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Enantioselective synthesis of α-methylene-γ-butyrolactones using chiral Pd(II)-SPRIX catalyst

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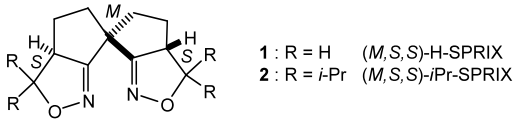
Abstract—Combination of $Pd(OCOCF_3)_2$ and (*M*,*S*,*S*)-*i*Pr-SPRIX ligand promoted the intramolecular cyclization of 2-alkynoates very effectively to form α-methylene-γ-butyrolactones in good yields with up to 92% ee.

Chiral metal complex catalyzed enantioselective reactions have gained a lot of interest in the synthesis of natural and non-natural biologically active compounds. In particular, Pd(0)-catalyzed enantioselective reactions have been extensively reported in the literature.[1] However, the redox type catalytic asymmetric reaction with Pd(II) species has received less attention due to the use of excess amount of oxidants to regenerate Pd(II) species from Pd(0) species formed in the catalytic cycle.[2] Recently, Lu and co-workers have developed the first example of asymmetric synthesis of α-methylene-γ-butyrolactones through the carbocyclization of enyne esters catalyzed by Pd(II) species using bidentate nitrogen-containing ligands.[3] The optically active α-methylene-γ-butyrolactones are useful chiral building blocks for construction of various natural products such as alkaloids, macrocyclic antibiotics, lignan lactones and pheromones.[4] Due to their wide range of biological properties and useful synthons in organic synthesis, considerable efforts have been devoted towards this class of compounds.[5,6]

We have recently reported new chiral spiro bis(isoxazoline) ligands (SPRIXs) (Fig. 1) for catalytic asymmetric reactions.[7–9] Indeed, the first enantioselective Wacker-type cyclization of alkenyl alcohol has been developed using Pd(II)-SPRIX catalysts.[8] The good affinity of SPRIXs for Pd(II) and the stability of SPRIXs under acidic and basic as well as oxidative conditions encouraged us to further explore the utility of SPRIXs as chiral ligand.[9] In this connection, herein we report the enantioselective synthesis of α-methylene-γ-butyrolactones by the $Pd(OCOCF_3)_2$-(*M*,*S*,*S*)-*i*Pr-SPRIX catalyzed intramolecular cyclization of (*Z*)-4′-acetoxy-2′-butenyl-2-alkynoates **3**.



1 : R = H (*M*,*S*,*S*)-H-SPRIX
2 : R = *i*-Pr (*M*,*S*,*S*)-*i*Pr-SPRIX

Figure 1.

First, the intramolecular cyclization of **3a** was examined using (*M*,*S*,*S*)-H-SPRIX (**1**)-$Pd(OAc)_2$ (20:10 mol%) and the reaction was proceeded smoothly to give the expected product α-(*Z*)-(1′-acetoxyethylidene)-β-vinyl-γ-butyrolactone **4a** in 76% yield with moderate enantioselectivity (Table 1, entry 1). In our previous study, we reported that the combination of (*M*,*S*,*S*)-*i*Pr-SPRIX (**2**) and $Pd(OCOCF_3)_2$ as the metal source was very effective in the Wacker-type cyclization and resulted in higher ee and yield.[8] Interestingly, when the cyclization of **3a** was carried out using (*M*,*S*,*S*)-*i*Pr-SPRIX (**2**) (20 mol%) and $Pd(OCOCF_3)_2$ (10 mol%) a significant improvement in the enantioselectivity as well as the yield was observed (Table 1, entry 3).[10] This result clearly suggests that substitution on SPRIX is very crucial and makes more favorable chiral environment around the palladium sphere which facilitate the formation of product with higher enantiomeric excess when compared to non-substituted SPRIX (**1**) for the present system. Other Pd(II) salts such as $Pd(acac)_2$, $(CH_3CN)_2PdCl_2$, $PdCl_2$(1,5-octadiene), $[(CH_3CN)_4Pd](BF_4)_2$ and $[CF_3COCH{=}C(O\text{-})CF_3]_2Pd$ with **2** were less

