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Enantioselective Wacker-Type Cyclization of 2-Alkenyl-1,3-diketones Promoted by Pd-SPRIX Catalyst

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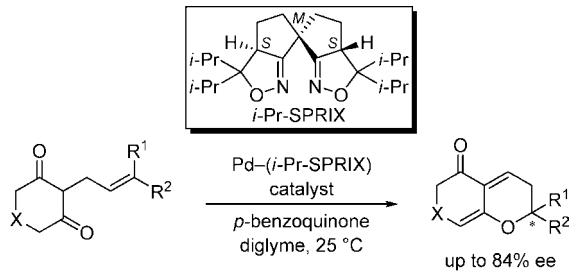
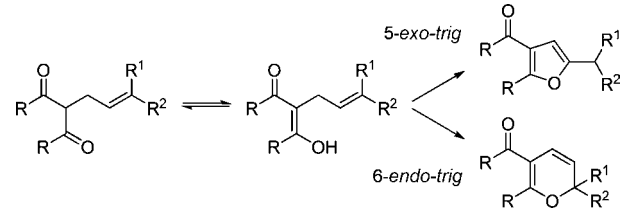
ABSTRACT



An enantioselective intramolecular Wacker-type cyclization of 2-alkenyl-1,3-diketones catalyzed by a Pd(II)−SPRIX complex was developed. The reaction proceeded in a 6-*endo-trig* mode to give the desired chromene derivatives with moderate to good enantioselectivity. Isomerization of C−C double bonds via a π-allyl Pd intermediate was involved as the key step.

The intramolecular Wacker-type cyclization using oxygen nucleophiles is one of the most important processes for the preparation of *O*-heterocycles.[1] Employment of hydroxy and carboxy groups as the oxygen functionality is well established to afford cyclic ethers and lactones, respectively. 1,3-Diketone moieties, which are equilibrated with the corresponding enol forms, have also proven to take part in the Wacker-type cyclization: 5-*exo-trig* cyclization constructs furan rings,[2,3] whereas pyran derivatives are formed in a 6-*endo-trig* cyclization (Scheme 1).[4,5] Since the carbonyl group is retained in the products, these transformations efficiently provide valuable synthons.[6] To our surprise, no enantioselective Wacker-type cyclizations of 1,3-diketones have been published yet. We have reported that spiro bis(isoxazoline)s (SPRIXs) bearing isoxazoline coordination units on a spiro backbone are effective chiral ligands in a variety of asymmetric oxidative reactions.[7,8] The high utility of SPRIXs stimulated us to explore an enantioselective catalysis using 1,3-diketone nucleophiles. Herein we report an enantioselective 6-*endo-trig* Wacker-type cyclization of

Scheme 1. Wacker-Type Cyclization of 1,3-Diketones



(1) For reviews, see: (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318.

(2) Han, X.; Widenhoefer, R. A. *J. Org. Chem.* **2004**, *69*, 1738.

(3) For related transformations using a Pd catalyst, see: (a) Hosokawa, T.; Murahashi, S.-I. *Heterocycles* **1992**, *33*, 1079. (b) Tenaglia, A.; Kammerer, F. *Synlett* **1996**, 576.

(4) Verotta, L.; Appendino, G.; Belloro, E.; Bianchi, F.; Sterner, O.; Lovati, M.; Bombardelli, E. *J. Nat. Prod.* **2002**, *65*, 433.

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2-alkenyl-1,3-diketone compounds **1** promoted by a Pd-SPRIX catalyst.

In oxidative cyclization of **1**, it was suspected that initial products, 7,8-dihydro-2*H*-chromen-5(6*H*)-ones **2**, were obtained as a racemate due to an electrocyclic ring-opening/closing sequence (Scheme 2a).[9] We conceived that isomerization of **2** to 6,7-dihydro-2*H*-chromen-5(3*H*)-ones **3** through a π-allyl Pd intermediate **A** would suppress such a problematic racemization. Indeed, reaction of 2-geranylcyclohexane-1,3-dione ((*E*)-**1a**) in the presence of a catalytic amount of Pd-*rac*-*i*-Pr-SPRIX complex furnished the desired **3a** in 47% yield (Scheme 2b). After extensive optimization of reaction conditions,[10] we succeeded in the isolation of enantiomerically enriched product. Thus, substrates (*E*)-**1a** were treated with 10 mol % $Pd(OCOCF_3)_3$, 12 mol % (*M*,*S*,*S*)-*i*-Pr-SPRIX, and 2 equiv of *p*-benzoquinone in diglyme at 25 °C to afford **3a** in 80% yield with 81% ee, accompanied by the negligible formation of **2a** (Table 1,

