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Enantioselective Cyclization of 4-Alkenoic Acids via an Oxidative Allylic C−H Esterification

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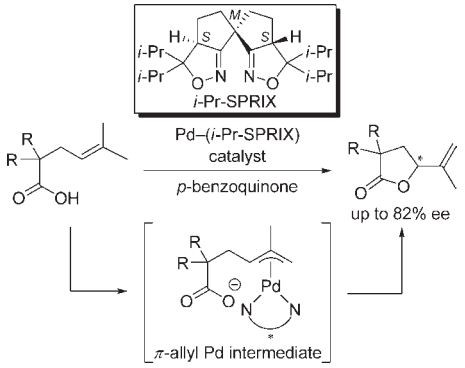
ABSTRACT



An enantioselective intramolecular oxidative cyclization of 4-alkenoic acids was developed. The reaction proceeded via a π-allyl Pd intermediate generated by an allylic C−H activation to give γ-lactone derivatives with moderate to good enantioselectivity. Spiro bis(isoxazoline) ligand, SPRIX, was indispensable for this asymmetric transformation.

A Pd-catalyzed allylic substitution, ordinarily referred to as the Tsuji−Trost reaction, is known to be one of the most practical methods in synthetic chemistry due to its broad applicability.[1,2] Installation of a leaving group on substrates is a prerequisite for the generation of a key π-allyl Pd intermediate. It has also been realized that a Pd(II)-catalyzed oxidative allylic C−H bond activation allows an emergence of the π-allyl Pd species without any leaving groups.[3] Hence, such oxidative functionalizations of allyl compounds have recently been refocused because of their environmental friendliness.[4,5] In this kind of reaction, a carboxy group serves as the nucleophile to afford allyl esters, which is usually difficult in the conventional allylic substitution due to the high reactivity of the products toward the catalysts.[6] Further expansion of this

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catalysis into asymmetric transformations has been reported. White and co-workers have accomplished an enantioselective allylic C−H acetoxylation using a combination of Pd(II)-bis(sulfoxide) and optically active Cr(III)-salen catalysts.[7] If enantioselective oxidative allylic substitutions were governed by only a chiral Pd catalyst, as in Tsuji−Trost reactions, they might offer a promising and eco-conscious synthetic protocol for obtention of optically active allyl esters. We have already discerned that SPRIX, a chiral ligand possessing isoxazoline coordination units on a spiro backbone, leads to Pd exhibiting a unique reactivity in asymmetric oxidative reactions upon coordination.[8] This exceptional property of SPRIX caused us to develop an enantioselective oxidative allylic substitution. Here, we disclose an enantioselective intramolecular oxidative C−H esterification promoted by the Pd−SPRIX catalyst.

In 1993, Larock and Annby independently published an oxidative cyclization of 4-alkenoic acids **1** producing racemic γ-lactones **2** in good yields (Scheme 1).[9] Since they mentioned the possibility of the π-allyl Pd mechanism,[10] we applied SPRIX to this catalytic reaction. To our delight, in the reaction of 5-methyl-2,2-diphenylhex-4-enoic acid (**1a**), the desired lactone product **2a** was obtained in an optically active form. Thus, **1a** was stirred with 10 mol % of $Pd(OAc)_2$, 11 mol % of (*M,S,S*)-*i*-Pr-SPRIX, and 4 equiv of *p*-benzoquinone in CH_2Cl_2 at 25 °C for 10 h to afford a 70% ee of 3,3-diphenyl-5-(prop-1-en-2-yl)-dihydrofuran-2(3*H*)-one (**2a**) quantitatively (Table 1, entry 1). Other chiral ligands were noticeably ineffective under identical conditions. Reactions using (−)-sparteine, (*S,S*)-*i*-Pr-BOXAX, and (*R*)-BINAP produced an enantiomerically enriched **2a** in low conversions and yields (entries 2−4). (*R,R*)-Bn-BOX rendered the consequent complex catalytically inactive in this oxidative cyclization (entry 5). Even though chiral Pd complex **3**, a valuable catalyst for an aymmetric Wacker-type cyclization of *o*-allylphenols,[11] expedited the reaction moderately, the optical purity of **2a** was as low as 10% ee (entry 6). A background reaction, without any chiral ligands added, was negligible even after 24 h, resulting in only a trace amount of **2a** (entry 7). These

