

group);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 207.2 (CO), 150.4-121.4 (Cs of quinoline & vinylic carbons), 42.5 ( $\alpha$ -carbon to CO), 33.3, 31.7, 31.0, 28.7, 25.2 ( $\beta$ -carbon & saturated carbons in cyclohexenyl group); IR spectrum (neat) 3040, 2929, 2856, 2835, 1691 (CO), 1595, 1571, 1496, 1447, 1369, 1331, 1256, 1170, 1135, 1117, 1046, 960, 935, 917, 829, 795, 763, 633  $\text{cm}^{-1}$ ; mass spectrum.  $m/e$  (assignment, relative intensity) 265 ( $\text{M}^+$ , 5.1), 264 ( $\text{M}^+-1$ , 9.2), 185 ( $\text{M}^+-\text{C}_6\text{H}_9+1$ , 17.7), 184 ( $\text{M}^+-\text{C}_6\text{H}_9$ , 67.4), 171 ( $\text{M}^+-\text{C}_7\text{H}_{11}+1$ , 13.6), 170 ( $\text{M}^+-\text{C}_7\text{H}_{11}$ , 8.8), 156 (50, quinolinyl- $\text{CO}^+$ ), 129 (29.4), 128 (31.4, quinolinyl $^+$ ); HRMS calcd for  $\text{C}_{18}\text{H}_{19}\text{NO}$  265.1467, found 265.1464.

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### Diastereoselective Coupling Reaction of Moisture Sensitive 2-(Trimethylsilyloxy)furan with Aldehydes in Aqueous Media

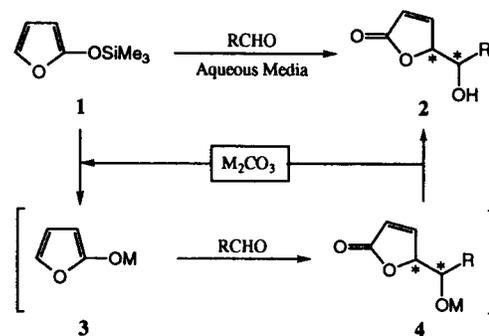
Chan-Mo Yu\*, Jongho Lee, Sung-Soo Lee, Ha-Soon Choi, and Seung-Ki Park†

Department of Chemistry,  
 Sung Kyun Kwan University,  
 Suwon 440-746, Korea

†Department of Chemistry,  
 The University of Suwon,  
 P.O.Box 77, Suwon 445-743, Korea

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The availability of efficient synthetic methodology for achieving diastereoselectivity in the construction of stereochemically rich compounds is of considerable current interest because allowed structures are featured in many useful substances.<sup>1</sup> In this regard, the aldol reaction and its numerous variants provide an excellent stereoselective route to  $\beta$ -hydroxy carbonyl compounds.<sup>2</sup> Even though the aldol reaction represents one of successful stereochemical courses in organic reaction, there are still limited scopes of reagents and reaction conditions for the stereoselection mainly due to equilibrium between aldolates through retroaldol and realdol.<sup>3</sup> In order to obtain useful levels of diastereoselectivity, specific enolates such as boron and titanium must be employed with particular substrates whereas more readily available alkali metal enolates often revealed their significant problems. We considered that the equilibrium could be controlled by the reaction in aqueous media through the protonation of aldolate from water. Recently, aqueous media or phase organic reactions have gained much attention from the organic



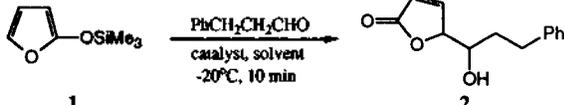
Scheme 1. Plausible Reaction Pathway.

