by sterically demanding *gem*-dialkyl groups.

2. Experimental

Typical procedure for palladium(II)-catalyzed spiro-cyclization: thoroughly degassed dimethylsulfoxide (DMSO) (3.0 ml) was injected under argon into a Pyrex Schlenk tube containing $[(MeCN)_4Pd](BF_4)_2$ (6.6 mg, 0.0150 mmol) and (a*S*)-PN-ligand **7** (16.0 mg, 0.0300 mmol), and this solution was stirred at room temperature for 5 min. Then **1** (0.300 mmol) and formic acid (5.6 μl, 0.150 mmol) were added, the

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[1] Precedent examples for ene-type spiro-cyclization catalyzed by palladium are limited in achiral version to give only racemic products (see [8]).

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tube was sealed with a screw cap. The mixture was stirred at 100 °C. The reaction mixture was washed with brine, and the ether-extracted organic layer was evaporated in vacuo and the residue was purified by short column chromatography (neutral silica-gel, pentane/ether = 10/1) to afford (*S*)-**2** and (*S*)-**3**.

High performance liquid chromatographic (HPLC) analyses were conducted on a JASCO PU-980, LG-980-02, DG-980-50, AS-950 and CO-966 instrument equipped with model UV-975 spectrometers as an ultra violet light; Chiral column were DAICEL-CHIRALCEL AD-H, AS, OB-H, OD-H; peak area were calculated by JASCO-BORWIN (Windows NT) as an automatic integrator. Capillary gas chromatographic (GC) analyses were conducted on a Shimadzu GC-14B instrument equipped with FID detector by using N_2 (75 kPa) as a carrier gas; peak area were calculated by a Shimadzu C-R6A as an automatic integrator; chiral column were CP-Cyclodextrin-β-2,3,6-M-19 (i.d. 0.25 mm × 25 m; CHROMPACK; GL Sciences Inc.) and CP-Chirasil-Dex CB (i.d. 0.32 mm × 25 m; CHROMPACK; GL Sciences Inc.); split ratio was 100:1.

2a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (m, 1H), 2.11 (m, 1H), 2.40–2.50 (2H), 3.61 (d, J = 8.4 Hz, 1H), 3.70 (s, 3H), 3.76 (d, J = 9.0 Hz, 1H), 4.74 (dd, J = 17.7, 2.4 Hz, 1H), 4.94 (dd, J = 17.7, 2.4 Hz, 1H), 5.45 (dt, J = 5.4, 2.4 Hz, 1H), 5.63 (t, J = 2.7 Hz, 1H), 5.98 (dt, J = 6.0, 2.1 Hz, 1H).

3a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 4H), 3.70 (s, 3H), 3.72 (s, 2H), 4.87 (d, J = 2.4 Hz, 2H), 5.68 (bs, 2H), 5.76 (t, J = 2.4 Hz, 1H).

2b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–2.22 (6H), 3.50 (d, J = 8.4 Hz, 1H), 3.71 (s, 3H), 3.82 (d, J = 8.7 Hz, 1H), 4.70 (dd, J = 17.7, 2.7 Hz, 1H), 4.98 (dd, J = 17.7, 2.7 Hz, 1H), 5.30 (dm, J = 10.2 Hz, 1H), 5.67 (t, J = 2.4 Hz, 1H), 5.99 (dt, J = 10.2, 3.6 Hz, 1H).

3b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–2.22 (6H), 3.63 (d, J = 8.7 Hz, 1H), 3.69 (d, J = 8.7 Hz, 1H), 3.71 (s, 3H), 4.82 (dd, J = 17.7, 2.7 Hz, 1H), 4.90 (dd, J = 17.7, 2.7 Hz, 1H), 5.68–5.80 (3H).

2c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59–1.85 (6H), 2.00–2.40 (2H), 3.52 (d, J = 9.0 Hz, 1H), 3.71 (s, 3H), 3.95 (d, J = 8.7 Hz, 1H), 4.72 (dd, J = 17.7, 2.7 Hz, 1H), 4.92 (dd, J = 17.7, 2.7 Hz, 1H), 5.32 (d, J = 12.0 Hz, 1H), 5.72 (t, J = 2.7 Hz, 1H), 5.90 (dt, J = 11.7, 5.7 Hz, 1H).

3c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–2.40 (8H), 3.64 (d, J = 9.0 Hz, 1H), 3.71 (s, 3H), 3.75 (d, J = 9.3 Hz, 1H), 4.75–4.91 (2H), 5.67 (m, 1H), 5.70 (t, J = 2.7 Hz, 1H), 5.93 (m, 1H).