Scheme 2. Working Hypothesis and Initial Attempt

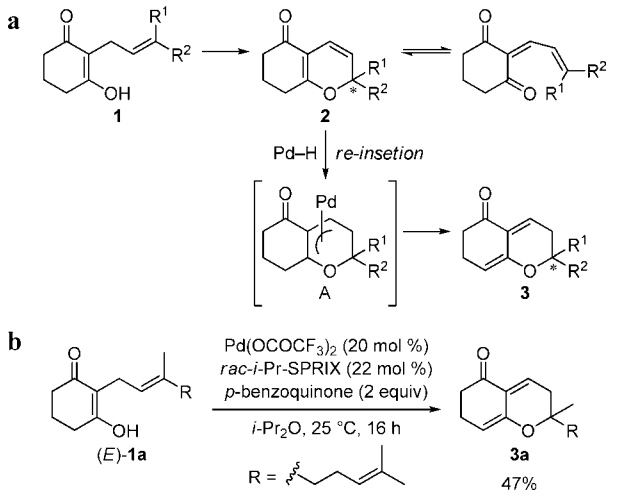
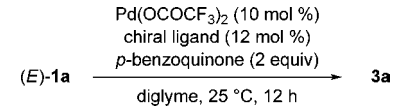
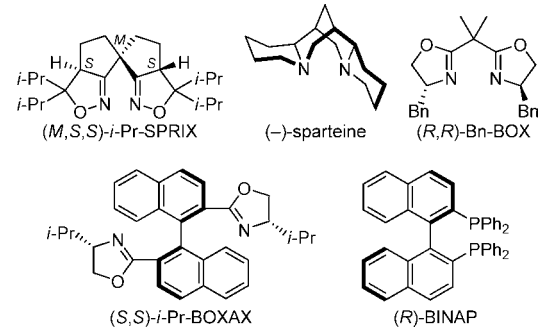


Table 1. Screening of Chiral Ligands in the Enantioselective Intramolecular Wacker-Type Cyclization of (*E*)-**1a**[a]



entry	chiral ligand	convn (%)[b]	yield (%)[b]	ee (%)[c]
1	(*M*,*S*,*S*)-*i*-Pr-SPRIX	100	80	81
2	(−)-sparteine	80	trace[d]	*rac*
3	(*R*,*R*)-Bn-BOX	50	ND[e]	
4	(*S*,*S*)-*i*-Pr-BOXAX	40	ND[e]	
5	(*R*)-BINAP	65	ND[e]	
6	none	10	trace	

[a] All reactions were performed in the presence of 10 mol % $Pd(OCOCF_3)_2$, 12 mol % chiral ligand, and 2 equiv of *p*-benzoquinone at 25 °C for 12 h in diglyme (0.2 M) under a nitrogen atmosphere. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Racemic **2a** was obtained in 14% yield. [e] Not detected (a complex mixture was obtained).



entry 1). It should be noted that under identical conditions, other known chiral ligands such as (−)-sparteine, (*R*,*R*)-Bn-BOX, (*S*,*S*)-*i*-Pr-BOXAX, and (*R*)-BINAP were ineffective (entries 2−5). A background reaction scarcely proceeded and resulted in only a trace amount of **3a** (entry 6). These results evidently demonstrate a great advantage of SPRIX for the enantioselective Wacker-type cyclization. Presumably, the Pd-SPRIX complex activates the olefin significantly because of its strong Lewis acidity.[8c]

Next, the scope of this enantioselective transformation was examined with various 2-alkenyl-1,3-diketones **1** (Table 2). Similar to (*E*)-**1a**, the reactions of geranylcyclohexane-1,3-dione substrates **1b** and **1c** gave the products **3b** and **3c** in moderate yields (58% and 70%) and sufficient selectivities (84% ee and 78% ee), respectively (entries 2 and 3). The pyran analog **1d**, however, did not afford the desired product (entry 4). Alkyl and aryl groups were tolerated on the olefin component (entries 5−7). Substrate **1h** bearing a 1,2-disubstituted alkenyl chain also participated in this 6-*endo*-*trig* cyclization to give **3h** in 68% yield with 52% ee (entry 8). No desired products were observed for cyclopentane-

(5) Pd-catalyzed C−C bond-forming reactions have also been reported; see: (a) Pei, T.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11290. (b) Pei, T.; Widenhoefer, R. A. *Chem. Commun.* **2002**, 650. (c) Pei, T.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 648. (d) Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 2056. (e) Yip, K.-T.; Li, J.-H.; Lee, O.-Y.; Yang, D. *Org. Lett.* **2005**, *7*, 5717.

