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Diastereoselective addition of organolithiums to 1,3-oxazolidines complexed with aluminum tris(2,6-diphenylphenoxide) (ATPH)

Takayasu Yamauchi,* Hiroyuki Sazanami, Yuuichi Sasaki and Kimio Higashiyama

Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa, Tokyo 142-8501, Japan

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Abstract—1,3-Oxazolidines were easily obtained by condensation of N-substituted (*R*)-phenylglycinol with aldehydes. Addition of organolithium reagents to 1,3-oxazolidines by complexation with the bulky Lewis acid aluminum tris(2,6-diphenylphenoxide) (ATPH) readily produced the corresponding chiral amines with good yield and high diastereoselectivity. The configuration of the new stereogenic center was shown to be opposite to that of adducts obtained for the same 1,3-oxazolidines using Grignard reagents. The best diastereoselectivity was achieved using *N*-isopropyl-1,3-oxazolidines. The mechanism of addition was deduced by determining the stereochemistry of the iminium–aluminum complex by NOE experiments.

1. Introduction

The diastereoselective addition of organometallic reagents to the C═N bond of chiral imines and their derivatives is useful for the asymmetric synthesis of chiral amines.[1] We have previously described a synthetic method for stereoselective preparation of both enantiomers of chiral amines from a single-enantiomer source, (*R*)-phenylglycinol, proceeding via the diastereoselective addition of Grignard reagents to 1,3-oxazolidines with excellent yield and diastereoselectivity.[2] It was previously alleged that addition of Grignard reagents occurred after formation of the ring-opened iminium intermediate, but addition of an organolithium reagent to 1,3-oxazolidine did not proceed for the unopened ring. It was considered that the reaction required activation to open the 1,3-oxazolidine ring. We tried to react 1,3-oxazolidines with organolithium reagents using various Lewis acids. Aluminum compounds might be effective additives to facilitate the reaction. One additive, bulky C_3 symmetrical ATPH, has been shown to have unique properties in various reactions by Yamamoto.[3] ATPH has a small opening in the ligand sphere and is known to give stable complexes with carbonyl compounds. Herein we report the diastereoselective addition of organolithium to 1,3-oxazolidine via activation with ATPH. Interestingly, the absolute configuration of the adducts obtained in the presence of ATPH was the opposite to that obtained by addition of Grignard reagents (Scheme 1). Other groups have also reported that some reactions with ATPH resulted in the reversal events of diastereoselectivity.[4]

2. Results and discussion

2.1. Addition of MeLi to 1a using various Lewis acids

For the addition of MeLi to 1,3-oxazolidines, an activator such as a Lewis acid is needed for cleavage of the 1,3-oxazolidine ring. To activate a diastereomer mixture of 1,3-oxazolidine **1a**,[2a] prepared easily from (*R*)-phenylglycinol, we tried various Lewis acids as additives (Scheme 2, Table 1). As expected, addition of MeLi to **1a** did not proceed without a Lewis acid (run 1). Some Lewis acids provided methylation to the 1,3-oxazolidine but with low yields and diastereoselectivity (runs 2, 3, and 8). Diastereoselective addition of MeLi was possible in the presence of $MgBr_2$ and Me_3Al (runs 9 and 12). Interestingly, the major adduct of methyl addition using ATPH, (*R*,*R*)-**2a**, differed from that obtained using the other Lewis acids (runs 13–16). This result also differed from previous research in which addition of MeMgBr to **1a** gave (*S*,*R*) **2a** in 94% yield and 68% de.[2a] It was assumed that the change in diastereoselectivity was caused by a virtually blocking of the reaction site due to the bulky structure of ATPH. After a series of activating experiments, the optimum activation time of **1a** with ATPH was found to be 2 h at rt. When the reaction time was prolonged, it resulted in a decreased yield (runs 13–15). As ATPH showed encouraging activity,

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* Corresponding author. Tel./fax: +81 3 5498 5768;
e-mail: yamauchi@hoshi.ac.jp