2d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70–2.60 (10H), 3.53 (d, J = 8.7 Hz, 1H), 3.70 (s, 3H), 3.98 (d, J = 8.7 Hz, 1H), 4.69 (dd, J = 17.7, 2.4 Hz, 1H), 4.69 (dd, J = 17.7, 2.4 Hz, 1H), 4.69 (dd, J = 17.7, 2.4 Hz, 1H), 4.91 (d, J = 11.7 Hz, 1H), 5.60 (dd, J = 12.0, 8.4 Hz, 1H), 5.71 (t, J = 2.4 Hz, 1H).

3d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80–2.40 (10H), 3.62 (d, J = 8.4 Hz, 1H), 3.70 (s, 3H), 3.75 (d, J = 8.7 Hz, 1H), 4.79 (dd, J = 17.7, 2.4 Hz, 1H), 4.88 (dd, J = 17.7, 2.4 Hz, 1H), 5.73 (dt, J = 10.8, 8.4 Hz, 1H), 5.68 (t, J = 2.7 Hz, 1H), 5.85 (dt, J = 10.5, 8.1 Hz, 1H).

2e: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00–2.20 (24H), 3.67 (d, J = 8.4 Hz, 1H), 3.70 (s, 3H), 3.84 (d, J = 8.7 Hz, 1H), 4.80 (d, J = 2.7 Hz, 2H), 5.33 (d, J = 15.9 Hz, 1H), 5.46 (dt, J = 15.3, 6.6 Hz, 1H), 5.69 (t, J = 2.7 Hz, 1H).

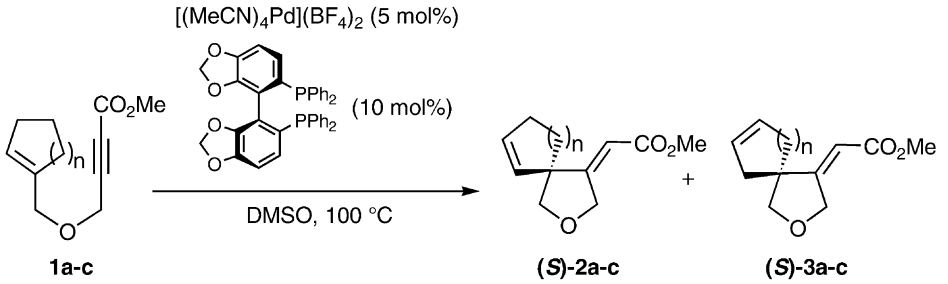
3. Results and discussion

First, in Pd^{II}-catalyzed spiro-cyclizations, we employed bidentate C_2-symmetric PP-ligand such as (*R*)-SEGPHOS ((4,4′-bi-1,3-benzodioxole)-5,5′-diyl-bis(diphenylphosphine)) [21], that has heen found to be so effective to substrates with acyclic olefin, for a variety of cyclic allyl progargyl ethers **1** under polar conditions ([$(MeCN)_4Pd$]$(BF_4)_2$/DMSO) (Table 1). However, reactions were rather slow, taking 72 h for full conversion. Enantioselectivities were unexpectedly low (21–38% e.e.), although the common membered spiro-products were obtained in good yields. Moreover, the olefin-migrations of the primary generated product **2** occurred in all cases leading to the secondary olefin regioisomer **3**.

Based on our mechanistic studies about the transition states for these C–C bond formation, we have already devised bidentate C_1-symmetric PN-ligands having binaphtyl backbone [22].[2] Therefore, PN-ligands bearing a chiral oxazoline unit [23–28] were investigated for substrate **1c** in Pd^{II}-catalyzed

[2] PN-ligands have been known to have advantages to prevent olefin-migrations in asymmetric Mizoroki–Heck reactions [29,30].