Scheme 1. Oxidative Cyclization of 4-Alkenoic Acids

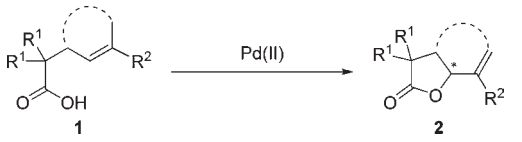
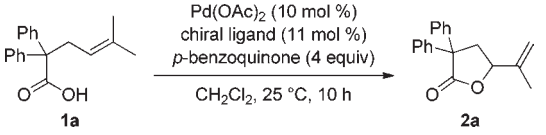
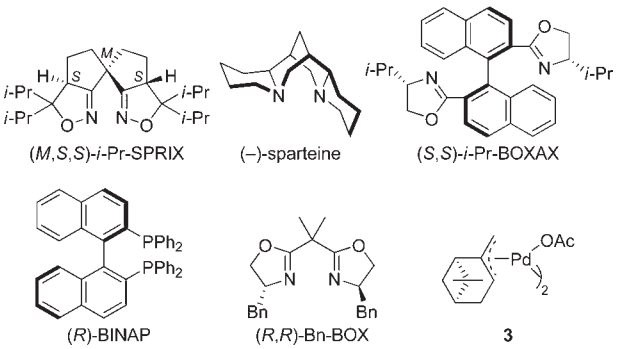


Table 1. Screening of Chiral Ligands in the Enantioselective Intramolecular Oxidative Cyclization of **1a**[a]



entry	chiral ligand	convn (%)[b]	yield (%)[b]	ee (%)[c]
1	(*M,S,S*)-*i*-Pr-SPRIX	100	>98	70
2	(−)-sparteine	24	10	57
3	(*S,S*)-*i*-Pr-BOXAX	27	4	51
4	(*R*)-BINAP	13	6	40
5	(*R,R*)-Bn-BOX	<2	ND[d]	—
6	**3**[e]	41	18	10
7[f]	none	11	5	—

[a] All reactions were performed in the presence of 10 mol % of $Pd(OAc)_2$, 11 mol % of chiral ligand, and 4 equiv of *p*-benzoquinone at 25 °C for 10 h in CH_2Cl_2 (0.1 M) under a nitrogen atmosphere. [b] Determined by ^1H NMR using *p*-hydroxyacetophenone as an internal standard. [c] Determined by HPLC analysis. [d] Not determined. [e] 5 mol % of complex **3** was used instead of $Pd(OAc)_2$. [f] 24 h.



(5) For representative recent reports of a catalytic reaction triggered by C−H bond activation, see: (a) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2990. (b) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 6541. (c) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (d) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070.

(6) A few examples were reported; see: (a) Trost, B. M.; Organ, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10320. (b) Kirsch, S.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 2866. Other metal catalysts can be used. Cu: (c) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 15572. Ru:(d) Kanbayashi, N.; Onitsuka, K. *J. Am. Chem. Soc.* **2010**, *132*, 1206.

(7) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448.

(8) For a review, see: (a) Bajracharya, G. B.; Arai, M. A.; Koranne, P. S.; Suzuki, T.; Takizawa, S.; Sasai, H. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 285. For recent examples, see: (b) Tsujihara, T.; Takenaka, K.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Am. Chem. Soc.* **2009**, *131*, 3452. (c) Tsujihara, T.; Shinohara, T.; Takenaka, K.; Takizawa, S.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Org. Chem.* **2009**, *74*, 9274. (d) Takenaka, K.; Tanigaki, Y.; Patil, M. L.; Rao, C. V. L.; Takizawa, S.; Suzuki, T.; Sasai, H. *Tetrahedron: Asymmetry* **2010**, *21*, 767. (e) Takenaka, K.; Mohanta, S. C.; Patil, M. L.; Rao, C. V. L.; Takizawa, S.; Suzuki, T.; Sasai, H. *Org. Lett.* **2010**, *12*, 3480. (f) Bajracharya, G. B.; Koranne, P. S.; Nadaf, R. N.; Gabr, R. K. M.; Takenaka, K.; Takizawa, S.; Sasai, H. *Chem. Commun.* **2010**, *46*, 9064. (h) Ramalingan, C.; Takenaka, K.; Sasai, H. *Tetrahedron* **2011**, *67*, 2889. (g) Takenaka, K.; Hashimoto, S.; Takizawa, S.; Sasai, H. *Adv. Synth. Catal.* **2011**, *353*, 1067.

