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Catalytic enantioselective bromolactonization of alkenoic acids in the presence of palladium complexes

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ABSTRACT

The catalytic enantioselective bromolactonization of alkenoic acids promoted by chiral palladium complexes has been developed, allowing facile synthesis of the corresponding γ-lactones with excellent enantioselectivity (up to 97% ee). The method reported represents a practical entry for the preparation of chiral γ-lactone derivatives.

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Halolactonization of unsaturated carboxylic acids is an important and fundamental synthetic transformation in organic chemistry as the corresponding halolactones are very useful building blocks, which can be employed as synthetic intermediates for divergent transformations.[1] Accordingly, the development of methods for the catalytic enantioselective halolactonizations has become of great interest, and some notable successes have been recorded.[2] Despite these significant advances, the catalytic enantioselective bromolactonization is still lacking because a suitable catalytic system remains elusive.[3–5] There have been a few reported examples of catalytic enantioselective bromolactonization of 4-aryl 4-pentenoic acids.[6] The Yeung group has reported the catalytic enantioselective bromolactonization in the presence of amino-thiocarbamate catalysts.[6a,c] The Borhan group has reported the enantioselective bromolactonization using a peptide bromoiodinane approach.[6c] Very recently, the Martin group described organocatalytic enantioselective bromolactonization using binol-derived bifunctional catalyst.[6d] Although, a few efficient methods have been achieved by these systems, an effective method for the catalytic asymmetric halolactonization of 4-aryl 4-pentenoic acids is highly desirable. To the best of our knowledge, there is no report for the enantioselective bromolactonization using chiral palladium complexes which are air- and moisture-stable.[7]

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[8] we recently reported asymmetric reactions using chiral palladium complexes.[9] Herein, we wish to describe the enantioselective bromolactonization of alkenoic acids catalyzed by palladium complexes.

To determine suitable reaction conditions for the catalytic enantioselective bromolactonization of alkenoic acids, we initially investigated the reaction system with 4-phenyl 4-pentenoic acid (**2a**) and bromine sources in the presence of 10 mol % of dicationic palladium complexes **1** (Fig. 1) in $CHCl_3$ at room temperature. The impact of the structure of brominating reagents was initially examined. The commonly used *N*-bromosuccinimide, *N*-bromophthalimide, *N*-bromosaccharin, dibromobarbituric acid, and dibromoisocyanuric acid gave bromolactoniation product as racemic mixture. Fortunately, we found that bromolactonization using 2,4,4,6-tetrabromocyclohexadienone (TBCO) as brominating reagent and catalyst **1a** proceeded with high yield and moderate enantioselectivity (Table 1, entry 1). To improve the enantioselectivity, we examined the impact of the structure of ligands of palladium complexes **1** on enantioselectivities (11–69% ee, Table 1, entries 1–12). Under the standard reaction conditions, catalyst **1c** gave better enantioselectivity (69% ee, Table 1, entry 3). Next, we examined the reaction in various solvents (Table 1, entries 13–19). The use of halogenated solvents such as CH_2Cl_2, $CHCl_2CH_2Cl$, CH_2Br_2, and CF_3CH_2OH gave the good results (Table 1, entries 13–15 and 19), where bromolactonization in toluene, THF, and MeOH led to lower enantioselectivities (Table 1, entries 16–18). Decreasing the catalyst loading to 5 mol % and lowering the temperature to −40 °C led to a slight decrease in the selectivities (Table 1, entries 20 and 21).

With optimal reaction condition in hand, we studied the generality of the enantioselective bromolactonization of 4-aryl