chemist because of chemical and environmental issues.<sup>4</sup> According to recent report, aldol condensation of silyl enol ether with aldehyde, so called Mukaiyama aldol,<sup>5</sup> in aqueous solution was realized with marginal diastereoselectivity (2-1 : 1) by the use of Lewis acid catalyst.<sup>6</sup> In this communication we describe that the coupling reaction of moisture sensitive 2-(trimethylsilyloxy)furan with aldehydes in the presence of catalytic amount of  $\text{M}_2\text{CO}_3$  ( $\text{M}=\text{K}, \text{Cs}$ ) in aqueous media ( $\text{THF}/\text{H}_2\text{O}$ ) afforded *erythro*-selective  $\delta$ -hydroxy- $\gamma$ -lactones in high yield with reasonable levels of diastereoselectivity. The choice of 2-(trimethylsilyloxy)furan is based on widely applicabilities of its coupling product.<sup>7</sup>

The rationale for the aqueous media carbonyl addition is outlined in Scheme 1. The alkali metal enolate can be generated from 1 as a consequence of the Si-O bond breaking mediated by alkali carbonate. The central step in this reaction can be formulated as an addition of enolate 3 to aldehyde with competition of direct protonation, involving the formation of aldolate 4 which is readily protonated to product 2 along with regeneration of catalyst. The basic solution would offer more possibility of C-C bond formation instead of protonation.

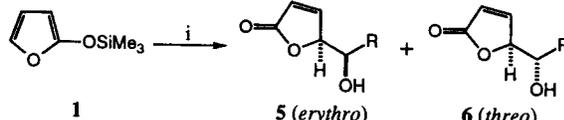
Our initial studies began with commercially available 2-(trimethylsilyloxy)furan and hydrocinnamaldehyde under the various reaction conditions. Preliminary investigations for the coupling indicated that the conversion to the corresponding lactone 2 could be realized with alkali metal carbonates, but would be unpromising with Lewis acid. Interesting observation was made that the reaction with  $\text{K}_2\text{CO}_3$  and  $\text{Cs}_2\text{CO}_3$  showed much better catalytic ability than the reaction with  $\text{Li}_2\text{CO}_3$  and  $\text{Na}_2\text{CO}_3$ ; these bases were generally superior and were chosen for systematic studies. Upon optimal, the reaction was conducted by the addition of 2-(trimethylsilyloxy)furan (1) to the homogeneous solution of hydrocinnamaldehyde in the presence of  $\text{K}_2\text{CO}_3$  (0.1 eq) at  $-20^\circ\text{C}$  in  $\text{THF}/\text{H}_2\text{O}$  (4 : 1). After being proceeded for 10 min at  $-20^\circ\text{C}$ , the reaction mixture was quenched by the addition of 10% aqueous HCl. After usual work up procedure, final purification was effected by silica gel chromatography to afford lactone in 68% isolated yield.

Diastereoselectivities were determined unambiguously by the direct comparison of  $^1\text{H}$  NMR spectral data of product with authentic samples prepared from the reaction of 1 with hydrocinnamaldehyde in the presence of catalytic amount (0.5 eq) of  $\text{BF}_3\text{OEt}_2$  at  $-78^\circ\text{C}$  for 4h in anhydrous  $\text{CH}_2\text{Cl}_2$ .<sup>8</sup> Major component of aqueous media coupling turned out to be *ery-*

**Table 1.** Preliminary Investigations


Entry	Catalyst (10 mol %)	Solvent	Yield, % <sup>a</sup>
1	K <sub>2</sub> CO <sub>3</sub>	THF : H <sub>2</sub> O (4 : 1)	68
2	K <sub>2</sub> CO <sub>3</sub>	dioxane : H <sub>2</sub> O (4 : 1) <sup>b</sup>	54
3	Li <sub>2</sub> CO <sub>3</sub>	THF : H <sub>2</sub> O (4 : 1)	24
3	Na <sub>2</sub> CO <sub>3</sub>	THF : H <sub>2</sub> O (4 : 1)	34
4	Cs <sub>2</sub> CO <sub>3</sub>	THF : H <sub>2</sub> O (4 : 1)	85
5	K <sub>2</sub> CO <sub>3</sub> /MgBr <sub>2</sub>	THF : H <sub>2</sub> O (4 : 1)	23
6	<i>t</i> -BuOK	THF : H <sub>2</sub> O (4 : 1)	33
7	MgBr <sub>2</sub>	THF : H <sub>2</sub> O (4 : 1)	0

<sup>a</sup> chromatographed yield. <sup>b</sup> reaction was run at 0 °C.

