Tetrahedron Letters, Vol. 33, No. 18, pp. 2547-2548, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Lewis Acid Promoted Asymmetric 1,4-Addition of Allyltrimethylsilanes to Chiral α,β-Unsaturated N-Acylamides

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Key Words: asymmetric induction, chiral α,β-unsaturated N-acyloxazolidinone, N-enoyl-sultams

Abstract: The 1,4-addition reaction of allyltrimethylsilane to α,β-unsaturated N-acyloxazolidinones or N-enoyl-sultams in the presence of *Lewis* acid proceeds in good chemical yield with high diastereomeric excess. The absolute configuration of the new asymmetric center is controlled by the nature of the Lewis acid via transition state A or B.

The introduction of a new asymmetric center at the β-position to a carboxylic acid has been a considerable challenge in synthetic organic chemistry.[1] Most of the reported efficient methods consist of the conjugate addition of organometallics to chiral α,β-unsaturated carboxylic acid derivatives. We here report a new route to generate an asymmetric center at C(β) of carboxylic acids via the Lewis acid promoted 1,4-addition of allyltrimethylsilane to α,β-unsaturated N-acyloxazolidinones[2] and N-enoylsultams. Although allyltrimethylsilane failed to react with α,β-unsaturated carboxylic acids or esters in the presence of Lewis acid,[3] we found that the use of α,β-unsaturated N-acyloxazolidinones as a Michael acceptor, and the use of $TiCl_4$ as a Lewis acid gave the corresponding conjugate allylation products in good yield.[4] The highly diastereoselective conjugate addition reaction to generate a new asymmetric center at the β-position of a carboxylic acid was achieved by using chiral α,β-unsaturated N-acyloxazolidinones and N-enoyl-sultams as the Michael acceptors. (eq. 1)

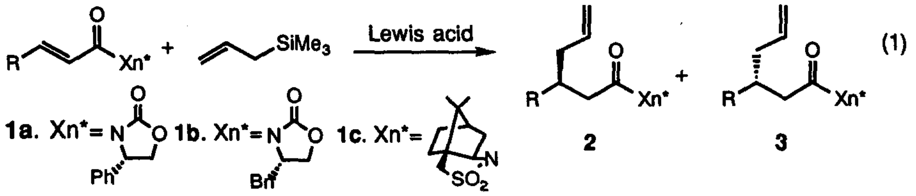
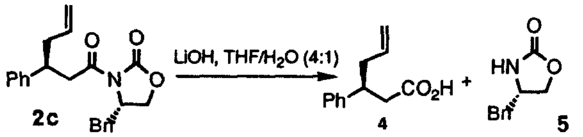


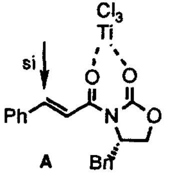
Table I outlines our results of Lewis acid promoted asymmetric 1,4-addition of allyltrimethylsilane to chiral α,β-unsaturated N-acylamides, such as (1a)[5], (1b)[5], or (1c)[6]. The typical reaction procedure is described for entry 5. To a CH_2Cl_2 (5 mL) solution of the chiral α,β-unsaturated N-acyloxazolidinone (**1a**, R=CH_3) (1 mmol) was added $TiCl_4$ (1.3 mmol) at -78 °C under nitrogen atmosphere. After stirring for 10 min, allyltrimethylsilane (1.5 mmol) was added into the dark-brown solution. The reaction mixture was stirred at -78 °C for 3 h and poured into a saturated sodium carbonate solution. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate. After removal of solvent, the residue was purified by flash column chromatography (10% ethylacetate in hexanes as eluent) to give 3-methyl-5-hexenoyloxazolidinone **2b** as a 92:8 diastereomeric mixture (by 200 MHz ^1H-NMR) in 88% yield as a colorless oil.

Table I. Asymmetric Conjugate Additions of Allyltrimethylsilane to α,β-Unsaturated N-Acylamides (Eq. 1)^{a}

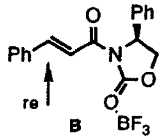
Entry	N-acylamide 1	Lewis acid	T(°C)/t(h)^{b}	products	ratio of 2/3,^{c}	yield of 2/3^{d}
1	**1a**, R=Ph	$BF_3 \cdot OEt_2$	25/48	**2a/3a**	44:56	66
2	**1a**, R=Ph	$SnCl_4$	25/24		N.R.	
3	**1a**, R=Ph	$TiCl_4$	25/24	**2a/3a**	67:33(95:5)	48
4	**1a**, R=CH_3	$TiCl_4$	25/1	**2b/3b**	80:20(80:20)	40
5	**1a**, R=CH_3	$TiCl_4$	-78/3	**2b/3b**	89/11(92:8)	88
6	**1b**, R=Ph	$TiCl_4$	25/48	**2c/3c**	75:25(99:1)^{e}	52^{e}
7	**1b**, R=CH_3	$TiCl_4$	-78/2	**2d/3d**	70:30(70:30)	87
8	**1c**, R=Ph	$TiCl_4$	25/24	**2e/3e**	71:29(83:17)	65
9	**1c**, R=CH_3	$TiCl_4$	25/24	**2f/3f**	78:22(93:7)	58

$^{a}CH_2Cl_2$ as a solvent unless otherwise mentioned, 1.3 equiv of $TiCl_4$, and 1.5-2.0 equiv of allyltrimethylsilane were used. ^{b}T = temperature, t = time.^{c}Diastereomeric isomer ratios were determined by using 200-MHz ^{1}H-NMR spectroscopy of the crude products. Values in parentheses refer to purified samples.^{d}Purified(flashed) yield. ^{e}Purified by recrystallization.





A



B

To determine the absolute stereochemistry, **2c** (de=50%) was saponified with LiOH in aqueous THF to give, after acidification, the corresponding carboxylic acid **4** in 84% yield and the chiral auxiliary **5** was recovered in 90% yield. The absolute configuration of **4** was S based on the specific rotation.[7] This indicated that conjugate addition of allyltrimethylsilane to **1b** (R = Ph) proceeded with C(β)-si-face preference when promoted by $TiCl_4$ via Ti-chelated transition state **A**. Alternatively when promoted with $BF_3 \cdot OEt_2$, this reaction proceeded slightly favorably with C(β)-re-face selection via a monocoordinated transition state **B** with anti-disposed NC=O/C=O groups (entry 1). A similar observation was reported by Dr. Oppolzer in their studies on the Lewis acid promoted conjugate addition of organocopper reagents to camphor-derivatives.[8]

In summary we have shown another examples of Lewis acid promoted asymmetric conjugate addition reactions to produce chiral β-substituted carboxylic acids. Extension of this concept to introduce a variety of non-organometallic nucleophiles to these systems are presently under investigation.

Acknowledgement: We thank the National Science Council of Republic of China (NSC 80-0208-M-037-03) for generous support of this program. We are grateful to Dr. Lendon Pridgen, Smithkline & Beecham Pharmaceuticals for the gift of chiral oxazolidinones and Dr. Jim-Min Fang, National Taiwan University, for the support of the spectra data and specific rotation of each enantiomers of compound **4**.

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(Received in Japan 11 January 1992)