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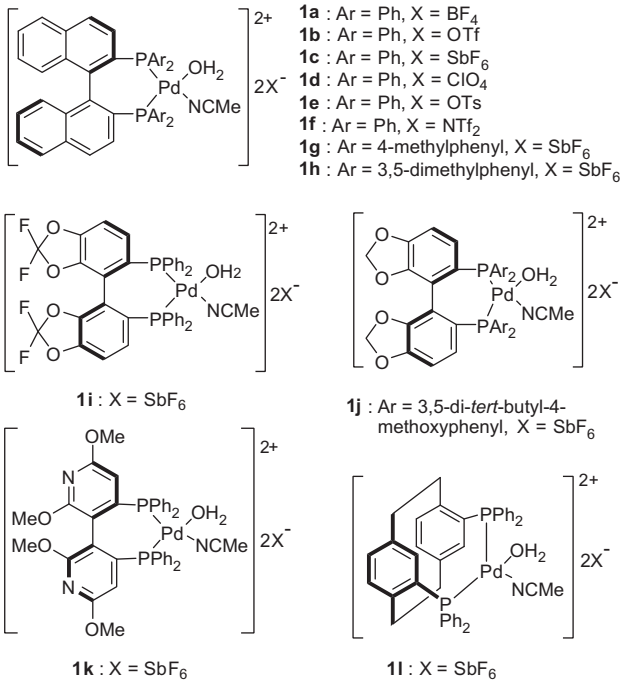
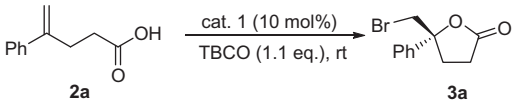


Figure 1. Structures of chiral palladium catalysts.

Table 1
Optimization of the reaction conditions[a]

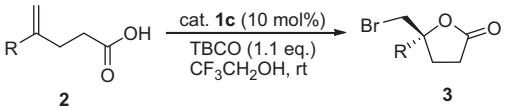


Entry	Cat. **1**	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	$CHCl_3$	9	92	17
2	**1b**	$CHCl_3$	2	97	11
3	**1c**	$CHCl_3$	2	99	69
4	**1d**	$CHCl_3$	2	95	65
5	**1e**	$CHCl_3$	2	93	13
6	**1f**	$CHCl_3$	2	97	61
7	**1g**	$CHCl_3$	2	91	17
8	**1h**	$CHCl_3$	2	90	22
9	**1i**	$CHCl_3$	2	92	65
10	**1j**	$CHCl_3$	2	92	57
11	**1k**	$CHCl_3$	2	98	15
12	**1l**	$CHCl_3$	2	93	47
13	**1c**	CH_2Cl_2	8	97	67
14	**1c**	$CHCl_2CH_2Cl$	8	95	39
15	**1c**	CH_2Br_2	8	98	53
16	**1c**	PhMe	8	97	10
17	**1c**	THF	3	95	3
18	**1c**	MeOH	7	98	5
19	**1c**	CF_3CH_2OH	2	98	75
20[d]	**1c**	CF_3CH_2OH	5	98	59
21[e]	**1c**	CF_3CH_2OH	5	90	62

[a] Reaction conditions: 4-phenyl 4-pentenoic acid (**2a**, 0.2 mmol), TBCO (0.22 mmol), catalyst (0.02 mmol) at room temperature.
[b] Isolated yield.
[c] Enantiopurity was determined by HPLC analysis using chiralpak IC column.
[d] 5 mol % catalyst loading.
[e] This reaction was carried out at −40 °C.

4-pentenoic acids **2** with TBCO in the presence of 10 mol % of catalyst **1c**.[10] As it can be seen by the results summarized in Table 2, the corresponding bromolactone products **3a**–**h** were obtained in high yields with moderate to excellent enantioselectivities (59–97% ee). A range of electron-donating and electron-withdrawing

Table 2
Catalytic enantioselective bromolactonization of alkenoic acids **2**[a]

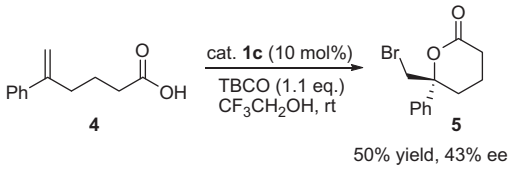


Entry	**2**, R	Time (h)	Yield[b] (%)	ee[c] (%)
1	**2a**, Ph	2	**3a**, 98	75
2	**2b**, 4-MeC_6H_4	2	**3b**, 97	85
3	**2c**, 4-$MeOC_6H_4$	1	**3c**, 99	97
4	**2d**, 4,5-$Me_2C_6H_3$	2	**3d**, 99	91
5[d]	**2e**, 4,5-$(MeO)_2C_6H_3$	8	**3e**, 77	95
6[e]	**2f**, 4-ClC_6H_4	2	**3f**, 97	89
7	**2g**, 2-thienyl	2	**3g**, 83	63
8	**2h**, 9-anthracenyl	2	**3h**, 90	59
9	**2i**, Me	12	**3i**, 72	32