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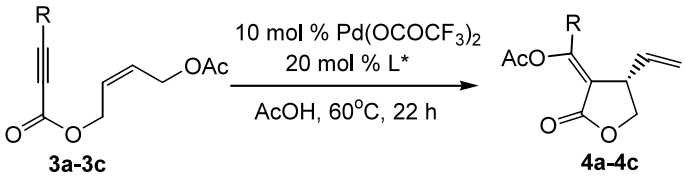
Table 1. Asymmetric Pd(II)-L* catalyzed cyclization of 4′-acetoxy-2′-butenyl-2-alkynoates **3**



Entry	R	L*	Pd-source	Yield (%)[a]	ee (%)[b,c]
1	Me (**3a**)	**1**	$Pd(OAc)_2$	76 (**4a**)	33
2	Me (**3a**)	**1**	$Pd(OCOCF_3)_2$	78 (**4a**)	38
3	Me (**3a**)	**2**	$Pd(OCOCF_3)_2$	85 (**4a**)	85
4[d]	Me (**3a**)	**2**	$Pd(OCOCF_3)_2$	70 (**4a**)	71
5	Ph (**3b**)	**2**	$Pd(OCOCF_3)_2$	65 (**4b**)	76
6	*n*-Pr (**3c**)	**2**	$Pd(OCOCF_3)_2$	82 (**4c**)	76
7	Me (**3a**)	**5**	$Pd(OCOCF_3)_2$	40 (**4a**)	20

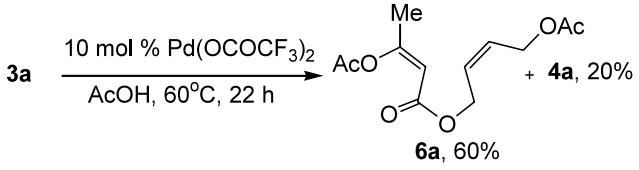
[a] Yield of isolated purified compound **4**.
[b] Determined by chiral stationary phase HPLC using Chiralcel OJ column and hexane:2-propanol (8:2) as eluent ($\lambda = 214$ nm).
[c] The major enantiomer had the (*S*) configuration (based on the known elution order).
[d] Using 10 mol% of **2**.

effective in terms of reactivity and enantioselectivity than that of $Pd(OCOCF_3)_2$-(*M*,*S*,*S*)-*i*Pr-SPRIX catalyst in the reaction of **3a**.[11] To probe the ligand acceleration effect, the reaction of **3a** with 10 mol% of $Pd(OCOCF_3)_2$ in the absence of SPRIX ligands gave the hydroacetoxylation product **6a** in 60% yield together with the cyclized product **4a** in 20% yield (Scheme 1). The above result strongly suggests that the bidentate SPRIX ligands play an important role in inhibiting the formation of hydroacetoxylation product **6** and accelerate the cyclization to form **4** in the enantioselective reaction. When the ligand ratio was reduced to 10 mol%, the optical purity of the product **4a** was decreased to 71% ee (Table 1, entry 4).

To further examine the scope of the $Pd(OCOCF_3)_2$-**2** catalyzed cyclization, the reactions with phenyl (**3b**) and *n*-Pr (**3c**) substituted substrates were investigated. The cyclization of **3b** and **3c** proceeded smoothly with good enantioselectivities (Table 1, entries 5 and 6). These results are comparable to the previous method using oxazoline ligands.[3] It should be noted that after completion of the reaction, the (*M*,*S*,*S*)-*i*Pr-SPRIX (**2**) ligand has been recovered.

In the case of chiral ligands (*S*)-**5**[12] (Fig. 2) and (*S*)-BINAP, the catalyst generated using ligand **5** afforded the product **4a** in low yield with low ee (Table 1, entry 7) whereas BINAP failed to promote the reaction and the substrate **3a** was recovered after 48 h.

Lu et al. noted that the formation of γ-butyrolactones is highly concentration dependent.[3b] At higher substrate concentration (1 M), the intermolecular coupling product **8** was formed along with cyclized product **4a** using (*R*)-2,2′-isopropylidene-bis(4-phenyl-2-oxzoline) (**7**) as ligand (Scheme 2). They obtained **4a** in 78% yield with 92% ee at 0.1 M concentration of **3a**. In contrast, when the reaction was performed at 1 M concentration using **2** as ligand, the cyclized product **4a** was formed



Scheme 1. $Pd(OCOCF_3)_2$-catalyzed reaction of **3a** in the absence of **2**.

