Highly Enantioselective Cr(salen)-catalyzed Reaction of 2-(Trimethylsilyloxy)furan and Aldehydes. Effect of Alcohol on Enantioselectivity

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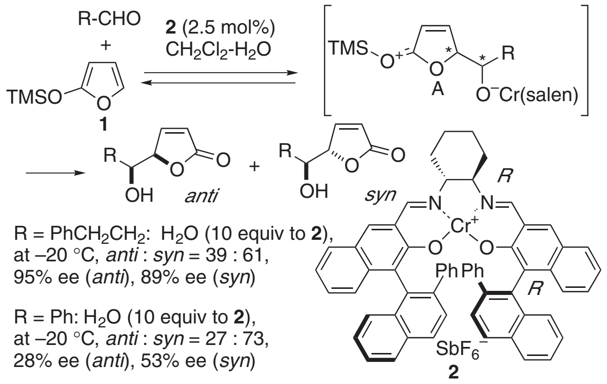
Reactions of 2-(trimethylsilyloxy)furan **1** and aldehydes catalyzed by a chiral cationic Cr(salen) complex proceeded with remarkably improved enantioselectivity, when a secondary alcohol was added. The role of the alcohol is acceleration of the conversion of an intermediary **1**-aldehyde adduct into the final product.

Lewis acid-catalyzed reactions of 2-(trimethylsilyloxy)furan **1** and electrophiles are convenient methods for preparing γ-substituted butenolides that are useful building blocks,[1–4] and much effort has been directed toward asymmetrization of these reactions. We have reported scandium- and copper-mediated enantioselective Michael addition reactions of **1**.[5] Subsequently, Evans et al. have demonstrated enantio- and diastereo-selective copper-mediated reactions of **1**.[6] On the other hand, Figadére et al. has reported that a titanium–BINOL complex catalyzes reaction of **1** and aldehydes with high enantioselectivity giving δ-hydroxy butenolides, albeit with moderate diastereoselectivity,[7] and the reaction shows autocatalysis.[8] We also examined the reaction of **1** and aldehydes with second-generation metallosalens[9] as chiral catalysts.[10] Of the metallosalens examined, (*R*,*R*)-Cr(salen) **2** was found to catalyze the reaction smoothly but its stereochemistry was not very reproducible. The Mukaiyama aldol reaction, the addition of a silyl enol ether to aldehyde, has been proposed to be reversible.[11] Since **1** is a silyl dienol ether, its addition to aldehyde was also considered to be reversible. We expected that the reproducibility would be improved if the undesired retro-reaction of intermediate **A** is suppressed by addition of a hydroxylic compound that should promote desilylation of **A** and dissociation of the product from Cr(salen) **2** (Scheme 1). Indeed, addition of water to the reaction medium remarkably improved the reproducibility, and high enantioselectivity was realized constantly in the reactions of alkanals.[10,12] However, much less selectivity was observed in the reaction of **1** and benzaldehyde. The principal reason for the poor selectivity was attributed to rapid retro-reaction that might occur even in the presence of water because the bond cleaved is a benzylic one. Although it has been reported that participation of a trimethylsilyl cation or its derivative as a Lewis acid catalyst vitiates the enantioselectivity of asymmetric Mukaiyama aldol reaction,[11,12c] it seemed unlikely that participation of intermediate **A** as Lewis acid caused the unusual selectivity of the reaction of benzaldehyde, since the Lewis acidity of **A** or the dissociation rate of trimethylsilyl cation from **A** is considered not to be affected strongly by the nature of the group R in **A**.

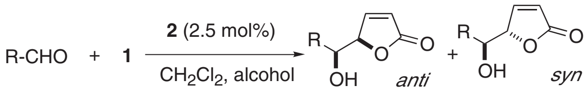
Water was effective as the additive but it does not interdiffuse well with dichloromethane. On the other hand, alcoholic compounds are well-mixable with dichloromethane and they are also expected to promote the desilylation from **A** and the dissociation of the product from Cr(salen). Thus, we examined the reaction of **1** and aldehydes in the presence of alcohol (Scheme 2).[13,14]



R = PhCH$_2$CH$_2$: H$_2$O (10 equiv to **2**), at –20 °C, *anti* : *syn* = 39 : 61, 95% ee (*anti*), 89% ee (*syn*)

R = Ph: H$_2$O (10 equiv to **2**), at –20 °C, *anti* : *syn* = 27 : 73, 28% ee (*anti*), 53% ee (*syn*)

Scheme 1.



Scheme 2.

With octanal as the test material, the additive effect of alcohol was explored at $-20\,^\circ$C (Table 1). When methanol was added, the reaction proceeded slowly with high enantioselectivity, albeit with only modest diastereoselectivity. This adverse effect of methanol was attributed to its coordination to the chromium ion and, partly, to protodesilylation of **1** (50% of **1** was decomposed, when **1** was stirred with **2** and methanol for 24 h). Accordingly, less nucleophilic trifuluoroethanol or bulkier *n*-hexanol was next examined to attain improved chemical yields. Enantioselectivity was slightly enhanced with *n*-hexanol, but diminished with trifuluoroethanol[15] (Entries 2 and 3). Thus, we next examined the effect of secondary and tertiary alcohols as additives. The addition of isopropyl alcohol further improved chemical yield, though stereoselectivity was not improved any more (Entry 4). On the other hand, addition of a more bulky secondary alcohol or tertiary alcohol reduced both stereoselectivity and chemical yield (Entries 5 and 6).