[a] Reaction conditions: 4-aryl 4-pentenoic acid (**2**, 0.2 mmol), TBCO (0.22 mmol), catalyst **1c** (0.02 mmol) in CF_3CH_2OH at room temperature.
[b] Isolated yield.
[c] Enantiopurity was determined by HPLC analysis using chiralpak IC column.
[d] This reaction was carried out at 0 °C in $CHCl_3$.
[e] 20 mol % catalyst loading.

substitutions on the aryl ring of the 4-aryl 4-pentenoic acids **2b–f** provided reaction products in high yields and high to excellent enantioselectivities. In particular, better results are obtained with substrates having electron rich aromatics. It is interesting because in the case of reported organocatalytic methods, such substrates tend to decrease the selectivity.[6] Heteroaryl- and naphthyl-substituted alkenoic acids **2g–h** provided products with moderate to high selectivity (59–63% ee, entries 7 and 8). However, diminished yield and enantioselectivity were observed with 4-alkyl-substituted 4-pentenoic acid **2i** (Table 2, entry 9). The absolute configuration of **3** was established by comparison of the optical rotation and chiral HPLC analysis with previously reported values.[6]

Furthermore, 5-phenyl 5-hexenoic acid **4** was also used as a substrate in this bromolactonization reaction with TBCO as the bromine source in the presence of 10 mol % of palladium complex **1c** in CF_3CH_2OH. It was found that the corresponding bromolactone product **5** was obtained in moderate yield and enantioselectivity (Scheme 1). The absolute configuration of **5** was established by comparison of the optical rotation and chiral HPLC analysis with previously reported values.[4a,6c]



Scheme 1. Catalytic enantioselective bromolactonization of 5-phenyl 5-hexenoic acid **4**.

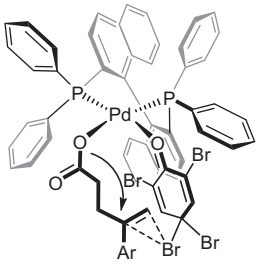


Figure 2. Plausible transition state model.

Although, the reason for the observed enantioselectivity is still unclear, we believe that 4-pentenoic acids **2** and TBCO are activated by the palladium catalyst **1**. Alkene of 4-pentenoic acids attacks electrophilic brominating reagent as shown in Figure 2. Then, carboxylate attacks the cyclic bromonium ion to afford the bromolactonization product (Fig. 2). Investigations to obtain the clear mechanistic feature are still in progress.

In summary, we have accomplished the efficient catalytic enantioselective bromolactonization of 4-aryl 4-pentenoic acids with TBCO in the presence of dicationic palladium complex as a chiral catalyst. The air- and moisture-stable palladium catalyst **1c** is highly effective to give high yields and moderate to excellent enantioselectivities (up to 97% ee) under mild reaction conditions. Further study of palladium-catalyzed enantioselective bromolactonization of various alkenoic acid derivatives is in progress.

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10. *Typical procedure for the bromolactonization of 4-phenyl 4-pentenoic acid (**2a**) with TBCO*: To a stirred solution of TBCO (90.1 mg, 0.22 mmol) and catalyst **1c** (25.2 mg, 0.02 mmol) in trifluoroethanol (2 mL) was added 4-phenyl 4-pentenoic acid (**2a**, 35.2 mg, 0.2 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature. After completion of the reaction, the resulting solution was concentrated in vacuo and the obtained residue was purified by flash chromatography (EtOAc/hexane, 1:3) to afford the 50 mg (98%) of the bromolactonization product **3a**. *(R)-5-(bromomethyl)-dihydro-5-phenylfuran-2(3H)-one (**3a**)*: $[\alpha]_D^{23}$ = +27.9 (*c* = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.34 (m, 5H), 3.74 (d, *J* = 11.4 Hz, 1H), 3.69 (d, *J* = 11.4 Hz, 1H), 2.84–2.76 (m, 2H), 2.60–2.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 140.6, 128.7, 128.5, 124.8, 86.3, 40.9, 32.3, 28.9); HPLC (85:15, *n*-hexane:*i*-PrOH, 214 nm, 0.6 mL/min) Chiralpack IC column, t_R = 25.4 min (major), t_R = 30.2 min (minor), 75% ee.