

Enantioselective Addition of 2-(Trimethylsilyloxy)furan to Aldehydes Using Cr(salen) as Catalyst. Effect of Water on Enantioselectivity

Yuko Matsuoka, Ryo Irie, and Tsutomu Katsuki*

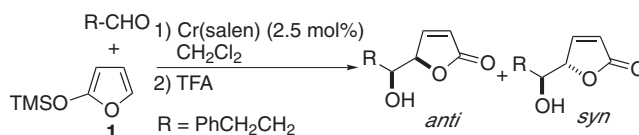
Department of Chemistry, Faculty of Science, Graduate School, Kyushu University 33,
CREST, Japan Science and Technology (JST), Hakozaki, Higashi-ku, Fukuoka 812-8581

(Received April 4, 2003; CL-030292)

Cationic (*R,R*)-Cr(salen) complex **2** was found to catalyze enantioselective addition of 2-(trimethylsilyloxy)furan to aldehydes to give 5-substituted butenolides, though diastereoselectivity was only modest. The presence of a small amount of water is essential for achieving high enantioselectivity.

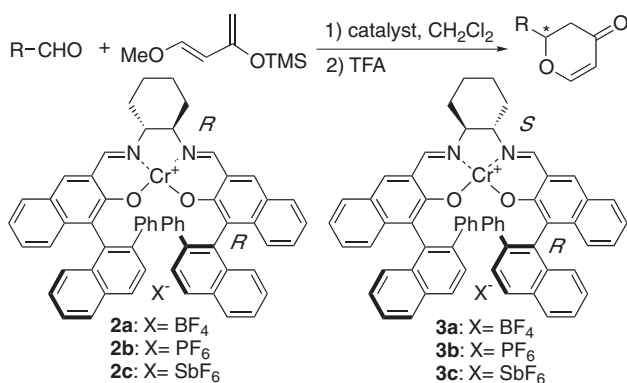
5-Substituted butenolide derivatives are useful building blocks for organic synthesis and many methods are available for their synthesis. Among them, Lewis acid-catalyzed reactions of 2-trimethylsilyloxyfuran **1** and electrophiles such as aldehyde,^{1,2} ketone,¹ and enone^{3,4} are the most straightforward ones. Thus, much effort has been directed toward asymmetrization of these Lewis acid-mediated reactions. We have reported that scandium-3,3'-bis(diethylaminomethyl)-1,1'-bi-2-naphthol and copper(II)-bisoxazoline complexes serve as catalysts for enantioselective Michael addition of **1** to 3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one.⁵ Evans et al. has revealed that copper(II)-bisoxazoline and -bis(oxazolynyl)pyridine complexes are useful also for addition of **1** to methyl pyruvate and benzyloxyacetaldehyde, respectively, achieving high enantio- and diastereoselectivity.⁶ On the other hand, Figadère et al. has described that addition of **1** to aldehydes is promoted with high enantioselectivity and modest diastereoselectivity by using a titanium-BINOL complex as the catalyst.^{7,8} They have also disclosed that, due to autocatalysis, the enantioselectivity of the reaction increases as the reaction proceeds.⁹ We recently found that second-generation cationic metallosalen complexes,¹⁰ especially cationic Cr(salen) (**2a** or **3a**), served as efficient catalysts for asymmetric hetero Diels–Alder reaction (Scheme 1),¹¹ in which enantiofaces of an aldehyde coordinated to the metallosalen complex are discriminated by the chirality of the salen ligand. Therefore, we expected that these metallosalen complexes

might serve as the catalyst also for enantioselective addition of **1** to aldehydes. In this paper, we describe our preliminary study on the Cr(salen)-mediated addition reaction.

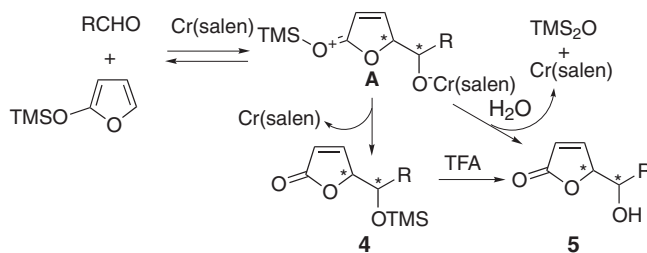


We first examined the addition of **1** to 3-phenylpropanal in dichloromethane at room temperature by using complexes **2** and **3** as the catalysts. The resulting silyl ethers were hydrolyzed to 6-hydroxybutenolide by treatment with trifluoroacetic acid (TFA). Among the catalysts explored, (*R,R*)-Cr(salen)s **2b** and **2c** showed good enantioselectivity, though diastereoselectivity was modest [**2b**: *anti:syn* = 65:35, 76% ee (*anti*), 65% ee (*syn*); **2c**: *anti:syn* = 43:57, 81% ee (*anti*), 52% ee (*syn*)].¹¹ In contrast, less enantioselectivity (<35% ee) was attained with (*R,S*)-Cr(salen)s (**3b** and **3c**). Lowering the reaction temperature increased enantioselectivity [**2c**: *anti:syn* = 44:56, 95% ee (*anti*), 84% ee (*syn*) at 0 °C]. Surprisingly, however, the enantioselectivities obtained with these Cr(salen)s as catalysts were found to be poorly reproducible. For example, **2c** provided *anti*-isomer of enantiomeric excess ranging from 80–95% ee at 0 °C.

