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Diastereoselective Ene Reaction of 3-Formyl-Δ^2-isoxazolines

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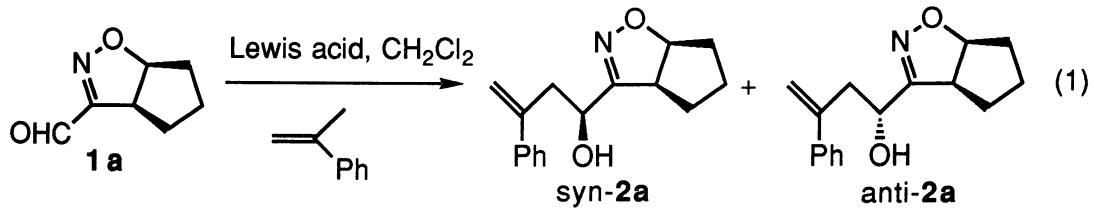
The ene reaction of 3-formyl-Δ^2-isoxazolines proceeds smoothly in the presence of appropriate Lewis acid. An efficient 1,3-asymmetric induction takes place to give syn- and anti-homoallyl alcohols in a stereoselective way.

The carbonyl-ene reaction[1a] is one of useful carbon-carbon bond forming reaction.[1] Recently, stereoselective methods using Lewis acid have been devised by several groups.[2] Chelation and non-chelation control should be an important strategy of controlling stereochemistry on carbon-carbon bond formation under Lewis acid conditions.[3] Δ^2-Isoxazolines are useful synthetic intermediates because they can be readily converted into various important compounds such as β-hydroxy ketones or γ-amino alcohols.[4] They also act as effective stereocontrolling elements because they have both relatively rigid ring conformation and coordinating heteroatoms which serve as a Lewis base.[5] In this paper, we report that the ene reaction of 3-formyl-Δ^2-isoxazolines[6] (**1**) achieves efficient 1,3 asymmetric induction under both chelation and non-chelation conditions.



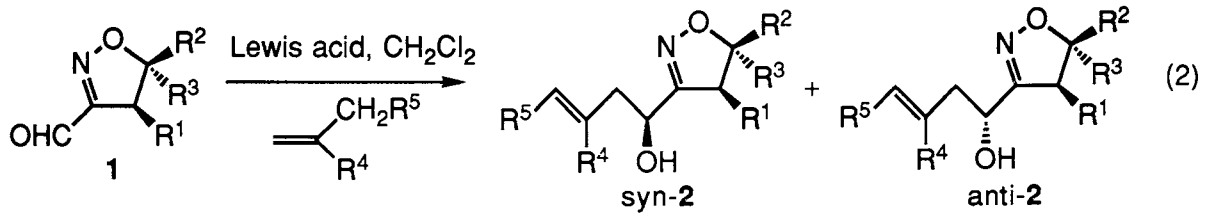
The ene reaction of 3-formyl-Δ^2-isoxazolines (**1a**) with α-methylstyrene was carried out (Eq. 1). The results are summarized in Table 1. Typical experimental procedures are as following: To a solution of **1a** (1.5 mmol) and α-methylstyrene (3 mmol) in CH_2Cl_2 was added an appropriate Lewis acid at -78 °C or ambient temperature. The resulting mixture was stirred until **1a** almost disappeared on TLC. After usual workup, the crude product was purified by flush column chromatography (silica gel/hexane-ethyl acetate 3:1) to give the ene adduct **2a**.

Table 1. Diastereoselective ene reaction of **1a**

Run	Lewis acid	(equiv.)	Temp/°C	Time/h	**2a**; Yield/%[a]	syn-**2a**/anti-**2a**[b]
1	$SnCl_4$	(1)	-78	1	70	99.5/0.5
2	$TiCl_2(Oi\text{-}Pr)_2$	(2)	r. t.	20	74	95/5
3	$TiCl_4$	(1)	-78 - r. t.	24	trace	-
4	$BF_3{\cdot}OEt_2$	(1)	-78 - r. t.	36	trace	-
5	Et_2AlCl	(1.5)	-78	3	59	0/100[c]

a) Isolated yield. b) Determined by HPLC analyses (cosmosil 5-PYE column was used.). c) The minor isomer was not detected on HPLC analyses.