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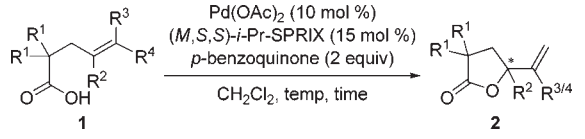
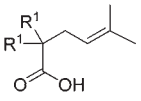
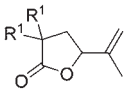
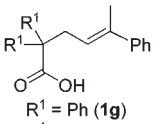
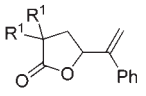
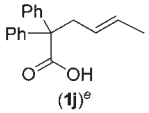
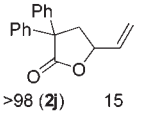
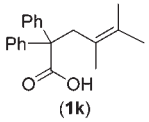
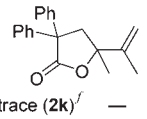
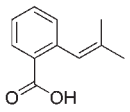
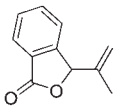
(10) A π-allyl Pd intermediate was also postulated for the synthesis of racemic γ-lactones **2** via a sequential coupling/cyclization reaction; see: (a) Larock, R. C.; Leuck, D. J.; Harrison, L. W. *Tetrahedron Lett.* **1987**, *28*, 4977. (b) Larock, R. C.; Leuck, D. J.; Harrison, L. W. *Tetrahedron Lett.* **1988**, *29*, 6399.

(11) Hosokawa, T.; Okuda, C.; Murahashi, S.-I. *J. Org. Chem.* **1985**, *50*, 1282 and references cited therein.

Table 2. Substrate Scope in the Enantioselective Intramolecular Oxidative Cyclization of **1**[a]



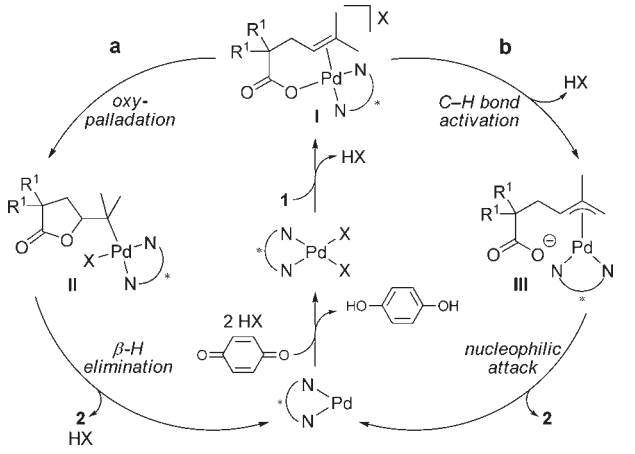
entry	substrate (**1**)	temp (°C) /time (h)	product (**2**) yield (%)[b]	ee (%)[c]
				
1[d]	R^1 = Ph (**1a**)	0/60	>98 (**2a**)	82
2	R^1 = Bn (**1b**)	25/60	>98 (**2b**)	48
3	R^1 = Me (**1c**)	25/60	>98 (**2c**)	55
4	R^1 = -$(CH_2)_5$- (**1d**)	25/60	>98 (**2d**)	68
5	R^1 = 1,1'-biphenyl-2,2'-diyl (**1e**)	25/60	>98 (**2e**)	78
6	R^1 = H (**1f**)	25/60	>98 (**2f**)	18
				
7	R^1 = Ph (**1g**)	25/100	55 (**2g**)	67
8	R^1 = Me (**1h**)	25/100	55 (**2h**)	37
9	R^1 = H (**1i**)	25/105	56 (**2i**)	41
				
