A New Asymmetric Wacker-Type Cyclization and Tandem Cyclization Promoted by Pd(II)-Spiro Bis(isoxazoline) Catalyst

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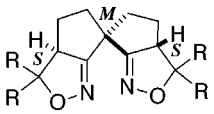
The Pd(II)-catalyzed selective oxidative transformations of alkenes have evolved into a highly useful methodology in synthetic organic chemistry.[1] The intramolecular version of the Wacker reaction, employing oxygen-containing nucleophiles, can provide various heterocyclic compounds.[2] Although catalytic asymmetric Wacker-type cyclizations of *o*-allylphenols have been reported,[3,4] no report has yet been made on alkenyl alcohols as starting materials. In this paper we report a new catalytic asymmetric Wacker-type cyclization of alkenyl alcohols promoted by chiral Pd(II)-spiro bis(isoxazoline) catalysts. Further, we also describe a new catalytic asymmetric tandem cyclization via an oxy-palladation, which gives a unique bicyclic ether compound in one step with up to 95% ee.

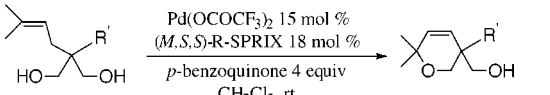
We previously reported the first design and synthesis of the novel spiro bis(isoxazoline) ligands (SPRIXs), which have a chiral spiro skeleton and two isoxazoline rings (Figure 1).[5,6] In view of the good affinity of SPRIXs for Pd(II) and the stability of SPRIXs under the oxidative condition, we envisioned the use of SPRIXs in Wacker-type cyclization. A catalyst system based on (*M*,*S*,*S*)-H-SPRIX (**1a**) and $Pd(OCOCF_3)_2$ promoted the asymmetric Wacker-type cyclization of alkenyl alcohol **2a** in the presence of *p*-bezoquinone in CH_2Cl_2 to give 6-endo cyclized product **3a** in 83% yield in 41% ee (Table 1, entry 1).[7−10] The 6-endo-regioselectivity would be attributed to the stability of the intermediary carbocation. Compared to use of the other two diastereomers of SPRIXs, the use of **1a** showed the highest catalytic activity and ee.[11] Moreover, the bulkiness of substituents on (*M*,*S*,*S*)-SPRIX affected enantioselectivity of products,[12] and by use of **1d**, **3a** was obtained in 70% yield in 70% ee (Table 1, entry 4). To our knowledge, this is the first report of the catalytic asymmetric Wacker-type cyclization of alkenyl alcohols.



1a : R = H (*M*,*S*,*S*)-H-SPRIX
1b : R = Me (*M*,*S*,*S*)-Me-SPRIX
1c : R = Et (*M*,*S*,*S*)-Et-SPRIX
1d : R = *i*-Pr (*M*,*S*,*S*)-*i*-Pr-SPRIX

Figure 1. Spiro bis(isoxazoline) ligands (SPRIXs).

Table 1. Catalytic Asymmetric Wacker-type Cyclization[a]

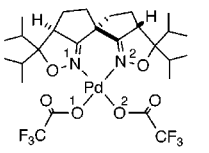


2a : R′ = Me
2b : R′ = Et
2c : R′ = Bn

3a : R′ = Me
3b : R′ = Et
3c : R′ = Bn

entry	R′	(*M*,*S*,*S*)-R-SPRIX	time (h)[b]	yield (%)	ee (%)[c]
1	Me (**2a**)	H-SPRIX (**1a**)	14	83	41
2	Me (**2a**)	Me-SPRIX (**1b**)	14	70	12
3	Me (**2a**)	Et-SPRIX (**1c**)	14	59	53
4	Me (**2a**)	*i*-Pr-SPRIX (**1d**)	21	70	70
5	Et (**2b**)	*i*-Pr-SPRIX (**1d**)	15	86	70
6	Bn (**2c**)	*i*-Pr-SPRIX (**1d**)	18	81	63[d]

[a] All reactions were carried out using in situ prepared catalyst by mixing $Pd(OCOCF_3)_2$ and SPRIX in CH_2Cl_2 at room temperature for 2 h. [b] Reaction was quenched after all of the starting material had been consumed. [c] Determined by chiral HPLC after conversion to the corresponding *p*-nitrobenzoyl ester. [d] Directly determined by chiral HPLC.



bond lengths and angles

Pd-N1	2.002 Å
Pd-N2	2.005 Å
Pd-O1	2.002 Å
Pd-O2	2.013 Å
N1-Pd-N2	88.34°
O1-Pd-O2	89.80°