Several Lewis acids were examined as a reaction catalyst. For example, the reaction took place smoothly under the conditions catalyzed by $SnCl_4$ or $TiCl_2(Oi\text{-}Pr)_2$ to afford **2a** in good yield (runs 1 and 2). The use of $TiCl_2(Oi\text{-}Pr)_2$ gave **2a** in better yield than the use of $SnCl_4$. Due to weak Lewis acidity of $TiCl_2(Oi\text{-}Pr)_2$, excess amounts of Lewis acid and room temperature were necessary for the reaction (run 2). 250 MHz ^1H NMR spectra exhibited that these **2a** consisted of an almost single isomer. Both $TiCl_2(Oi\text{-}Pr)_2$ and $SnCl_4$ gave the identical stereoisomer of **2a**. The stereochemistry of the major isomer of **2a** was found to be syn-**2a** in comparison of ^1H NMR spectra after its conversion to **3**.[7] The diastereomer ratios of **2a** were determined by HPLC analyses on cosmosil 5-PYE column as shown in Table 1. The syn-selectivity of $SnCl_4$ is better than $TiCl_2(Oi\text{-}Pr)_2$ because the $SnCl_4$ catalyzed reaction proceeds at -78 °C. Other Lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ afforded only trace amounts of **2a** (runs 3 and 4). However, Et_2AlCl served as an effective Lewis acid for the reaction (run 5). Although the yield of **2a** was not so high, the opposite stereoisomer, anti-**2a**, was formed under this condition exclusively. The stereoselectivity was very high because syn-**2a** was not detected on HPLC analysis. Thus, syn-**2a** and anti-**2a** can be prepared in stereoselective way by the choice of Lewis acids.



(2)

The reaction was applied to other kinds of **1** (Eq. 2). The results are summarized in Table 2. The choice of Lewis acid is important to get anti-**2** or syn-**2** in high stereoselective way. For example, the ene reaction to α-methylstyrene, isobutene, or methylenecyclohexane proceeded smoothly under the condition catalyzed by $SnCl_4$ to give syn-**2** in good yield (runs 1, 4, 7, and 10). The syn-selectivity of $SnCl_4$ is usually better than 96/4. In some cases, anti-**2** could not be detected under this reaction conditions (run 4). The syn-selectivity of $TiCl_2(Oi\text{-}Pr)_2$ is usually lower than that of

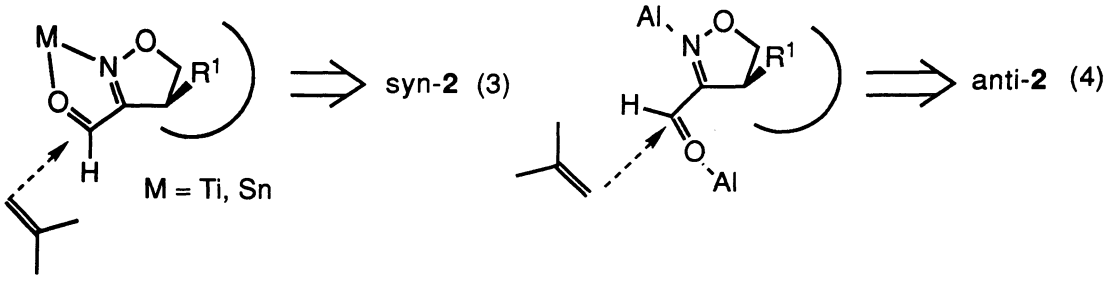
Table 2. The ene reaction of **1**

Run	1	R^1	R^2	R^3	R^4	R^5	Lewis acid (equiv.)	Temp/°C	Time/h	2;	Yield/%[a]	syn/anti[b]
1	**1a**	$-(CH_2)_3-$		H	Me	H	$SnCl_4$ (1)	-78	1	**2b**	83	99/1
2	**1a**	$-(CH_2)_3-$		H	Me	H	$TiCl_2(Oi\text{-}Pr)_2$ (2)	r. t.	48	**2b**	35	94/6
3	**1a**	$-(CH_2)_3-$		H	Me	H	Et_2AlCl (1.5)	-78	1	**2b**	19	25/75
4	**1a**	$-(CH_2)_3-$		H	$-(CH_2)_4-$		$SnCl_4$ (1)	-78	1	**2c**	93	100/0[c]
5	**1a**	$-(CH_2)_3-$		H	$-(CH_2)_4-$		Et_2AlCl (1.5)	-78	4	**2c**	13	37/63
6	**1b**	Me	i-Pr	H	Ph	H	$TiCl_2(Oi\text{-}Pr)_2$ (2)	r. t.	20	**2d**	77	90/10
7	**1b**	Me	i-Pr	H	Ph	H	$SnCl_4$ (1)	-78	2	**2d**	58	96/4
8	**1b**	Me	i-Pr	H	Ph	H	Et_2AlCl (1.5)	-78	2	**2d**	37	1/99
9	**1c**	Ph	H	Ph	Ph	H	$TiCl_2(Oi\text{-}Pr)_2$ (2)	r. t.	6	**2e**	72	82/18
10	**1c**	Ph	H	Ph	Ph	H	$SnCl_4$ (1)	-78	2	**2e**	59	96/4
11	**1c**	Ph	H	Ph	Ph	H	Et_2AlCl (1.5)	-78	4	**2e**	0	-
12	**1d**	H	Ph	H	Ph	H	$TiCl_2(Oi\text{-}Pr)_2$ (2)	r. t.	14	**2f**	56	54/46
13	**1d**	H	Ph	H	Ph	H	Et_2AlCl (1.5)	-78	4	**2f**	26	47/53

a) Isolated yield. b) Determined by HPLC analyses (cosmosil 5-PYE column was used.). c) The minor isomer was not detected on HPLC analyses.