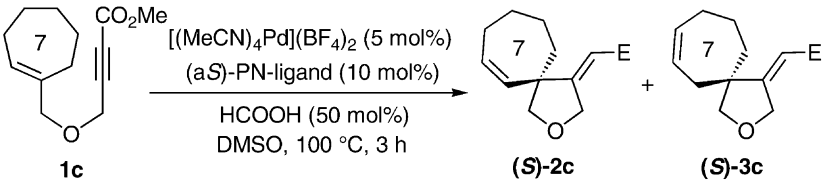
Table 1
Enantioselective ene-type spiro-cyclization of 1,6-enyne ethers **1** catalyzed by cationic Pd^{II} complex with (*R*)-SEGPHOS[a]



Entry	Substrate	Reaction time (h)	Yield (%) (e.e. (%)[b])		Total e.e. value (%)
			2	**3**	
1	**1a** ($n = 1$)	72	35 (23)	21	23
2	**1b** ($n = 2$)	72	20 (8)	52 (27)	21
3	**1c** ($n = 3$)	16	0 (–)	99 (38)	38

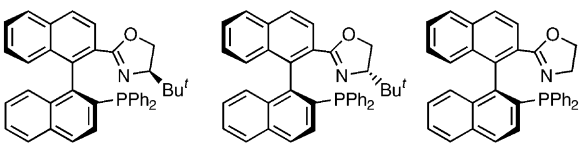
[a] Reactions were carried out in thoroughly-degassed DMSO at 100 °C with 5 mol% of $[(MeCN)_4Pd](BF_4)_2$ and 10 mol% of (*R*)-SEGPHOS.
[b] The e.e. value were based on chiral GC and/or HPLC analyses.

Table 2
Enantioselective ene-type spiro-cyclization of 1,6-enyne ether **1c** catalyzed by cationic Pd^{II} complexes with chiral PN-ligand[a]



Entry	PN-ligand	Yield (%) (e.e. (%)[b])		Total e.e. value (%)
		2c	**3c**	
1	(a*S*, *R*)-**5a**	22 (96)	77 (78)	82
2	(a*S*, *S*)-**5b**	32 (88)	65 (76)	80
3	(a*S*)-**6**	58 (61)	23 (27)	51

[a] Reaction were carried out in thoroughly-degassed DMSO at 100 °C with 5 mol% of $[(MeCN_4Pd)](BF_4)_2$, 10 mol% of PN-ligand and 50 mol% of HCOOH.
[b] The e.e. value were based on chiral GC and/or HPLC analyses.



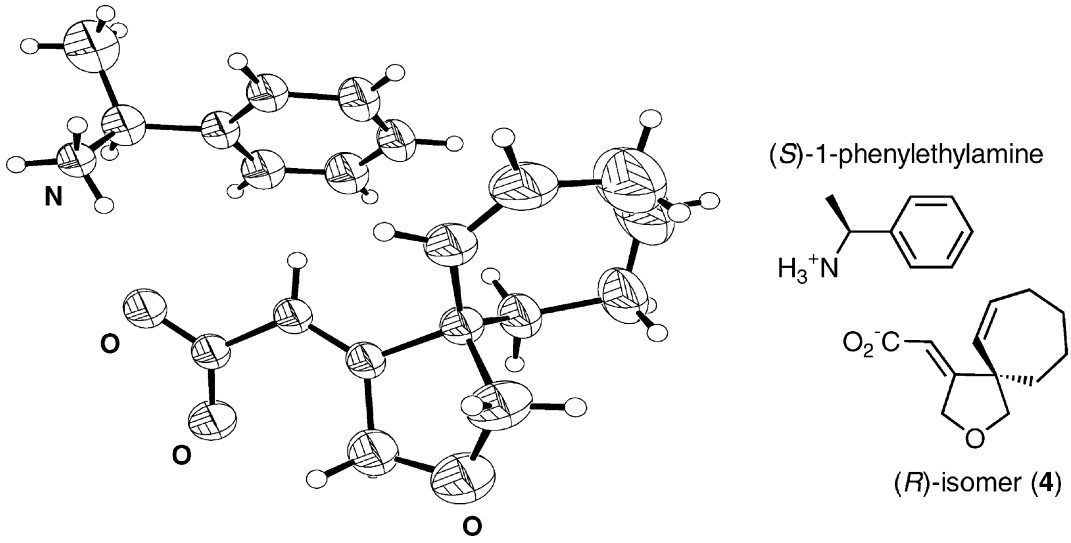


Fig. 1. ORTEP representation and structual formula of the (*S*)-1-phenylethylamine salt ((*R*)-derivative (**4**) from (a*R*)-PN-ligands).