(6) For examples, see: (a) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935. (b) Hu, H.; Harrison, T. J.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 3782. (c) Wayne Lee, W.-W.; Gan, L.-M.; Loh, T.-P. *Synlett* **2005**, 2473. (d) Lee, Y. R.; Lee, W. K.; Noh, S. K.; Lyoo, W. S. *Synthesis* **2006**, 853. (e) Rawat, M.; Prutyanov, V.; Wulff, W. D. *J. Am. Chem. Soc.* **2006**, *128*, 11044.

(7) For a review, see: Bajracharya, G. B.; Arai, M. A.; Koranne, P. S.; Suzuki, T.; Takizawa, S.; Sasai, H. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 285.

(8) For recent examples, see: (a) Bajracharya, G. B.; Koranne, P. S.; Tsujihara, T.; Takizawa, S.; Onitsuka, K.; Sasai, H. *Synlett* **2009**, 310. (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.

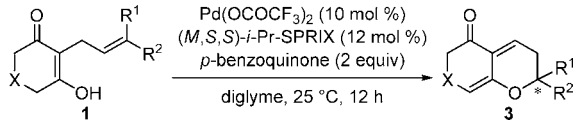
(9) (a) Gosink, T. A. *J. Org. Chem.* **1974**, *39*, 1942. (b) de Groot, A.; Jansen, B. J. M. *Tetrahedron Lett.* **1975**, *16*, 3407. (c) Li, C.; Johnson, R. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 5095.

(10) See Supporting Information for details.

(11) The major enantiomer was opposite to that obtained in the reaction of (*E*)-**1a**.

(12) For selected examples of deuterium labeling studies on mechanism in the Wacker-type cyclizations, see: (a) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036. (b) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468. (c) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778.

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



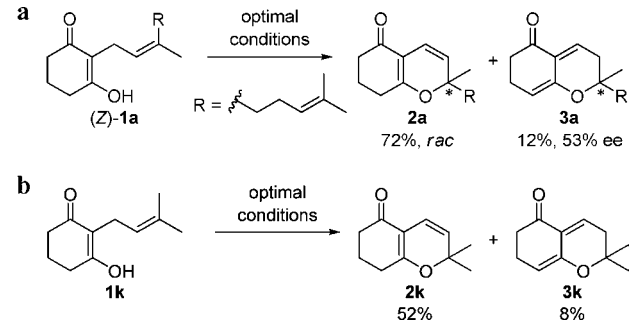
entry	substrate (**1**)	product (**3**) yield (%)[b]	ee (%)[c]
1	X = CH_2 ((*E*)-**1a**)	80 (**3a**)	81
2[d]	X = CHMe (**1b**)	58 (**3b**)	84
3	X = CMe_2 (**1c**)	70 (**3c**)	78
4	X = O (**1d**)	ND[e] (**3d**)	—
5[f]	R = Bu (**1e**)	60 (**3e**)	51
6[g]	R = *i*-Pr (**1f**)	53 (**3f**)	67
7	R = Ph (**1g**)	38 (**3g**)	65
8	(**1h**)	68 (**3h**)	52
9	(**1i**)	ND[e] (**3i**)	—
10	(**1j**)	NR[h] (**3j**)	—

[a] All reactions were carried out in the presence of 10 mol % $Pd(OCOCF_3)_2$, 12 mol % (*M*,*S*,*S*)-*i*-Pr-SPRIX, and 2 equiv of *p*-benzoquinone at 25 °C for 12 h in diglyme (0.2 M) under a nitrogen atmosphere. The starting material was almost consumed at the end of the reaction in each case (except for entries 4, 9, and 10). [b] Isolated yield. [c] Determined by HPLC analysis. [d] The diastereomeric ratio was determined to be 83:17 by ^{1}H NMR spectrum. Data for the major diastereomer are given. [e] Not detected (a complex mixture was obtained). [f] 17 h. [g] 20 h. [h] No reaction.

1,3-dione derivative **1i** and acetylacetone derivative **1j** (entries 9 and 10). Interestingly, in the reaction of 2-neryl-cyclohexane-1,3-dione ((*Z*)-**1a**), **3a** was not the major product (12% yield, 53% ee).[11] Instead, nonisomerized product **2a** was obtained in 72% yield, which was a racemate as we suspected (Scheme 3a). Dimethylallyl substrate **1k** exhibited the same trend as in the reaction of (*Z*)-**1a**, namely, producing **2k** in 52% yield (Scheme 3b). These results imply that substituents on olefin considerably affect the pathway of this enantioselective cyclization.