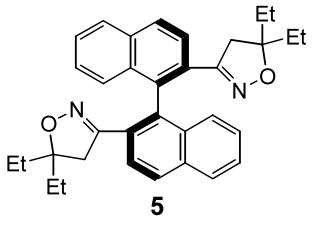
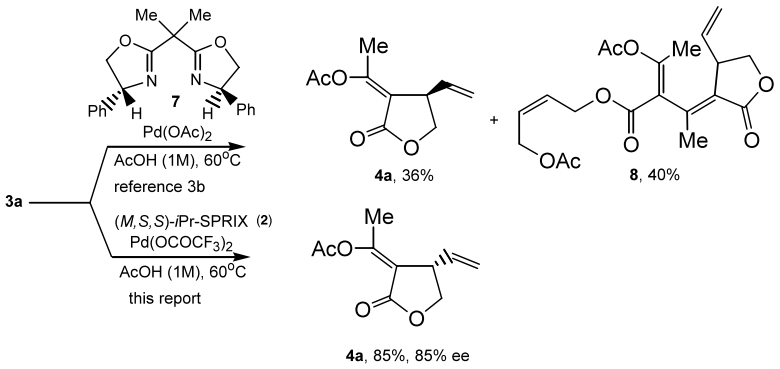


Figure 2.

exclusively (Scheme 2). We then studied the effect of temperature on $Pd(OCOCF_3)$-**2** catalyzed cyclization of **3a** to **4a** and found that the enantioselectivity was significantly affected at different temperatures (Table 2). For example, when the reaction was carried out at 40°C, the enantiomeric excess was found to be lower than at 60°C (Table 2, entries 1 and 2). This observation is slightly different from the reported method where at low temperature the ee was increased slightly (Table 2, entries 5 and 6).[3] At higher temperatures, the cyclized product was formed in 75 and 65% yield with 82 and 76%, ee respectively (Table 2, entries 3 and 4). In order to check the effect of additive, the cyclization of **3a** was performed in the presence of 1 equivalent of lithium acetate using $Pd(OCOCF_3)_2$-**2** catalyst in AcOH and very high yield was obtained with the same enantioselectivity (Table 2, entry 7).



Scheme 2.

Table 2. Temperature and additive effect on Pd(II)-**2** catalyzed cyclization of **3a** to **4a** in AcOH for 22 h

Entry	Ligand	Pd-source	Additive	Temp. (°C)	Yield (%)	Ee (%)[a]
1	**2**	$Pd(OCOCF_3)_2$	–	40	70	55
2	**2**	$Pd(OCOCF_3)_2$	–	60	85	85
3	**2**	$Pd(OCOCF_3)_2$	–	80	75	82
4	**2**	$Pd(OCOCF_3)_2$	–	100	65	76
5[b]	Pymox	$Pd(OAc)_2$	–	40	89	83
6[b]	Pymox	$Pd(OAc)_2$	–	60	88	81
7	**2**	$Pd(OCOCF_3)_2$	1 equiv. LiOAc	60	90	86

[a] Determined by chiral HPLC using chiralcel OJ column and hexane:2-propanol (8:2) as eluent ($\lambda = 214$ nm).
[b] Results in Ref. 3 using (*R*)-phenyl substituted pyridyl monooxazoline (pymox) ligand.

Furthermore the solvent effect on the cyclization of **3a** to **4a** using Pd(II)-**2** catalyst has been studied and the results are presented in Table 3. When the reaction was performed using a mixture of solvent (AcOH:CH_3CN, 1:1), **4a** was obtained in 80% yield and 67% ee (entry 1). Similar results were also observed using the combination of THF and AcOH (1:1, entry 2). The enantioselectivity of product was found to be sensitive to the addition of polar solvents. In the reaction of **3a** using 10:1 ratio of toluene and AcOH, the Pd(II)-**2** catalyst gave 10% of the target product **4a** with 72% ee along with uncylized product **9** (entry 3).[13] On the other hand, when the reaction of **3a** was carried out using 10:1 ratio of AcOH and toluene, the enantioselectivity of **4a** was improved to 88% ee with 85% yield (entry 4). We were pleased to observe that the activity of the catalyst was dramatically enhanced by the addition of MS 4A affording the product **4a** in 87% yield with 92% ee (entry 5). We have also performed the Pd(II)-**2** catalyzed cyclization of **3a** using 1:1 ratio of AcOH and ionic liquid (1-butyl-3-methyl-imidazolium tetrafluoroborate) and the cylized product **4a** was obtained in 60% yield with 68% ee (entry 6).