It is well known that aldol-type reactions⁸ are reversible and the suppression of the reversed reaction is essential to obtain the product(s) under kinetic conditions.¹³ In the present reaction, the addition of **1** to aldehyde gives an intermediate **A** which competitively undergoes the reversed reaction and the migration of trimethylsilyl group to end up with silyl ether **4** (Scheme 2). From the above results, however, it was considered that a trace amount of an impure hydroxylic ingredient such as water promoted conversion of the intermediate **A** to hydroxy lactone **5**. The conversions of **A** to **4** and **5** should be irreversible.¹³ Thus, we expected that the stereochemistry of the present reaction would become reproducible by adding water which accelerates the conversion from **A** to **5** and suppress the undesired reversed reaction.^{14,15}



Scheme 1.



Scheme 2.

In order to evaluate the effect of water on enantioselectivity, **2c** was first dried in vacuo at 70 °C followed by the subsequent addition of the wet dichloromethane solvents prepared with a calculated amount of water and 3-phenylpropanal at room temperature. The solutions were cooled to -20 °C and **1** was added at the temperature. Consequently, the enantioselectivity was improved as the water content increased and the optimal enantioselectivity was observed when water amounted to ten equivalents of the catalyst (Table 1). The results obtained in the presence of water were highly reproducible.¹⁶

Table 1. Effect of water on enantioselectivity in the addition reaction of **1** to 3-phenylpropanal with **2c**^a

Entry	Water/ 2c	Yield/%	<i>anti:syn</i>	% ee (<i>anti</i>)	% ee (<i>syn</i>)
1	2	96	52:48	84	52
2	3	96	51:49	86	61
3	6	96	46:54	90	79
4	10	91	39:61	95	89
5	12	96	39:61	93	89

^aIsolated yield of a mixture of *anti*- and *syn*-products.

^bDetermined by HPLC analysis using chiral column (DAICEL CHIRALPAK AS-H, hexane/isopropanol = 9/1).

The reactions of other alkanals were also examined at -20 °C in the presence of water (Table 2).¹⁷ The reactions of non-branched alkanals gave *anti*- and *syn*-products of high enantiomeric excesses (>94% and >88%, respectively), while the enantiomeric excess of the products derived from cyclohexanecarboxaldehyde was somewhat diminished (Entry 4). However, diastereoselectivity was only modest in all instances. These results suggested that the chiral salen ligand effectively blocked one enantioface of the coordinated alkanal, which **1** approached from its open side far-off the stereocontrolling unit of the ligand. In contrast, enantioselectivity of the addition of **1** to benzaldehyde was moderate (Entry 5). This suggested that the retro-addition occurred rapidly in this reaction even in the presence of water, probably because the bond was cleaved at the benzylic position in the retro-addition.

In conclusion, we were able to demonstrate that second-generation cationic (*R,R*)-Cr(salen) complexes catalyze addition reaction of **1** to alkanals in the presence of water in a highly enantioselective manner, though diastereoselectivity of the reactions remains insufficient. Further study on the reaction mechanism is under way.

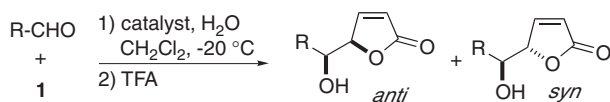


Table 2. Reactions of **1** and alkanals in the presence of **2c**^a

Entry	R	Yield/% ^b	<i>anti:syn</i> ^c	%ee (<i>anti</i>) ^d	%ee (<i>syn</i>) ^d
1	CH ₃ (CH ₂) ₅	88	53:47	94	90
2	CH ₃ (CH ₂) ₆	70	48:52	97	92
3	Ph(CH ₂) ₃	74	42:58	95	88
4	<i>c</i> -C ₆ H ₁₁	44	45:55	84	80
5	C ₆ H ₅	56	27:73	28	53

^aReaction was carried in dichloromethane at -20 °C with the molar ratio of aldehyde:**1**:**2c**:H₂O = 1:1.2:0.025:0.25.

^bFootnote a in Table 1. ^cRef. 12. ^dFootnote b in Table 1.

