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Pd^{II}/Pd^{IV} Catalytic Enantioselective Synthesis of Bicyclo[3.1.0]hexanes via Oxidative Cyclization of Enynes

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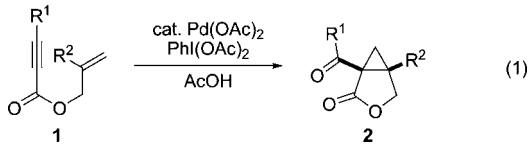
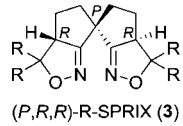
Asymmetric catalysis is unarguably an efficient and economically feasible protocol for the synthesis of optically active organic compounds in both academia and industry. Palladium is one of the most widely used metals in such processes. Compared to the impressive development of enantioselective reactions through the Pd^0/Pd^{II} catalytic cycle,[1] only minimal attention has been devoted to exploring asymmetric Pd^{II}/Pd^{IV} catalysis. Recently, catalytic reactions via Pd^{IV} intermediates generated from a Pd^{II} precursor by the action of a powerful oxidant (*e.g.* a hypervalent iodine reagent) have been developed.[2−5] In 2007, the Tse and Sanford groups independently reported an exquisite Pd^{II}/Pd^{IV} catalytic cyclization of enynes **1** affording lactones **2** with a bicyclo[3.1.0]hexane skeleton (eq 1).[6,7] Since such a molecule in optically pure form has been utilized successfully for the synthesis of an antiherpetic agent,[8a] a protein kinase C-β inhibitor (JTT-010),[8b] and an anticonvulsant drug (pregabalin),[8c] **2** promises to be a versatile building block for biologically active molecules. Hence we decided to investigate a catalytic enantioselective synthesis of **2** from **1**.



1 **2** (1)

We have found that spiro bis(isoxazoline) compounds **3**, abbreviated as SPRIXs, serve as effective chiral ligands in Pd-catalyzed enantioselective transformations.[9] The high affinity of SPRIXs for Pd^{II} and the remarkable stability of SPRIXs under oxidative conditions prompted us to utilize them in asymmetric reactions involving key Pd^{IV} intermediates. Herein we report an enantioselective oxidative cyclization of enyne derivatives catalyzed by the Pd−SPRIX complex, which is, to the best of our knowledge, the first example of asymmetric Pd^{II}/Pd^{IV} catalysis.

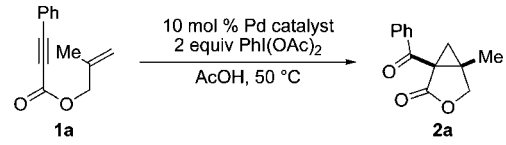


(*P*,*R*,*R*)-R-SPRIX (**3**)

R = *i*-Pr : **3a**
Et : **3b**
Me : **3c**
H : **3d**

Treatment of 2-methylallyl phenylpropiolate (**1a**) with 10 mol % of $Pd(OCOCF_3)_2$ and (*P*,*R*,*R*)-*i*-Pr-SPRIX **3a** in the presence of 2 equiv of $PhI(OAc)_2$ in AcOH at 50 °C afforded 1-benzoyl-5-methyl-3-oxabicyclo[3.1.0]hexan-2-one (**2a**)[10] in 80% yield with 45% ee (Table 1, entry 1). When the reaction was conducted without (*P*,*R*,*R*)-**3a** under otherwise identical conditions, a 94% yield of **2a** was obtained (entry 2). Noteworthy is that no enantioselectivity

Table 1. Optimization of Reaction Conditions[a]



1a **2a**

entry	Pd catalyst	time (h)	yield (%)[b]	ee (%)[c]
1	$Pd(OCOCF_3)_2$ + (*P*,*R*,*R*)-**3a**	8	80	45
2	$Pd(OCOCF_3)_2$	8	94	—
3	$Pd(OCOCF_3)_2$ + (*R*)-BINAP	8	56	*rac*
4	$Pd(OCOCF_3)_2$ + (−)-sparteine	8	87	*rac*
5	$Pd(OCOCF_3)_2$ + (*S*,*S*)-*t*-Bu-BOX	8	39	2
6	$Pd(OCOCF_3)_2$ + (*S*,*S*)-*i*-Pr-BOXAX	8	71	4
7	$Pd(OCOCF_3)_2$[(*P*,*R*,*R*)-**3a**]	8	79	56
8[d]	$Pd(OCOCF_3)_2$[(*P*,*R*,*R*)-**3a**]	8	88	77
9[d,e]	$Pd(OCOCF_3)_2$[(*P*,*R*,*R*)-**3a**]	30	96[f]	85
10[d,e,g]	$Pd(OCOCF_3)_2$[(*P*,*R*,*R*)-**3a**]	120	89[f]	92
11[d,e,g,h]	$Pd(OCOCF_3)_2$[(*P*,*R*,*R*)-**3a**]	120	87[f]	91