The above results suggested that a secondary alcohol of appropriate bulkiness accelerated the conversion of the resulting intermediate **A** to butenolides without retarding the addition of **1** to aldehydes. On the other hand, less nucleophilic or sterically bulky alcohol did not accelerate the conversion sufficiently, so that the retro-addition of the intermediate **A** and low stereoselective reaction catalyzed by **A**[11,12c] competed with the

Table 1. Addition of **1** to octanal catalyzed by Cr(salen) **2**[a]

Entry	Additive	Yield/%	*anti*:*syn*	% ee (*anti*)	% ee (*syn*)
1	CH_3OH	18	45:55	98	94
2	CF_3CH_2OH	54	51:49	86	61
3	n-$C_6H_{13}OH$	64	45:55	99	96
4	$(CH_3)_2CHOH$	90	45:55	99	97
5	$(i$-$C_3H_7)_2CHOH$	75	50:50	93	92
6	t-C_4H_9OH	53	51:49	91	77

[a]Reactions were carried out at −20 °C for 24 h with molar ratio of aldehyde:**1**:**2**:additive = 1:1.2:0.025:1.

desired reaction and reduced the enantioselectivity. From the above results, we expected that the addition of an appropriate secondary alcohol would suppress the retro-addition reaction in the reaction of benzaldehyde. Indeed, the reaction proceeded with high enantioselectivity together with good diastereoselectivity in the presence of isopropyl alcohol (Table 2, Entry 1). The reaction of *p*-chlorobenzaldehyde also showed similar stereochemistry in the presence of the alcohol, though it was carried out at 0 °C (Entry 2). The retro-reaction rates of diastereomeric intermediates **A** should be different. From the above results, we expected that the diastereoselectivity in the reaction of octanal might be improved by raising the reaction temperature in the presence of excess alcohol. Indeed, the reaction at 0 °C showed slightly better diastereoselectivity (Entry 3), but further raising the temperature to 25 °C diminished enantioselectivity without improving diastereoselectivity. Other examples under optimized conditions are shown in the Table. Reactions of 4-phenylbutanal and cyclohexanecarbaldehyde proceeded with high enantioselectivity (Entries 4 and 5). The reaction of 2,2-dimethylpropanal was sluggish even at 0 °C (Entry 6).

Table 2. Addition reactions of **1** to various aldehydes in the presence of isopropyl alcohol[a]

Entry	Aldehyde/R[b]	Yield/%	*anti*:*syn*	% ee (*anti*)	% ee (*syn*)
1[c]	Ph	86	15:85	75	93
2	p-ClC_6H_4	89	11:89	70	94
3	n-C_7H_{15}	98	40:60	99	97
4	$PhCH_2CH_2CH_2$	94	37:63	99	97
5	c-C_6H_{11}	93	30:70	88	93
6	t-C_4H_9	trace	—	—	—

[a]Reactions were carried out at 0 °C for 24 h unless otherwise noted. [b]R is synonymous with R in Scheme 2. [c]Conducted at −20 °C.

Methanol coordinated with the chromium ion (vide supra). Thus, it seemed reasonable to consider that secondary alcohols also coordinate with the chromium ion, change the conformation of the chiral salen ligand, and affect the stereoselection by Cr(salen) **2**. In order to explore this possibility, we carried out the reaction of **1** and 3-phenylpropanal at −20 °C in the presence of optically active secondary alcohols, 1-phenylethanol (**3**) and methyl lactate (**4**). However, the reactions in the presence of enantiomeric alcohols showed almost identical stereoselectivity, indicating that coordination of a secondary alcohol had minimal effect on the stereochemistry [(*R*)-**3**: 93%, *anti*:*syn* = 39:61, 96% ee (*anti*), 94% ee (*syn*); (*S*)-**3**: 98%, *anti*:*syn* = 37:63, 98% ee (*anti*), 95% ee (*syn*); (*R*)-**4**: 96%, *anti*:*syn* = 43:57, 99% ee (*anti*), 96% ee (*syn*); (*S*)-**4**: 94%, *anti*:*syn* = 46:54, 97% ee (*anti*), 92% ee (*syn*)]. The observed variance of diastereoselectivity with the alcohols might suggest that the desilylation rates of diastereomeric intermediates **A** depend on the alcohol used (vide supra), though its chirality affects it to a minimal extent due to the distance between the silyl group and other chiral centers in **A**.

In conclusion, we were able to demonstrate that the stereochemistry of (*R*,*R*)-Cr(salen)-catalyzed reaction of **1** and aldehydes was improved by addition of a secondary alcohol, which is considered to suppress the retro-reaction of the intermediary **1**-aldehyde adduct **A**.

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13 In the reviewing process of our previous communication (Ref. 10), the reviewers gave useful comments on the reaction mechanism, which helped to promote the present study. We are grateful for the reviewer's comments.

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15 The *O*-trimethylsilylated product was obtained, instead of the desired δ-hydroxy butenolide.

16 Typical experimental procedure (Table 2, Entry 3): To a solution of (*R*,*R*)-**2** (2.8 mg, 2.5 mol%), octanal (16 µL, 0.10 mmol), and isopropanol (7.6 µL) in dichloromethane (250 µL) was added **1** (20 µL, 0.12 mmol) at 0 °C under nitrogen. After being stirred for 24 h, the reaction mixture was concentrated in vacuo, and chromatgraphed on silica gel (hexane/ethyl acetate = 6/4) to give a mixture of the corresponding diastereomeric butenolide. The diastereomer ratio was determined by ^1H NMR (400 MHz) analysis. The enantiomeric excess of the resulting butenolides was determined by HPLC analysis using chiral column (DAICEL CHIRALPAK AS-H, hexane/isopropanol = 9/1).

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