References and Notes

- a) M. Asaoka, N. Sugimura, and H. Takei, *Bull. Chem. Soc. Jpn.*, **52**, 1953 (1979). b) C. W. Jefford, D. Jaggi, and J. Boukouvalas, *Tetrahedron Lett.*, **28**, 4037 (1987).
- a) D. W. Brown, M. M. Campbell, A. P. Taylor, and X. Zhang, *Tetrahedron Lett.*, **28**, 985 (1987). b) G. Casiraghi, L. Colombo, G. Rassu, and P. Spanu, *Tetrahedron Lett.*, **30**, 5325 (1989). c) T. Bauer, *Tetrahedron: Asymmetry*, **7**, 981 (1996).
- T. Fukuyama and L. Yang, *Tetrahedron Lett.*, **27**, 6299 (1986).
- M. A. Brimble, M. T. Brimble, and J. J. Gibson, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 179.
- H. Kitajima and T. Katsuki, *Synlett*, **1997**, 568.
- a) D. A. Evans, C. S. Burgey, M. C. Kozlowski, and S. W. Tregay, *J. Am. Chem. Soc.*, **121**, 686 (1999). b) D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell, and R. J. Staples, *J. Am. Chem. Soc.*, **121**, 669 (1999).
- M. Szlosek, X. Franck, B. Figadère, and A. Cavé, *J. Org. Chem.*, **63**, 5169 (1998).
- This addition is a Mukaiyama aldol-like reaction with dienol silyl ether.
- M. Szlosek and B. Figadère, *Angew. Chem., Int. Ed. Engl.*, **39**, 1799 (2000).
- Metallosalens possessing a binaphthyl unit are referred to as second-generation metallosalens: Y. N. Ito and T. Katsuki, *Bull. Chem. Soc. Jpn.*, **72**, 603 (1999).
- a) J. Mihara, T. Hamada, T. Takeda, R. Irie, and T. Katsuki, *Synlett*, **1999**, 1160. b) K. Aikawa, R. Irie, and T. Katsuki, *Tetrahedron*, **57**, 845 (2001). c) J. Mihara, K. Aikawa, T. Uchida, R. Irie, and T. Katsuki, *Heterocycles*, **54**, 395 (2001).
- In ¹H NMR analysis, the protons at the carbinol carbons in the *syn*-products derived from octanal, cyclohexanecarboxaldehyde, and benzaldehyde have been reported to appear in ca. 0.1–0.3 ppm higher than the corresponding protons in the *anti*-products (Ref. 9). The relative configurations of the products derived from other aldehydes were tentatively assigned according to this report.
- E. M. Carreira, in "Comprehensive Asymmetric Catalysis III," ed. by E. N. Jacobsen, A. Pfaltz, and H. Yamamoto, Springer, Berlin (1999), Vol. 29.1, p 997.
- For the previous discussions of water effect on asymmetric Mukaiyama aldol reactions, see: a) M. Sodeoka, K. Ohrai, and M. Shibasaki, *J. Org. Chem.*, **60**, 2648 (1995). b) O. Fujimura, *J. Am. Chem. Soc.*, **120**, 10032 (1998). c) S. Kobayashi, S. Nagayama, and T. Busujima, *Tetrahedron*, **55**, 8739 (1999). d) Y. Yamashita, H. Ishitani, H. Shimizu, and S. Kobayashi, *J. Am. Chem. Soc.*, **124**, 3292 (2002).
- The effects of water might be manifold. We cannot rigorously exclude the possibility that water could prevent **A** from promoting the non-enantioselective reaction (Ref. 13 and 14c). Coordination of water and hydration of the counter anion would also change the catalyst structure as suggested by the reviewers. After this manuscript was submitted, however, secondary alcohols have been found to be effective as additives and enantiomeric alcohols to produce the same additive effect. Thus, the coordination of the hydroxylic ingredients to the catalyst is unlikely to be significant for the change of the stereochemical outcome. The utilities of alcoholic additives are currently under investigation.
- The reaction with complex **2a** in the absence of water did not proceed, but the reaction in the presence of water showed high enantioselectivity [54%, *anti:syn* = 41:59, 92% ee (*anti*) and 90% ee (*syn*), at -20 °C].
- Typical experimental procedure: (*R,R*)-**2c** (2.8 mg, 2.5 mol%) was dissolved in dichloromethane (250 µL) including 0.45 µL of water, under nitrogen. To the solution was added aldehyde (0.10 mmol) and the mixture was cooled to -20 °C. **1** (20 µL, 0.12 mmol) was added to the mixture and stirred for 24 h. The reaction mixture including **4** and **5** was treated with TFA (10% THF solution), concentrated in vacuo, and chromatographed on silica gel (hexane/ethyl acetate = 6/4) to give a mixture of the corresponding diastereomeric butenolide **5**. The diastereomer ratio was determined by ¹H NMR (400 MHz) analysis. The enantiomeric excess of the resulting butenolides was determined as described in footnote b in Table 1.