[a] All reactions were carried out in the presence of 10 mol % of the palladium complex and/or the chiral ligand and 2 equiv of $PhI(OAc)_2$ at 50 °C in AcOH (0.1 M) under an argon atmosphere unless otherwise noted. [b] NMR yield based on hydroquinone dimethylether as an internal standard. [c] Determined by HPLC analysis (Daicel Chiralpak AS-H). [d] In AcOH−MeCN (9:1). [e] With an additional 5 mol % of **3a**. [f] Isolated yield. [g] At 30 °C with 4 equiv of $PhI(OAc)_2$. [h] Under air.

was observed with other known chiral ligands such as (*R*)-BINAP, (−)-sparteine, (*S*,*S*)-*t*-Bu-BOX, and (*S*,*S*)-*i*-Pr-BOXAX (entries 3−6).[11] Presumably, (*R*)-BINAP and (−)-sparteine did not work as ligands because of the formation of a phosphine oxide and an ammonium salt, respectively. From the ^1H NMR analysis in AcOH-d_4, it became obvious that (*S*,*S*)-*t*-Bu-BOX decomposed, whereas *i*-Pr-SPRIX **3a** was stable even in the presence of $PhI(OAc)_2$. These results clearly demonstrate the high stability of **3a** under such oxidative and acidic conditions, which has proven to be crucial for this asymmetric Pd^{II}/Pd^{IV} catalysis. Preformed $Pd(OCOCF_3)_2$[(*P*,*R*,*R*)-**3a**] complex gave a better result compared to the complex prepared in situ (entries 1 and 7). Solvent screening showed that a 9:1 mixture of AcOH and CH_3CN increased the selectivity to 77% ee (entry 8). Addition of an extra 5 mol % of (*P*,*R*,*R*)-**3a** suppressed the background reaction effectively to furnish **2a** in 96% yield with 85% ee (entry 9). Upon lowering the temperature, better enantioselectivity was observed. Thus, **2a** was obtained in 89% yield with 92% ee when the reaction was performed at 30 °C for 120 h with 4 equiv of $PhI(OAc)_2$ (entry 10).[12] Furthermore, the reaction proceeded with no loss of efficiency or selectivity under air (entry 11).

To explore the substrate scope of this asymmetric cyclization, we examined a variety of enynes (Table 2). Alkyl and aryl substituents having an electron-withdrawing as well as an electron-

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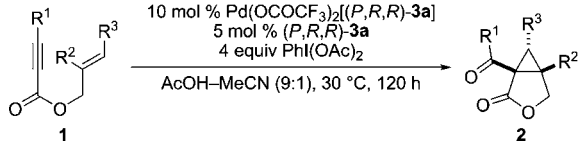
Table 2. Substrate Scope of Asymmetric Oxidative Cyclization of Enynes **1**[a]



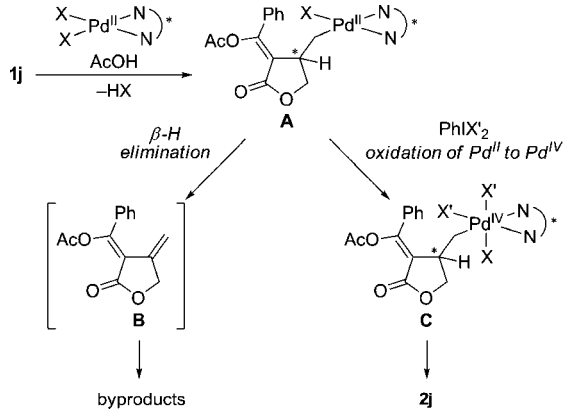
1 **2**

entry	**1**	R^1	R^2	R^3	**2**	yield (%)[b]	ee (%)[c]
1	**1a**	Ph	Me	H	**2a**	89	92
2	**1b**	Pr	Me	H	**2b**	66	87
3	**1c**	4-ClC_6H_4	Me	H	**2c**	78	93
4[d]	**1d**	4-$MeOC_6H_4$	Me	H	**2d**	89	80
5	**1e**	2-naphthyl	Me	H	**2e**	92	91
6	**1f**	Ph	Et	H	**2f**	78	91
7	**1g**	Ph	BOM	H	**2g**	81	94
8	**1h**	Ph	Ph	H	**2h**	14	83
9	**1i**	Ph	Me	CO_2Et	**2i**	trace	ND[e]
10[d]	**1j**	Ph	H	H	**2j**	23	84
11[f,g]	**1j**	Ph	H	H	**2j**	62	95

