Received: January 3, 2016 | Accepted: January 8, 2016 | Web Released: January 16, 2016 CL-160004

Chiral Ammonium Hypoiodite Salt-catalyzed Enantioselective Oxidative Cycloetherification to 2-Acyl Tetrahydrofurans

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2-Acyl tetrahydrofuran is a fundamental structure in natural products and pharmaceuticals. We achieved chiral quaternary ammonium hypoiodite salt-catalyzed enantioselective oxidative cycloetherification of δ-hydroxyketone derivatives. The corresponding 2-acyl tetrahydrofurans were obtained in high chemical yield with high enantioselectivity.

Keywords: 2-Acyl tetrahydrofuran | Chiral ammonium hypoiodite catalysis | Oxidative cycloetherification

Tetrahydrofuran (THF) is a ubiquitous and privileged core structure in biologically active compounds.[1] In particular, a tetrahydro-2-furoyl skeleton is found in many pharmaceuticals, such as terazosin,[2] alfuzosin,[3] faropenem,[4] and cathepsin K inhibitor[5] (Figure 1). While some of these are used as racemic mixtures, the configuration at the *C*2-position of 2-acyl THFs is often important for their biological activities.[2–5] For the synthesis of these pharmaceuticals, tetrahydrofuran-2-carboxylic acid (**1**) has been used to introduce the tetrahydro-2-furoyl moiety.[2–5] Thus, the development of a straightforward method for the preparation of enantioenriched **1** is an important subject in synthetic organic chemistry and medicinal chemistry.

Although numerous methods have been developed for the asymmetric synthesis of tetrahydrofurans,[1] little is known about the direct enantioselective synthesis of 2-acyl THF. Conventionally, biologically active compounds that contain a chiral tetrahydro-2-furoyl moiety have been prepared by the enzyme-catalyzed kinetic resolution of racemic mixtures or the diastereoselective hydrogenation of furan-2-carboxylic acid derivatives with chiral auxiliaries.[6] In contrast, to the best of our knowledge, only three enantioselective methods have been developed for the preparation of 2-acyl THFs. Baiker and colleagues developed enantioselective hydrogenation of furan-2-carboxylic acid by using Pd/Al_2O_3 and cinchonidine catalysts (Scheme 1a).[7] However, the product was obtained with low enantioselectivity. Zhou and colleagues reported a copper-catalyzed enantioselective intramolecular O–H insertion of ω-hydroxy-α-diazoesters to

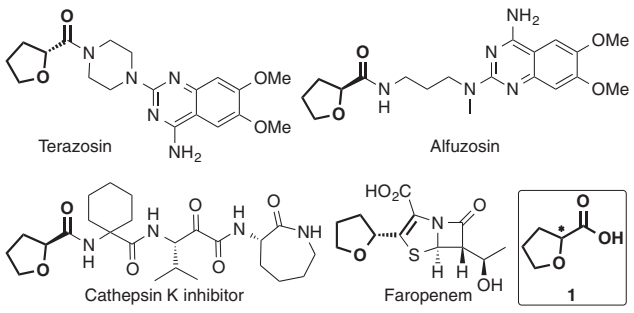
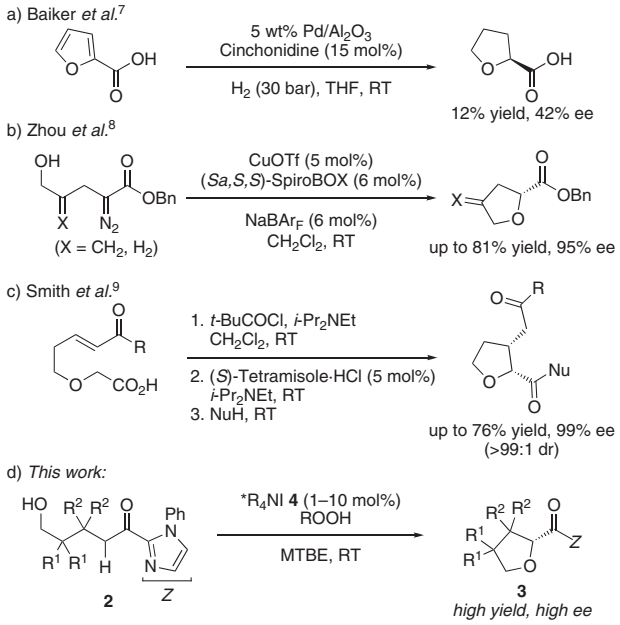


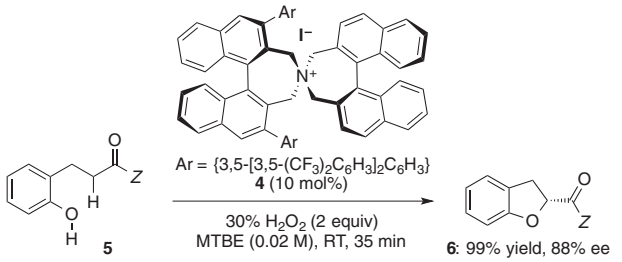
Figure 1. 2-Acyl THF-derived pharmaceuticals.