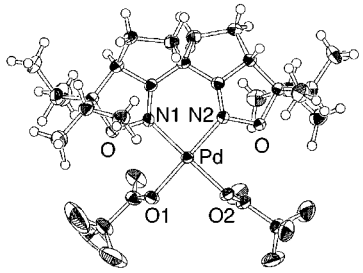


Figure 2. X-ray structure of $Pd(OCOCF_3)_2$-**1d.**

It is notable that the use of known asymmetric catalysts such as $Pd(OCOCF_3)_2$-(*S*,*S*)-ip-boxax,[4] $Pd(OCOCF_3)_2$-BINAP, $Pd(OCOCF_3)_2$-bis(oxazolinyl)propane,[13,14] and $[(3,2,10\text{-}\eta^3\text{-pinene})PdOAc]_2$[3] did not promote the reaction of **2** to give **3**. Monodentate oxazoline ligands[15] gave racemic products (40−50%).[16]

In an effort to clarify the active catalytic species of this reaction, we succeeded in obtaining a single crystal of the Pd-**1d** complex. The X-ray crystallographic analysis of this single crystal revealed that **1d** coordinated to Pd with two nitrogen atoms (Figure 2).[17] Using these single crystals, Wacker-type cyclization of **2b** gave the product **3b** in 80% yield in 69% ee, which was comparable to the result using in situ-prepared catalysis (Table 1, entry 5).[18]

Having developed the Wacker-type cyclization of alkenyl alcohol, we focused on a Pd-catalyzed asymmetric tandem

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(6) SPRIX is an abbreviation of *spi*ro bis(*i*so*x*azoline).

(7) The combinations of (*M*,*S*,*S*)-H-SPRIX and Pd-salts other than $Pd(OCOCF_3)_2$ (e.g., $Pd(OAc)_2$, $Pd(CH_3CN)_4(BF_4)_2$, $PdCl_2$, $PdCl_2$-AgOTf) resulted in low yield.

(8) As solvent effects: CH_3CN (86%, 39% ee), MeOH (41%, 36% ee), THF (35%, 27% ee), toluene (45%, 36% ee).

(9) Four equivalents of *p*-benzoquinone were used for a smooth reaction.

(10) The use of $Cu(OAc)_2$ and O_2 system: 43%, 27% ee, after 48 h.

(11) (*M*,*R*,*R*)-H-SPRIX (30%, 3% ee, after 30 h) and (*M*,*S*,*R*)-H-SPRIX (74%, 22% ee, after 28 h).

(12) Substituted SPRIXs (**1b**−**d**) were readily synthesized in a manner similar to that of **1a**. Experimental details are provided in the Supporting Information. Enantiomerically pure SPRIXs were obtained by chiral stationary phase column chromatography (DAICEL CHIRALPAK AD (ϕ 2 cm × 25 cm)).

(13) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.

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(16) For the results with known Pd-catalysts, see Supporting Information. The reaction with 15 mol % $Pd(OCOCF_3)_2$ without chiral ligand gave racemic **3a** in 63% after 14 h.

(17) Crystal data: orthorhombic; space group $P2_12_12_1$; a = 15.310(3) Å, b = 24.61(1) Å, c = 8.283(3) Å; V = 3120(1) Å^3, Z = 4; Mo Kα radiation (−75 °C); R = 0.049, Rw = 0.050.

(18) Decomposition of **1d** was not observed on NMR under the reaction process.

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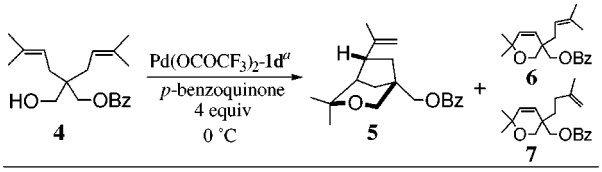
Table 2. The Pd-Catalyzed Asymmetric Tandem Cyclization via the Oxy-palladation



entry	cat. (mol %)	solvent (v/v)	time (h)	yield[c] (%)	product ratio (ee (%)) 5	6	7
1	20	CH_2Cl_2	85[b]	96	68 (95)	5 (45)	27 (60)
2	20	MeOH	24[b]	95	83 (68)	5 (26)	12 (31)
3	20	THF	85	22	20 (88)	77 (11)	3 (22)
4	20	toluene	85	16	17 (85)	74 (31)	9 (45)
5	10	CH_2Cl_2/MeOH (10/1)	28[b]	92	83 (89)	2 (29)	15 (52)
6	10	CH_2Cl_2/MeOH (1/1)	24[b]	99	89 (82)	3 (36)	8 (57)