$SnCl_4$ (runs 2, 6, and 9). On the other hand, Et_2AlCl usually afforded anti-**2** in stereoselective way. The reaction to α-methylstyrene took place with high anti-selectivity to give almost pure anti-**2** (run 8). However, the anti-selectivity fell to about 3:1 to 2:1 for the reaction to isobutene or methylenecyclohexane (runs 3 and 5). The reaction of **1c** under Et_2AlCl condition did not give adduct **2e** (run 11). These stereoselectivities were not observed in absence of the substituent on C^4 position of isoxazoline ring (runs 12 and 13).

The stereoselectivity of the reaction is attributed to chelation and non-chelation control. For example, $TiCl_2(Oi\text{-}Pr)_2$ and $SnCl_4$ likely coordinate on the oxygen atom of the formyl group and the nitrogen atom of Δ^2-isoxazoline ring to form bicyclic complex as shown in Eq. 3. The olefin attacks from the opposite side of R^1 group to give syn-**2** predominantly. On the other hand, Et_2AlCl catalyzed ene reaction proceeds via non-chelation conformation to give anti-**2** preferentially (Eq. 4).



As the high stereoselectivity can be readily achieved by a facile manipulation,

this method provides a useful method for a carbon skeletons containing multi asymmetric centers.

References

1) a) K. Mikami, T. Terada, M. Shimizu, and T. Nakai, *Yuki Gosei Kagaku Kyokai Shi,* **48**, 292 (1990); b) B. B. Snider, *Acc. Chem. Res.*, **13**, 426 (1980); c) J. K. Whitesell, *ibid.*, **18**, 280 (1985).

2) J. K. Whitesell, A. Bhattacharya, C. M. Buchanan, H. H. Chen, D. Deyo, D. James, C. -L. Liu, and M. A. Minton, *Tetrahedron*, **42**, 2993 (1986); J. K. Whitesell, R. M. Lawrence, and H. -H. Chen, *J. Org. Chem.*, **51**, 4779 (1986); S. Sakane, K. Maruoka, and H. Yamamoto, *Tetrahedron*, **42**, 2203 (1986); K. Mikami, T. -P. Loh, and T. Nakai, *Tetrahedron Lett.*, **29**, 6305 (1988); K. Maruoka, Y. Hoshino, T. Shirasaka, and H. Yamamoto, *ibid.*, **29**, 3967 (1988); K. Mikami, T. -P. Loh, and T. Nakai, *J. Chem. Soc., Chem. Commun.*, 1430 (1988); K. Mikami, M. Terada, and T. Nakai, *J. Am. Chem. Soc.*, **111**, 1940 (1989); K. Mikami, M. Terada, and T. Nakai, *ibid.*, **112**, 3949 (1990); K. Mikami, K. Takahashi, and T. Nakai, *ibid.*, **112**, 4035 (1990); K. Mikami, T. -P. Loh, and T. Nakai, *Tetrahedron Asymmetry*, **1**, 13 (1990); K. Mikami, M. Kaneko, T. -P. Loh, M. Terada, and T. Nakai, *Tetrahedron Lett.*, **27**, 3909 (1990).

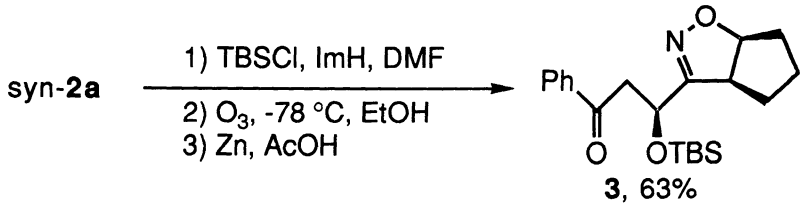
3) M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, **23**, 556 (1984); M. T. Reetz, "Organotitanium Reagents in Organic Synthesis," Springer Verlag, Berlin (1986); T. Fujisawa and Y. Ukaji, *Yuki Gosei Kagaku Kyokai Shi*, **47**, 186 (1989).

4) P. Caramella and P. Grünanger, "1,3-Dipolar Cycloaddition Chemistry," ed. by A. Padwa, John Wiley & Sons, New York, (1984), Vol. 1, p. 291; D. P. Curran, "Advanced in Cycloaddition," JAI Press Inc., Greenwich, Connecticut (1988); A. P. Kozikowski, *Acc. Chem. Res.*, **17**, 410 (1984); V. Jäger, H. Grund, R. Franz, and R. Ehrler, *Lect. Heterocycl. Chem.*, **8**, 79 (1985); K. B. G. Torsell, "Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis," VCH, Weinheim (1988).

5) a) A. Kamimura and S. Marumo, *Tetrahedron Lett.*, **31**, 5053 (1990); b) P. A. Wade, D. T. Price, P. J. Carroll, and W. P. Dailey, *J. Org. Chem.*, **55**, 3051 (1990).

6) A. Kamimura and T. Nishiguchi, submitted for publication.

7) ^{1}H NMR spectrum of **3** converted from syn-**2a** exhibited an identical spectrum of **3** which was made from $TiCl_4$ catalyzed aldol reaction of **1a** followed by silylation.[5a)]



3, 63%

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