Scheme 1. Previous examples and this work on the enantioselective synthesis of 2-acyl THFs.

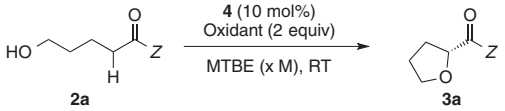
give the corresponding 2-acyl THFs (Scheme 1b).[8] Although high enantioselectivities were achieved, the substrates were limited to highly reactive α-diazoesters. On the other hand, Smith and colleagues reported a chiral Lewis base-promoted enantioselective Michael addition/lactonization reaction of enone acids followed by nucleophilic ring-opening (Scheme 1c).[9] Although the corresponding *cis*-3-substituted 2-acyl THFs were obtained with excellent enantio- and diastereoselectivities, in situ activation of carboxylic acid with pivaloyl chloride is required to generate a Michael donor. Moreover, compound **1**, which is an essential core for many pharmaceuticals, as shown in Figure 1, is not easily synthesized. Thus, the development of an efficient and highly enantioselective method for the synthesis of highly valuable 2-acyl THF derivatives is still needed. Here, we report chiral hypoiodite salt-catalyzed enantioselective oxidative cycloetherification of δ-hydroxyketones **2** to 2-acyl THF **3** in high yield and with high enantioselectivity (Scheme 1d).

Recently, we have developed enantioselective oxidative cyclization reactions of β-(2-hydroxyphenyl) ketones **5** into 2-acyl-2,3-dihydrobenzofuran derivatives **6** catalyzed by chiral quaternary ammonium[10] hypoiodite salt catalysts (Scheme 2).[11a] The hypoiodite salts were generated in situ from the corresponding ammonium iodides **4** in the presence of hydrogen peroxide, *tert*-butyl hydroperoxide (TBHP), or cumene hydroperoxide (CHP) as an oxidant.[11–13]



Scheme 2. Enantioselective cycloetherification of β-(2-hydroxyphenyl) ketones **5**.

Table 1. Enantioselective cycloetherification of δ-hydroxyketones **2a**



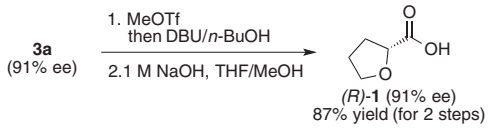
Entry	Oxidant	x/M	Time/h	**3a**, Yield[a]/%, ee[b]/%
1	30% H_2O_2	0.02	24	<5[c], —
2	TBHP	0.02	18	55, 82
3	CHP	0.02	2	75, 90
4	CHP	0.2	2	81, 91 (98)[d]

[a]Isolated yield. [b]Evaluated by HPLC analysis. The absolute configuration of **3a** was determined by comparing the optical rotation of **1** derived from **3a** to the value in the literature.[6a–6c] [c]Unreacted **2a** was recovered (>95%). [d]After a single recrystallization. For details, see the Supporting Information.

We envisioned that our chiral hypoiodite catalysis could be used for the enantioselective synthesis of 2-acyl THFs **3** by using δ-hydroxyketones **2** as substrates. However, the oxidative cyclization of δ-hydroxyketone **2a** did not proceed and only a trace amount of the desired product **3a** was obtained under conditions identical to those for β-(2-hydroxyphenyl) ketone **5** with hydrogen peroxide as an oxidant (Table 1, Entry 1 versus Scheme 2). Since the cyclization of **2** proceeded much more slowly than that of **5**, a catalyst-inactivation path (i.e., disproportionation or reductive decomposition of hypoiodite species)[11,13] might proceed preferentially. As in our previous studies,[11b,13b] to decelerate the oxidation of iodide and suppress the catalyst-inactivation path, alkyl hydroperoxides were evaluated as weaker oxidants instead of hydrogen peroxide. As a result, the desired product **3a** was obtained in 55% yield with 82% ee by the use of TBHP in methyl *tert*-butyl ether (MTBE) (Entry 2). The reactivity and enantioselectivity were further increased by the use of CHP in place of TBHP (Entry 3). Moreover, to our delight, **3a** could be obtained in higher chemical yield under more concentrated conditions (0.2 M) without any loss of enantioselectivity (Entry 4). In sharp contrast, highly diluted conditions (0.02 M) were required to induce high enantioselectivity for the oxidative cyclization of ketophenols **5** (Scheme 2).[11] Almost optically pure **3a** could be obtained after a single recrystallization (Entry 4).