**Table 2.** Aldol Reaction of **1** with Aldehydes in Aqueous Media


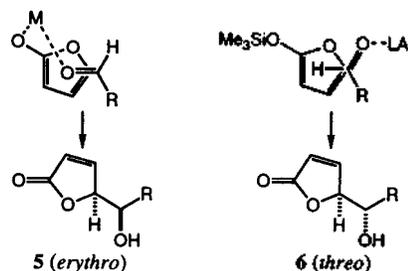
Entry	RCHO	Catalyst <sup>a</sup>	5 : 6 <sup>b</sup>	Yield <sup>c</sup>
1	PhCH <sub>2</sub> CH <sub>2</sub> CHO	K <sub>2</sub> CO <sub>3</sub>	87 : 13	68
2		Cs <sub>2</sub> CO <sub>3</sub>	75 : 25	85
3	<i>i</i> -PrCHO	K <sub>2</sub> CO <sub>3</sub>	83 : 17	67
4		Cs <sub>2</sub> CO <sub>3</sub>	78 : 22	63
5	PhCHO	K <sub>2</sub> CO <sub>3</sub>	81 : 19	73
6		Cs <sub>2</sub> CO <sub>3</sub>	83 : 17	81
7	PhCH=CHCHO	K <sub>2</sub> CO <sub>3</sub>	77 : 23	73
8		Cs <sub>2</sub> CO <sub>3</sub>	82 : 18	74
9	<i>n</i> -C <sub>5</sub> H <sub>11</sub> CHO	K <sub>2</sub> CO <sub>3</sub>	85 : 15	63
10		Cs <sub>2</sub> CO <sub>3</sub>	83 : 17	87
11	PhCH <sub>2</sub> CH <sub>2</sub> CHO	BF <sub>3</sub> ·OEt <sub>2</sub> <sup>d</sup>	22 : 78	64

<sup>a</sup> 10 mol %. <sup>b</sup> Determined by the analysis of 300 MHz <sup>1</sup>H NMR spectra. <sup>c</sup> Chromatographed yield. <sup>d</sup> Reaction was run at -78 °C in dried CH<sub>2</sub>Cl<sub>2</sub>.

*thro* in contrast to *threo* selectivities observed in the Lewis acid catalyzed reaction in organic phase. These results are summarized in Table 2.

With our research scope of carbonyl addition of **1** in aqueous media based on preliminary investigations, we turned our attention next to examine feasibility of this reaction with various aldehydes. Several reactions for the diastereoselective synthesis of  $\delta$ -hydroxy- $\gamma$ -lactones were conducted under the identical condition, and proved to be effective. Representative results are listed in Table 2.

Although the role of metal carbonate to catalyze the reaction as an enolate must be a consequence of the bond breaking between Si-O, the exact stereochemical outcome and mechanistic behavior have not been rigorously elucidated. However, the observed preference for relative stereochemis-

**Figure 1.** Proposed Stereochemical Courses.

try of *erythro* for the  $\delta$ -hydroxy- $\gamma$ -lactones from the aqueous aldol between **1** and aldehydes could be explained on the basis of chelating model compared to anti-periplanar model for *threo* favorably in Lewis acid promoted reaction. This prediction was based on the optimum electronic distribution and minimum steric repulsion between chelated enolate and substrate, the optimum arrangement being as depicted in Figure 1.

In summary, this paper described an efficient aldol reaction of moisture sensitive 2-(trimethylsilyloxy)furan with aldehydes in aqueous media in good yields with reasonable levels of diastereoselectivity which promises to be widely useful. Studies are in progress to extend this method to more complicate system including reactions with chiral aldehydes to establish three contiguous absolute stereoselection.