10	(**1j**)[e]	35/48	>98 (**2j**)	15
				
11	(**1k**)	25/140	trace (**2k**)[f]	—
				
12	(**1l**)	35/60	>98 (**2l**)	40

[a] All reactions were carried out in the presence of 10 mol % of $Pd(OAc)_2$, 15 mol % of (*M,S,S*)-*i*-Pr-SPRIX, and 2 equiv of *p*-benzoquinone in CH_2Cl_2 (0.1 M) under a nitrogen atmosphere. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 4 equiv of *p*-benzoquinone were used. [e] The *E*/*Z* ratio was 86:14. [f] No reaction.

observations indubitably indicate a curious character for SPRIX in the Pd-catalyzed oxidative cyclization.

After optimization of reaction conditions,[12] we found an improvement of the enantioselectivity. Thus, the employment of 15 mol % of (*M,S,S*)-*i*-Pr-SPRIX and 2 equiv of *p*-benzoquinone at 0 °C led to a quantitative formation of **2a**, whose enantiomeric excess had now reached 82% (Table 2, entry 1). The scope of this transformation was next investigated with a variety of 4-alkenoic acids **1**. Substituents R^1 at the α-position of the carbonyl group had no significant influence on the chemical yields. Treatment of **1b** (R^1 = Bn) and **1c** (R^1 = Me) furnished the products **2b** and **2c** in quantitative yields and moderate selectivities (48% ee and 55% ee), respectively (entries 2 and 3). Spiro-type lactone products **2d** having a cyclohexane ring and **2e** having a fluorene ring were also formed satisfactorily (entries 4 and 5). The simple substrate, 5-methylhex-4-enoic acid (**1f**), could participate in this cyclization to give the hop lactone **2f**[13] quantitatively, albeit with only 18% ee (entry 6). An aromatic group was tolerated on the olefin component: products **2g**–**i** were obtained in reasonable yields with moderate enantioselectivities (entries 7–9). When **1j** bearing a crotyl group was subjected to the reaction conditions, **2j** was produced quantitatively despite the low enantiopurity (entry 10). This result reflects a considerable relationship between substituents on the olefin and enantioselectivity. However, the reaction of **1k** hardly proceeded, probably due to the steric hindrance of the olefin (entry 11). Utilization of the benzoic acid substrate **1l** resulted in a quantitative construction of an isobenzofuranone with 40% ee (entry 12).

Scheme 2. Two Possible Pathways for the Enantioselective Oxidative Cyclization of **1**



It is possible that the reaction is initiated by coordination of the 4-alkenoic acids **1** to the Pd(II)–SPRIX complex to give intermediate **I** (Scheme 2). There are two plausible pathways to γ-alkenyl-γ-lactone products **2** from **I**. One is the traditional Wacker process consisting of an oxypalladation and a subsequent β-H elimination of the resultant **II** (pathway a).[14] The other includes π-allyl Pd intermediate **III** generated by a C–H bond activation at the allylic position (pathway b). To probe whether the latter pathway was indeed operative, we performed several control experiments. Reaction of 2,2-diphenylhex-5-enoic acid (**1j′**), a structural isomer of **1j**, furnished the five-membered γ-lactone **2j** quantitatively with 15% ee (Scheme 3a).[15]

(12) See Supporting Information for details.

(13) Pai, Y.-C.; Fang, J.-M.; Wu, S.-H. *J. Org. Chem.* **1994**, *59*, 6018.

(14) *Anti*-oxypalladation was proposed for the cyclization of a cyclohexenyl substrate based on deuterium-labeling studies. See: Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778.

(15) No olefin isomer **1j** was detected when the reaction was quenched in advance of its completion (after 2 h). See: ref 9b.