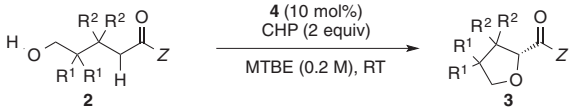
The (*N*-phenylimidazol-2-yl)carbonyl group of **3a** was easily transformed to give (*R*)-**1** (Scheme 3).[2–5]

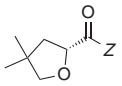
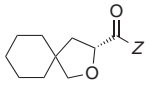
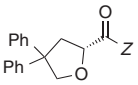
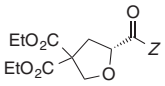
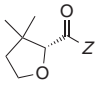
We examined various substituted δ-hydroxyketones **2** under optimized conditions (Table 2). The oxidative cyclization of



Scheme 3. Derivatization of **3a** to (*R*)-**1**.

Table 2. Enantioselective cycloetherification of substituted δ-hydroxyketones **2**[a]



Entry	Product	**3**	Time/h	**3**, Yield/%, ee/%
1		**3b**	2	95, 92
2[b]			24	58, 92
3[c]			24	31, 92
4[d]			6	93, 92
5		**3c**	2	98, 95
6		**3d**	2	95, 89
7		**3e**	2	95, 78
8		**3f**	24	30, 59

[a]Unless otherwise noted, a solution of **2** (0.1 mmol), **4** (10 mol %) and CHP (2 equiv) in MTBE (0.2 M) was stirred at room temperature. Isolated yields are reported. Ee was determined by HPLC analysis. The absolute configuration of **3b**–**3f** was assigned by analogy. [b]Reaction was performed with **4** (1 mol %) in the presence of K_2CO_3 (1 equiv) in MTBE (0.02 M). [c]Reaction was performed with **4** (1 mol %) in MTBE (0.02 M). [d]Reaction was performed with **2b** (4.1 mmol) and **4** (2 mol %) in the presence of K_2CO_3 (1 equiv) in MTBE (0.02 M).

γ,γ-dialkyl-substituted **2b** and **2c** gave the corresponding 2-acyl THFs **3b** and **3c** in higher chemical yield with higher enantioselectivities than that of **3a** (Entries 1 and 5). The catalyst loading could be reduced to 1 mol % for the oxidation of highly reactive **2b** without reducing the enantioselectivity (Entry 2). Although the reaction did not proceed to completion, the chemical yield of **3b** was increased about 2-fold (TON was up to 58) in the presence of 1 equivalent of potassium carbonate, which is required to regenerate the catalytic active species from inert species (Entry 2 versus Entry 3).[11b] This method could be applied to a gram-scale reaction. The oxidation of **2b** on a 1.1-gram scale with 2 mol % of **4** in the presence of potassium carbonate gave **3b** in 93% yield (1.02 g) with 92% ee (Entry 4). The oxidation of γ,γ-diphenyl- and γ,γ-diester-substituted **2d** and **2e** gave the corresponding **3** quantitatively (Entries 6 and 7). However, the enantioselectivity was reduced to 78% ee for **3e** (Entry 7). On the other hand, the oxidation of β,β-dimethyl-substituted **2f** was sluggish, presumably due to steric reasons, and **3f** was obtained in low chemical yield with moderate enantioselectivity (Entry 8).

In summary, we developed a quaternary ammonium hypoiodite salt-catalyzed oxidative cyclization of δ-hydroxyketones to give chiral THF derivatives with high enantioselectivity. This environmentally benign method could provide various chiral 2-acyl THFs for the discovery of new drug candidates, which might be difficult to access by previous methods.

Financial support for this project was partially provided by CREST from JST, JSPS.KAKENHI (Nos. 24245020, 25105722, 15H05755 and 15H05484), the Program for Leading Graduate Schools: IGER Program in Green Natural Sciences (MEXT), and JSPS Research Fellowships for Young Scientists (H.H.).

Supporting Information is available on http://dx.doi.org/10.1246/cl.160004.

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