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syn- and anti-Selective Preparation of 3-Substituted-Δ^2-Isoxazolines

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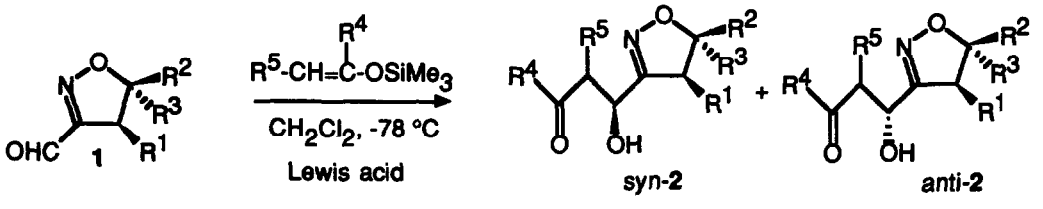
Summary: Both syn- and anti- isomers of 3-substituted-Δ^2-isoxazolines can be prepared in a stereoselective way by the aldol reaction of 3-formyl-Δ^2-isoxazolines and silyl enol ethers in the presence of appropriate Lewis acid.

Recently, Δ^2-isoxazoline has become an important intermediate in organic synthesis.[1-3] This heterocycle can be readily converted into a γ-amino alcohol or a β-hydroxy ketone.[4,5] The relative stereochemistry between C^4 and C^5 on the ring depends solely on geometry of the starting olefins, because concerted cycloaddition process between a nitrile oxide and an olefin proceeds in a stereospecific way. However, the cycloaddition of chiral nitrile oxides or their derivatives to olefin usually takes place in non-stereoselective way to give mixtures of a pair of diastereomers.[6-8] It is meaningful to develop a useful method for a stereoselective carbon-carbon bond formation on the side chain of the ring.[9,10] 3-Formyl-Δ^2-isoxazoline should be a good candidate for this purpose. However, there have been a few reports concerning on this compound.[11] In this paper, we report stereoselective introduction of substituents on C^3 position can be readily achieved by the aldol reaction of 3-formyl-Δ^2-isoxazolines. Two possible diastereomers can be prepared with high stereoselectivity by the use of $TiCl_4$ or $BF_3{\cdot}OEt_2$, respectively.

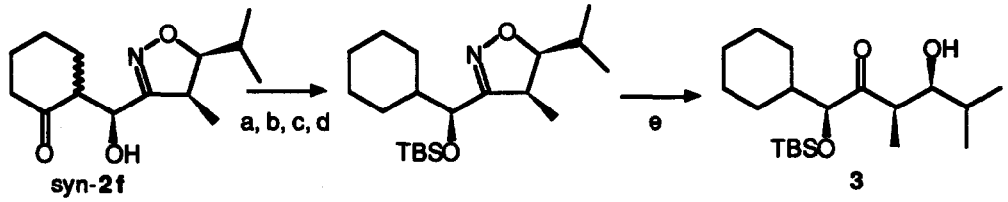


Scheme 1

Treatment of 3-formyl-Δ^2-isoxazoline **1** with various kinds of silyl enol ethers in the presence of appropriate Lewis acid afforded corresponding aldol adducts **2** (Scheme 1).[12] The results are summarized in Table 1. Various kinds of Lewis acids can be used for the reaction. While $TiCl_4$, $ZnBr_2$, and $BF_3{\cdot}OEt_2$ give **2a** in good yield (run 1, 3, 5), $SnCl_4$ and $AlCl_3$ result in low to moderate yield of **2a** (run 2 and 4). The reaction with high reactive silyl enol ether proceeds smoothly in the presence of catalytic amounts of $TiCl_4$ (run 1, 6, 8, 11, 15). The products usually consist of a pair of diastereomers, which are syn-**2** and anti-**2**. Their ratios were determined by HPLC analyses. $TiCl_4$