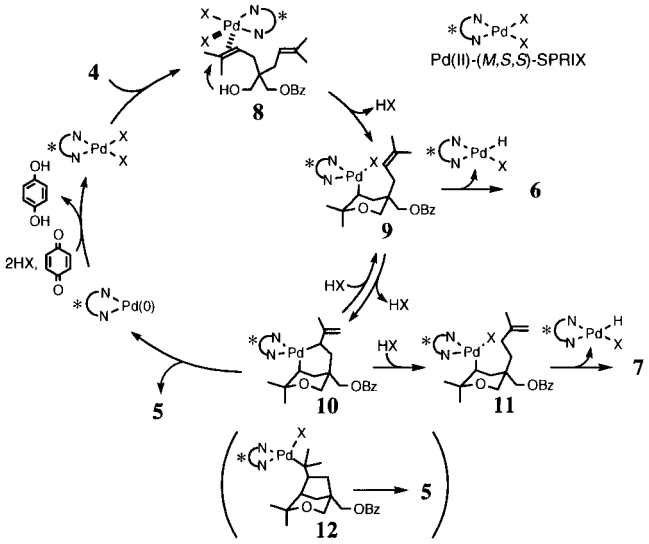
[a] Pd catalyst was prepared in situ by mixing $Pd(OCOCF_3)_2$ and **1d** (Pd:**1d** 1:1.2) at room temperature for 2 h. [b] Reaction was quenched after all of compound **4** had been consumed. [c] Total yield of Wacker-type cyclization products.

cyclization via oxy-palladation using a Pd-SPRIX catalyst. Tandem reactions, which can form several bonds without isolating the intermediates, are a useful and important topic of synthetic chemistry.[19] If the alkyl Pd(II) intermediates resulting from an intramolecular oxy-palladation are trapped by alkenes, the variety of heterocyclic compounds can be synthesized in a single step.[20] In the case of substrate **4**, which contains two C−C double bonds, the $Pd(OCOCF_3)_2$-**1d** catalyst efficiently gave a bicyclic compound **5**[21] as a single diastereomer. The tandem product **5** was obtained in 95% ee in CH_2Cl_2, along with dihydropyranes **6** and **7**, which were generated by β-elimination (the ratio of **5**:**6**:**7** = 68:5:27) (Table 2, entry 1).[21,22]

MeOH as a solvent increased the ratio of the bicyclic compound **5**, though the ee of **5** was slightly decreased (Table 2, entry 2). Balancing the factors of yield and ee of **5** led to the use of a mixed CH_2Cl_2/MeOH solvent system, which realized good yield and ee of **5** (Table 2, entries 5 and 6). In the mixed solvent system, the reaction proceeded with 10 mol % of the catalyst.

The plausible mechanism of tandem cyclization is shown in Scheme 1. Intramolecular nucleophilic attack of the hydroxy group at the activated C−C double bond of the complex **8** would afford the alkyl Pd(II) intermediate **9**, then another C−C double bond would coordinate to Pd(II) intramolecularly. Further C−C bond

Scheme 1. Plausible Mechanism of Tandem Cyclization via the Oxy-palladation



formation would afford the bicyclic product **5** via the formation of a palladacycle **10** or a direct insertion intermediate **12**. The monocyclic products **6** and **7** would be the result of β-elimination from the intermediates **9** and **11**, respectively. When the isolated monocyclic product, either **6** or **7**, was again treated under the tandem cyclization conditions, **10** was not obtained and the monocyclic product was recovered without isomerization. This result would indicate that **5** was produced in a sequential reaction. The addition of MeOH increased the yield of the tandem product **5**, and suppressed the generation of β-elimination product **7**. This effect of MeOH would be responsible for the acceleration of the reductive elimination from the palladacycle intermediate **10**.

In summary, we developed the catalytic asymmetric Wacker-type cyclization of alkenyl alcohols promoted by a Pd-SPRIX catalyst. Moreover, we demonstrated the Pd-catalyzed asymmetric tandem cyclization via the oxy-palladation in up to 95% ee. The details of the mechanism of the tandem cyclization and its application to the synthesis of biologically important compounds are now under investigation.

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Supporting Information Available: Detailed experimental procedures and ^1H, ^{13}C NMR, NOE, IR, mass spectra, and X-ray crystallographic analysis data for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA005920W

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(21) The absolute configurations of the major enantiomers of **5**−**7** have not been determined yet. For the determination of the product ratio of **5**:**6**:**7**, and for the elucidation of relative configuration of **5** by NOE study, see Supporting Information.

(22) Without **1d**, the Wacker cyclization of **4** proceeded very slowly to give **6** as the major product.