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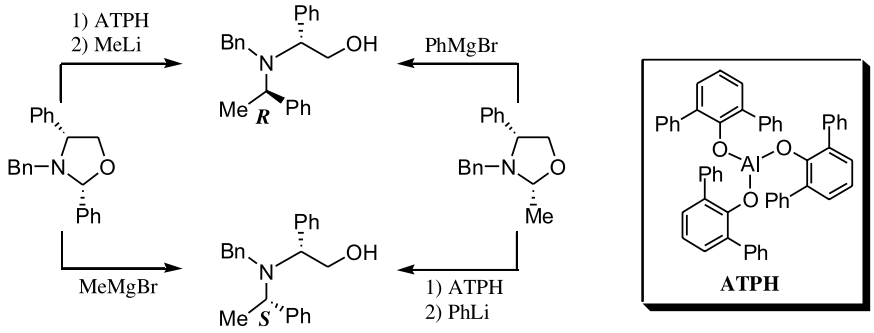
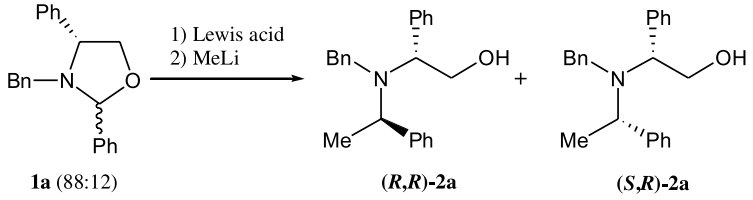


Scheme 1.



Scheme 2.

Table 1. Addition of MeLi to **1a** with Lewis acid

Run	Lewis acid	Activation time (h)	Reaction temperature (°C)	Reaction time (h)	Yield (%)	Ratio (*R*,*R*/*S*,*R*)[a]
1	—	—	rt	20	NR	—
2[b]	BF_3OEt_2	1	rt	20	34	43:57
3[b]	BCl_3	1	rt	20	17	38:62
4	$SnCl_2$	2	−50	20	NR	—
5	$MnBr_2$	2	−50	20	NR	—
6	Et_2Zn	2	−50	20	NR	—
7	$Ln(Otf)_3$	2	−50	20	NR	—
8	$Yb(Otf)_3$	2	−50	20	41	37:63
9	$MgBr_2$	2	−50	20	68	15:85
10	YCl_3	2	−50	20	NR	—
11[b]	Me_3Al	1	rt	20	Trace	—
12[b]	Me_3Al	2	−50	20	72	20:80
13	ATPH	1	−50	20	62	79:21
14	ATPH	1	−50	72	56	67:33
15	ATPH	1	−50	168	19	80:20
16	ATPH	2	−50	20	86	78:22

[a] Estimated by ^{1}H NMR spectrum.
[b] This reaction was carried in THF solvent.

further research looked into the effect of the *N*-substituent of 1,3-oxazolidines at −50 °C.

2.2. Diastereoselective additions of organolithium reagents to N-substituted 1,3-oxazolidines complexed with ATPH

To probe the influence of the *N*-substituent of 1,3-oxazolidine, organolithium reagents were added to various 1,3-oxazolidines complexed with ATPH (Scheme 3, Table 2). N-Substituted 1,3-oxazolidines (**1a–c**,[2a] **1d**,[2b,c] **1f–h**[2a]) were prepared from (*R*)-phenylglycinol in three steps as noted in the literature. **1e** was also prepared from (*R*)-phenylglycinol in the same manner. The diastereomers of **1a–h** were confirmed to be inseparable mixtures in thermodynamic equilibrium differing at the 2 position of the 1,3-oxazolidine ring, and their ratios in $CDCl_3$ were determined from the ^{1}H NMR peak intensities of the 2-H of 1,3-oxazolidine. Addition of organolithium reagents to **1a–h** with ATPH as the Lewis acid gave **2a–e** in 62–98% yield with 78:22 ∼ >99:1 diastereoselectivity. The adducts obtained with ATPH, with the exception of substrate **1b**, showed opposite diastereoselectivities to the adducts obtained with Grignard reactions. The isomer ratios of the adducts were determined from the ^{1}H NMR peak intensity of the 2-Me. The absolute configurations of **2a–c**,[2a] **2d**[2b,c] were previously reported. Treatment of the single isomers (*R*,*R*)-**2e** and (*S*,*R*)-**2e** with TFA gave (*R*,*R*)-**3** in 77% yield