and $SnCl_4$ give syn-**2a** in high stereoselectivity (run 1 and 2). $ZnBr_2$ shows moderate syn-selectivity (run 3). The opposite isomer, anti-**2a**, is also prepared in the presence of $AlCl_3$ or $BF_3{\cdot}OEt_2$ (run 4 and 5). $BF_3{\cdot}OEt_2$ shows a somewhat better selectivity than $AlCl_3$. Since the formation of syn- and anti-**2a** is now possible, the reactions of other kinds of **1** are carried out. $TiCl_4$ always exhibits high syn-selectivity except the case of R^1 = H (run 6, 8, 10, 11 and 13). This selectivity is not observed in absence of substituent on C^4 to give 1:1 mixture of anti-**2g** and syn-**2g** (run 15). Relative stereochemistry between C^4 and C^5 does not affect the syn-selectivity. On the other hand, while anti-**2** is obtained as an almost single isomer from 4,5-cis substituted **1** under the $BF_3{\cdot}OEt_2$ catalyzed conditions (run 5, 7, and 14), 4,5-trans substituted **1** gives a diastereomeric mixture of **2**, whose ratio is about 6:4 to 7:3 (run 9 and 12). Some selectivity is observed in absence of the substituent on C^4 to give **2g** in 24/76 diastereomer ratio (run 16).

The stereochemistry of **2** was confirmed on comparison with ^1H NMR spectra after the conversion of syn-**2f** to **3** (Scheme 2).[13]

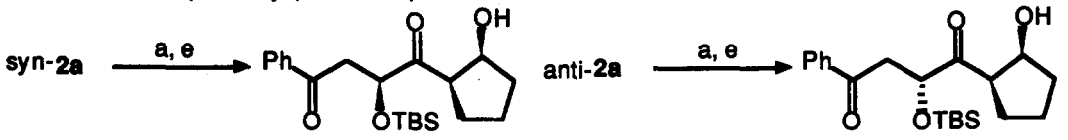


syn-**2f** **3**

a: TBSCl, ImH, DMF, 60 °C b: $NaBH_4$ c: NaH, CS_2, MeI d: Bu_3SnH, AIBN, 80 °C
e: Raney-Ni, H_2, $B(OH)_3$

Scheme 2

These compounds can be readily converted into corresponding hydroxy ketones under the hydrogenation condition.[14] For example, syn-**2a** and anti-**2a** gave compound **4** and **5** as a single diastereomer, respectively (Scheme 3).



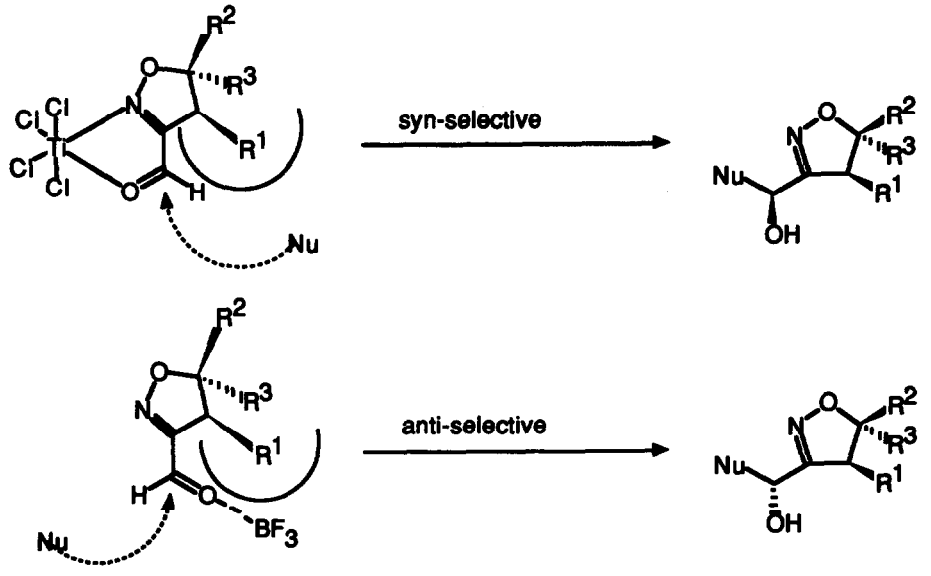
Scheme 3 **4** 47% **5** 47%

This reaction pathway can be explained via chelation or non-chelation control of Lewis acid (Scheme 4).[15-19] For example, $TiCl_4$ can coordinate to the oxygen in the formyl group and the nitrogen atom in the Δ^2-isoxazoline ring to form five membered ring.[10] A nucleophile can attack from the less hindered site, which is opposite site to R^1 group, to give syn-**2** predominantly. In BF_3 system, on the other hands, this chelation is not formed but dipolar repulsion of C=O and C=N bond governs the conformation of **1** to give anti-**2** selectively. In both cases, the substituents on C^4 play an important role to determine the stereochemistry of the products. Further application of this reaction is now proceeding in our laboratory.