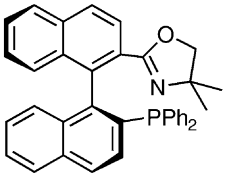
spiro-cyclizations. In sharp contrast to PP-ligand, PN-ligands **5a** and **5b** having a *tert*-Bu oxazoline unit were found to be effective to give the spiro-product **2c** with (*S*)-sense in excellent yields and good enantioselectivities (over 80% e.e.) with olefin-migrations (Table 2, entries 1 and 2). The absolute configuration of **2c** was determined by X-ray crystallographic analysis,[3] as a chiral amine salt of the corresponding carboxylic acid **4** with (*S*)-1-phenylethylamine. ORTEP drawings are shown in Fig. 1. On the other hand, PN-ligand **6** having no alkyl substituent in oxazoline unit showed poor enantiomeric excess (total 51% e.e., entry 3). These results imply that the center of chirality (*R* or *S*) at the 4-position of the oxazoline is *not* important but the presence of sterically demanding alkyl substituent is necessary to achieve higher enantioselectivity.

Finally, our effective (a*S*)-PN-ligand **7**, *doubly* substituted by methyl groups, was executed. For 7-membered ring **1c**, PN-ligand **7** provided the corresponding spiro-products **2c** and **3c** with higher enantiomeric excess (total 84% e.e.) and in excellent yield (Table 3, entry 3). Even for other membered rings, spiro-cyclization proceeded successfully; as a total value, 88% e.e. and 95% yield for 5-membered ring **1a** (entry 1), 71% e.e. and 83% yield for 6-membered ring **1b** (entry 2). For **1a** with PN-ligand **7**, olefin-migration was prevented, so that enantio-enriched **2a** was major product with isomeric **3a**. Medium 8-membered ring substrate **1d** also cyclized successfully in 84% e.e. and 94% yield (entry 4). For large ring system of 15-membered ring **1e**, spiro-cyclization proceeded successfully not accompanying with the olefin-migration, to afford the single product **2e** in 83% e.e. and in almost quantitative yield (entry 5).[4]

[3] **2c** was converted to the corresponding carboxylic acid **4** through hydrolysis, and then crystallized as a diastereomeric salt of (*S*)-1-phenylehtylamine in a CH_2Cl_2–hexane–AcOEt mixture at room temperature. Crystal data for this salt in X-ray analysis: formula $C_{12}H_{16}O_3{\cdot}C_8H_{11}N$, orthorhombic, space group $P2_12_12_1$ (#19), $a = 14.205(2)$ Å, $b = 19.760(3)$ Å, $c = 6.735(3)$ Å, $V = 1890.5(10)$ Å^3, $Z = 4$, and $D = 1.157$ g/cm^3. X-ray diffraction data were collected on a Rigaku AFC7R diffractometer with graphite-monochromated Mo Kα ($\lambda = 0.71069$ Å) at -20 °C and the structure was solved by direct methods (SIR97). The final cycle of full-matrix least-squares refinement was based on 2492 observed reflections ($I > 3s(I)$) and 226 variable parameters and converged to $R = 0.0447$ and $R_w = 0.1358$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-188150. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[4] In the presence of 50 mol% of HCOOH, side-product which was reduced in acetylene unit to olefin was obtained in accompany with the desired product **2e**. The presence of HCOOH retards the olefin migrations in all cases.

Table 3
Enantioselective ene-type spiro-cyclization of 1,6-enyne ethers **1** catalyzed by cationic Pd^{II} complexes with (a*S*)-*gem*-dimethyl PN-ligand **7**[a]



(a*S*)-7

Entry	Substrate (ring size)	Reaction time (h)	Yield (%) (e.e. (%)[b])		Total e.e. value (%)
			2	**3**	
1	**1b** (5)	3	88 (88)	7	88
2	**1b** (6)	22	63 (84)	20 (31)	71
3	**1c** (7)	3	13 (88)	78 (83)	84
4	**1d** (8)	6	33 (93)	61 (80)	84
5[c]	**1e** (15)	11	>90 (83)	0 (–)	83

[a] Reactions were carried out in thoroughly-degassed DMSO at 100 °C with 5 mol% of $[(MeCN)_4Pd](BF_4)_2$, 10 mol% of PN-ligand **7** and 50 mol% of HCOOH unless otherwise noted.
[b] The e.e. value were based on chiral GC and/or HPLC analyses.
[c] In the absence of HCOOH.

4. Conclusions

We have established highly efficient ene-type spiro-cyclization of allyl propargyl ethers catalyzed by cationic palladium(II) with a new PN-ligand bearing achiral *gem*-dimethyl oxazoline unit. Wide scope of spiro-compounds, from common to large membered ether rings, were synthesized in high to excellent enantioselectivities almost quantitatively. This is the first example of the asymmetric ene-type spiro-cyclization and of great potential for other ring formations including heterocycles and carbocycles.

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