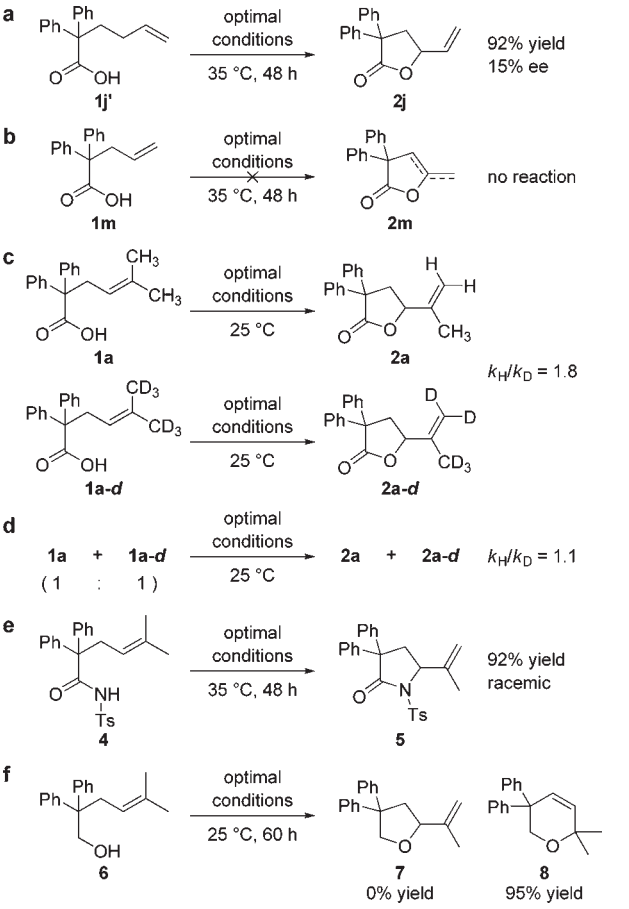
(16) It was reported that the Wacker-type cyclization of **1m** gave the unsaturated γ-lactones **2m**. See: Rudler, H.; Harris, P.; Parlier, A.; Cantagrel, F.; Denise, B.; Bellassoued, M.; Vaissermann, J. *J. Organomet. Chem.* **2001**, *624*, 186.

No reaction took place when 2,2-diphenylpent-4-enoic acid (**1m**) was employed as a substrate (Scheme 3b).[16] These results suggest a lower possibility for the Wacker mechanism. Additionally, the intermolecular kinetic isotope effect (KIE) between substrates **1a** and **1a-*d*** was evaluated under the standard conditions (Scheme 3c). The KIE value (k_H/k_D) was determined to be 1.8 by comparing the initial rates in both reactions.[17] Interestingly, when the competitive reaction using a 1:1 mixture of **1a** and **1a-*d*** was conducted, the KIE value was diminished to 1.1 (Scheme 3d). This phenomenon implies reversible coordination of the substrates to Pd prior to the C−H bond activation.[18] Preliminary study of the utility of other nucleophiles clearly shows the decisive role of the carboxy group in the enantioselective oxidative cyclization (Scheme 3e and 3f).[19] From the above examination, we infer that the present enantioselective cyclization catalyzed by Pd−SPRIX involves the allylic C−H bond activation through a precoordination complex such as intermediate **I** (Scheme 2, pathway b).

In summary, we have developed an enantioselective oxidative cyclization of 4-alkenoic acids **1**, where a π-allyl Pd intermediate is involved. The SPRIX ligand was pivotal in acquiring optically active γ-alkenyl-γ-lactone products **2**. We believe that this transformation is the first example of an enantioselective oxidative allylic C−H functionalization directed by only a chiral Pd catalyst. Careful study on the detailed reaction mechanism is currently in progress.

Acknowledgment. This work was partly supported by the JSPS (Grant-in-Aid for Scientific Research (B), No. 22350041). We also thank the technical staff of the Comprehensive Analysis Center of ISIR for their assistance.

Scheme 3. Preliminary Mechanistic Study



Supporting Information Available. Experimental procedures, details for optimization of the reaction conditions, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) This ratio is quite similar to the reported values for an allylic C−H oxidative alkylation (2.2) and amination (1.64−1.88), which have been proposed to proceed via a π-allyl Pd intermediate. See: refs 4i and 4r.

(18) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936 and references cited therein.

(19) Although the reason why **8** was obtained as a sole product has been uncertain, the Wacker-type cyclizations using a hydroxy nucleophile are disposed to proceed in a 6-*endo-trig* fashion with SPRIX. See: Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907. Also see: refs 8d and 8e.