Table 1. Stereoselective Aldol Reaction of Silyl Enol Ethers to **1**.

run	1	R^1	R^2	R^3	R^4	R^5	Lewis acid (eq)	time (h)	2; yield (%)[a]	syn/anti[b]
1	**1a**	$-(CH_2)_3-$		H	Ph	H	$TiCl_4$	(0.1) 1	**2a**; 89	96/4
2	**1a**	$-(CH_2)_3-$		H	Ph	H	$SnCl_4$	(0.1) 1	**2a**; 48	96/4
3	**1a**	$-(CH_2)_3-$		H	Ph	H	$ZnBr_2$	(1.0) 2	**2a**; 93	63/37
4	**1a**	$-(CH_2)_3-$		H	Ph	H	$AlCl_3$	(1.0) 2	**2a**; 57	11/89
5	**1a**	$-(CH_2)_3-$		H	Ph	H	$BF_3{\cdot}OEt_2$	(1.0) 4	**2a**; 90	4/96
6	**1a**	$-(CH_2)_3-$		H	Ph	Me	$TiCl_4$	(0.1) 1	**2b**; 99	98/2[c]
7	**1a**	$-(CH_2)_3-$		H	Ph	Me	$BF_3{\cdot}OEt_2$	(1.0) 2	**2b**; 94	2/98[d]
8	**1b**	Ph	H	Ph	Ph	H	$TiCl_4$	(0.1) 1	**2c**; 76	96/4
9	**1b**	Ph	H	Ph	Ph	H	$BF_3{\cdot}OEt_2$	(1.0) 1	**2c**; 89	39/61
10	**1b**	Ph	H	Ph	t-Bu	H	$TiCl_4$	(1.3) 48	**2d**; 70[e]	96/4
11	**1c**	Me	H	Me	Ph	H	$TiCl_4$	(0.1) 6	**2e**; 93	93/7
12	**1c**	Me	H	Me	Ph	H	$BF_3{\cdot}OEt_2$	(1.0) 8	**2e**; 54	27/73
13	**1d**	Me	i-Pr	H	$-(CH_2)_4-$		$TiCl_4$	(1.0) 1	**2f**; 70	97/3
14	**1d**	Me	i-Pr	H	$-(CH_2)_4-$		$BF_3{\cdot}OEt_2$	(1.0) 2	**2f**; 89	4/96
15	**1e**	H	Ph	H	Ph	H	$TiCl_4$	(0.1) 2	**2g**; 96	53/47[f]
16	**1e**	H	Ph	H	Ph	H	$BF_3{\cdot}OEt_2$	(1.0) 2	**2g**; 88	24/76[f]

a) Isolated yield. b) Determined by HPLC analyses. c) Diastereomer ratio on syn- PhC(=O)CH(Me)-CH(OH)- was 81/17. d) Diastereomer ratio on anti- PhC(=O)CH(Me)-CH(OH)- was 71/27. e) Dehydrated olefin was isolated in 17% yield. f) Stereochemistry of **2g** was not determined.



Scheme 4

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12. Typical experimental procedures are as following: To a solution of **1** (1 mmol) and silyl enol ether (1.3 mmol) in methylene chloride (10 mL) was added Lewis acid at -78 °C and the resulting mixture was stirred for 1-48 h till compound **1** disappeared on TLC. After the reaction was over, the solution was poured into 1 M HCl and extracted with ethyl acetate for three times. Purification of crude products by silica gel column chromatography gave pure adduct **2** in 54-99% yield. HPLC analyses were carried out on using TSK-gel ODS-80T column.
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