Table 3. Effect of solvent on Pd(II)-**2** catalyzed cyclization of **3a** to **4a**[a]

Entry	Solvent	Yield **4a** (%)	ee (%)
1	CH_3CN:AcOH (1:1)	80	67
2	THF:AcOH (1:1)	82	67
3	Toluene:AcOH (10:1)	10	72
4	Toluene:AcOH (1:10)	85	88
5	Toluene:AcOH (1:10)[b]	87	92
6	$[BMIM][BF_4]$[c]:AcOH (1:1)	60	68

[a] Reaction time was 22 h.
[b] MS 4A (100 mg/1 mmol of **3a**).
[c] 1-Butyl-3-methyl-imidazolium tetrafluoroborate.

As far as the reaction mechanism is concerned, it is expected to involve the nucleophilic attack of acetate on palladium coordinated alkyne followed by the intramolecular olefinic insertion and ring closure to give butyrolactones and the active catalyst via deacetoxypalladation.[3] On the basis of present results, the formed intermediate is stable enough in reaction medium and facilitate the formation of cyclized product much faster than that of protonolysis product (Scheme 3).

In summary, we have presented a new combination of $Pd(OCOCF_3)_2$-**2** protocol for the enantioselective synthesis of α-methylene-γ-butyrolactones in good yield with up to 92% ee. Future study will be focused on the improvement of enantioselectivity and development of reusable catalyst using ionic liquid as solvent.

Acknowledgements

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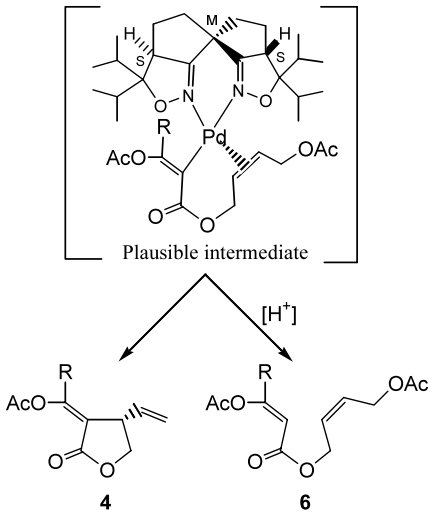

Scheme 3.

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10. Typical procedure: To a stirred solution of $Pd(OCOCF_3)_2$ (8.3 mg, 0.025 mmol) and (*M*,*S*,*S*)-*i*Pr-SPRIX (18.7 mg, 0.050 mmol) in acetic acid (1.0 mL) at 60°C was added **3a** (50 mg, 0.25 mmol) in acetic acid (2.0 mL). The reaction mixture was stirred for 22 h at 60°C. After completion of the reaction, diethyl ether (50 mL) was added and the mixture was washed with $NaHCO_3$ (2×20 mL) and brine (2×20 mL). The ether layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was subjected into column chromatography on silica gel (hexane:ethyl acetate 8.5:1.5), affording **4a** as oil. Analytical data for **4a**, **4b**, **4c** and **6a** matched with the literature report.[3]
11. Combinations of **2** with other Pd(II)-salts: $Pd(acac)_2$ (52%, 45% ee), $(CH_3CN)_2PdCl_2$ (65%, 50% ee), $PdCl_2$(1,5-octadiene) (62%, 56% ee), $[(CH_3CN)_4Pd](BF_4)_2$ (50%, 45% ee) and $[CF_3COCH{=}C(O\text{-})CF_3]_2Pd$ (55%, 46% ee).
12. Shinohara, T.; Wakita, K.; Arai, M. A.; Arai, T.; Sasai, H. *Heterocycles* **2003**, *59*, 587–593.
13. The structure of compound **9** was confirmed by IR (cm^{-1}), NMR and Mass spectroscopy. IR: 1734, 1716, 1655, 1363, 1225. ^1H NMR ($CDCl_3$): δ 2.10 (s, 3H), 2.30 (s, 3H), 3.40 (s, 2H), 4.66 (d, $J=5.2$ Hz, 2H), 4.74 (d, $J=5.3$ Hz, 2H), 5.80–5.70 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 20.94, 30.24, 49.91, 59.89, 60.75, 127.22, 128.48, 166.59, 170.51, 200.03. HRMS (ESI-TOF): calcd for $C_{10}H_{14}NaO_5$ 237.0739. Found 237.0767.