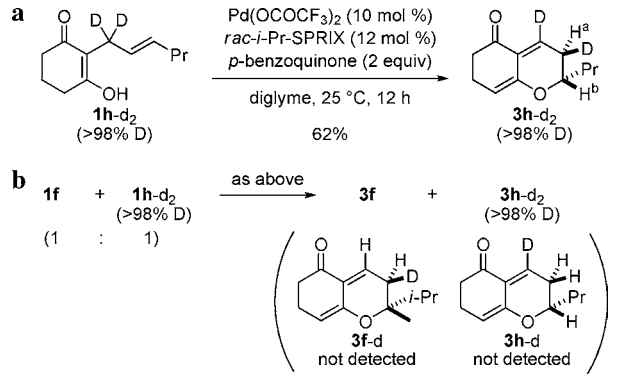
To elucidate our working hypothesis shown in Scheme 2a, deuterium labeling experiments were carried out.[12] When substrate **1h**-d_2 was subjected to the optimal conditions using *rac*-*i*-Pr-SPRIX, we obtained the anticipated product **3h**-d_2,

Scheme 3. Reactions of (*Z*)-**1a** and **1k**



in which one deuterium was shifted to the adjacent carbon, as a single diastereomer (Scheme 4a). This result clearly

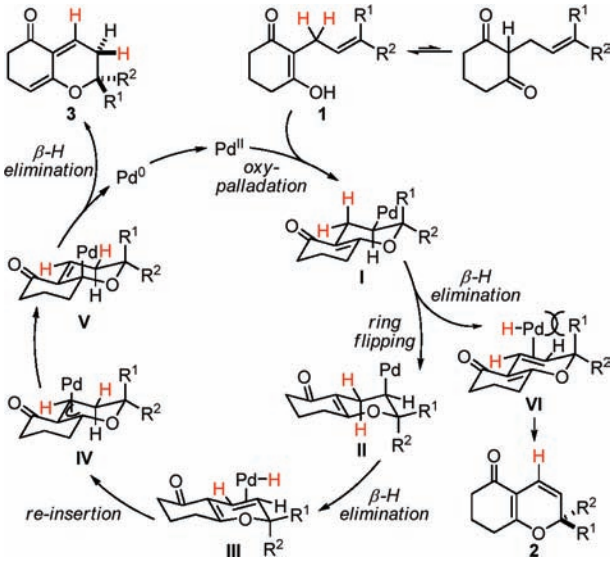
Scheme 4. Deuterium Labeling Experiments



supports the expected β-H elimination/reinsertion array. The coupling constant between H^a and H^b in the six-membered ring ($^3J_{HH}$ = 9.6 Hz), corresponding to a coupling of axial protons, identified its relative configuration as depicted. Accordingly, the Pr group and the shifted deuterium were positioned *trans* to each other. A crossover experiment revealed that such a β-H elimination/reinsertion sequence occurred intramolecularly. Thus, no crossover products **3f**-*d* and **3h**-*d* were detected in the reaction of a 1:1 mixture of **1f** and **1h**-d_2 (Scheme 4b).

A plausible catalytic cycle for this oxidative cyclization of **1** is illustrated in Scheme 5. As in the conventional Wacker-type cyclization, this enantioselective catalysis appears to be commenced by a nucleophilic attack of the enolic hydroxy group to the tethering alkene activated by the Pd-SPRIX complex. On the basis of the results in Table 2 and Scheme 3, we speculated that the steric environment around Pd in intermediate **I** would be essential for controlling the reaction pathway. The R^2 substituent bulky enough to interact with the neighboring Pd atom causes ring flipping (intermediate **II**). The subsequent β-H elimination produces Pd-H speicies **III**, which converts to π-allyl Pd complex **IV** by reinsertion. At this stage, the high electrophilicity of Pd-SPRIX may contribute to the stability of **III**, from which

Scheme 5. Plausible Mechanism



product **2** is not released easily. Finally, β-H elimination from **V** furnishes **3** and Pd^0, of which the latter is oxidized by the action of *p*-benzoquinone to regenerate the Pd^{II} catalyst. When R^2 is less bulky, i.e., Me groups in both (*Z*)-**1a** and **1k**, β-H elimination would happen directly from the intermediate **I**. The resulting Pd-H moiety in **VI** seems to be immediately liberated due to the compelling steric repulsion with the axial substituent R^1, leading to the nonisomerized product **2**.

In summary, we have developed an enantioselective 6-*endo-trig* Wacker-type cyclization of 2-alkenyl-1,3-diketones, where the SPRIX ligand plays a crucial role for obtaining optically active chromene derivatives. This reaction is thought to proceed by way of a π-allyl Pd intermediate. Transformation of products **3** to biologically active compounds and full investigation into the reaction mechanism are currently ongoing and will be reported in due course.

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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.

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