[a] Reaction conditions: **1** (0.15 mmol), $Pd(OCOCF_3)_2$[(*P*,*R*,*R*)-**3a**] (10 mol %), (*P*,*R*,*R*)-**3a** (5 mol %), and 4 equiv of $PhI(OAc)_2$ in AcOH (1.35 mL)−MeCN (0.15 mL) at 30 °C for 120 h. In each case, the starting material was almost consumed at the end of the reaction. [b] Isolated yield. [c] Determined by HPLC analysis. [d] For 96 h. [e] Not determined. [f] For 72 h. [g] 4 equiv of $PhI(OCOCF_3)_2$ were used instead of $PhI(OAc)_2$. BOM = benzyloxymethyl.

donating group are tolerated on the alkyne component (entries 2−5). Similar to **1a**, the reactions of **1f** (R^2 = Et) and **1g** (R^2 = benzyloxymethyl) gave the products **2f** and **2g** in good yields (78% and 81%) and high enantioselectivities (91% ee and 94% ee), respectively (entries 6 and 7). Despite the low chemical yield, not only alkyl-substituted allyl moieties but also the phenyl-substituted substrate **1h** participated in this cyclization to afford **2h** with 83% ee (entry 8). The product **2i** was obtained in only trace amounts, probably due to the steric hindrance of the CO_2Et group (entry 9). Although **1j** bearing an allyl group was consumed more quickly than the methallyl substrate **1a**, the corresponding product **2j** was isolated in only 23% yield (entry 10). We speculated that β-H elimination from the alkyl−Pd intermediate **A** competed significantly with the oxidation of Pd^{II} to Pd^{IV} (intermediate **C**), resulting in the formation of byproduct via the possible diene product **B** (Scheme 1). A more powerful oxidant would therefore promote

Scheme 1. Plausible Pathway to Byproducts in the Reaction of **1j**



the desirable oxidation process producing **2j**. As expected, the use of $PhI(OCOCF_3)_2$ in lieu of $PhI(OAc)_2$ led to a pronounced increase of the yield to 62% (entry 11). It should be noted that in this case the enantioselectivity was also improved to 95% ee.[13]

In summary, we have developed the first asymmetric Pd^{II}/Pd^{IV} catalysis using hypervalent iodine reagents as the oxidant, which provided two contiguous chiral quaternary carbon centers. Chiral ligand *i*-Pr-SPRIX **3a** is found to be suitable for the oxidative cyclization of enynes **1**,[14] leading to bicyclic lactones **2**[15] with up to 95% ee. The unique robustness of **3** may allow us to realize various asymmetric Pd^{II}/Pd^{IV} catalyses. Further investigation into the application of SPRIX ligands to such catalytic enantioselective syntheses and transformation of the products **2** to biologically active molecules are now in progress.

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Supporting Information Available: Experimental details including screening of the reaction conditions and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Since NMR data of **2a** are very consistent with those reported in ref 6b, the relative configuration is certainly established as depicted.
(11) Abbreviations: (*R*)-BINAP = (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; (*S*,*S*)-*t*-Bu-BOX = 2,2-bis[(4*S*)-4-*tert*-butyl-2-oxazolin-2-yl]propane; (*S*,*S*)-*i*-Pr-BOXAX = (*S*)-2,2′-bis[(4*S*)-4-isopropyl-2-oxazolin-2-yl]-1,1′-binaphthyl.
(12) The results using other SPRIX ligands: **3b**: 88% yield, 60% ee; **3c**: 91% yield, 59% ee; **3d**: 65% yield, 25% ee. See Supporting Information.
(13) Although improvement of the enantioselectivity was also observed for other substrates by using $PhI(OCOCF_3)_2$, the chemical yield was drastically diminished: for example, **1a**: 32% yield, 96% ee.
(14) Preliminary examination using enyne substrates with either an ether or an amide linkage gave an inseparable mixture in each case.
(15) The absolute configuration of the products is tentatively assigned to be (1*R*,5*S*) by comparison of the sign of optical rotation with the value for a similar compound reported in refs 8a and 8c.

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