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### Stereoselective Synthesis of Acyltetrahydrofurans via Bicyclic Oxazines

Hyo Won Lee

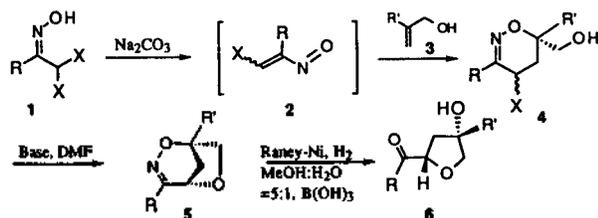
Department of Chemistry,  
Chungbuk National University,  
Cheongju 361-763, Korea

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It is useful to use a heterocycle as a precursor or an intermediate for functionalization or structural transformation of organic compounds. Monohalo-substituted oxazines can be utilized for the preparation of tetrahydrofurans. Herein we would like to report the utilization of  $\alpha,\alpha$ -dihalooximes in the preparation of *cis*-5-acyltetrahydrofuran-3-ols via 4-halo-5,6-dihydro-4*H*-[1,2]oxazines.

It has been known that hetero-Diels-Alder reaction of *in situ* generated nitrosoalkenes from  $\alpha$ -halooximes with alkenes provides dihydro-4*H*-oxazines.<sup>1,2</sup> The attachment of a halogen atom at the 4 position of oxazine with 6-hydroxymethyl can lead to a tetrahydrofuran ring via intramolecular nucleophilic substitution of the halogen atom by hydroxy group. The reductive cleavage at N-O bond of oxazine ring yields the *cis*-2-acyltetrahydrofuran-5-ol.

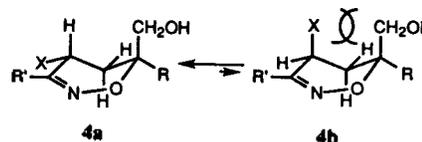
In our synthetic plan  $\alpha,\alpha$ -dihalooximes **1** were taken to provide monohalo-substituted oxazine derivatives. (Scheme 1) Accordingly dihaloketones were treated with hydroxylamine hydrochloride in MeOH at room temperature for 2-4 days to provide **1**. Halovinyl nitroso compounds **2**, which were *in situ* generated by the reaction of **1** with Na<sub>2</sub>CO<sub>3</sub>, underwent [4+2] cycloaddition with allylic alcohols **3** to give isomeric mixture of 5,6-dihydro-4-halo-1,2-oxazines **4**.<sup>3</sup> However, when these oxazines were treated with a base such as NaH or KH, 2,6-dioxo-3-azabicyclo[3.2.1]oct-3-enes **5** were obtained. The rationale for this stereoselectivity is that when a

Scheme 1. Reaction Pathway to *cis*-2-Acylfuran-5-ol.Table 1. Conversion of Oxime **1** to Ketone **6** via Oxazine Derivatives **4** and **5**

Entry	Oximes <b>1</b>	Alcohols <b>3</b>	Oxazines <b>4</b>		Ketones <b>6</b>
			(% Yield)	Oxazines <b>5</b> (% Yield)	
1 <sup>a</sup>	R=Me, X=Cl	R'=H	25	47	75
2 <sup>a</sup>	R=Me, X=Cl	R'=Me	45	62	91
3	R=Ph, X=Br	R'=H	69	73	78
4	R=Ph, X=Br	R'=Me	76	91	73
5	R= <i>p</i> -ClPh, X=Br	R'=H	81	75	85
6	R= <i>p</i> -ClPh, X=Br	R'=Me	98	76	92

<sup>a</sup>KH was used to generate bicyclic oxazine **5**, otherwise NaH was used.

mixture of two halo isomers **4** was reacted under the basic condition, the equilibrium shifted toward thermodynamically more stable **4a**, which was then replaced by the pending hydroxyl group to furnish the bicyclic product **5**.



The reductive cleavage of N-O bond of bicyclic oxazines **5** with Raney Nickel (methanol : H<sub>2</sub>O = 5 : 1) gave stereoselectively acyltetrahydrofurans **6** in good yield.<sup>4</sup> The results were shown in Table 1.

Currently synthetic applications of this methodology for the preparation of other medium size cyclic ethers are in progress.

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