## Catalytic Asymmetric Addition of Organolithiums to Aldimines

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Summary: An asymmetric 1,2-addition of organolithiums to imines (1) was catalyzed by a substoichiometric amount  $(0.05 \sim 0.3 \text{ equivalent})$  of a chiral aminoether (2) to provide the corresponding optically active amines (3).

We report the unprecedented catalytic asymmetric 1,2-addition reaction of organolithiums with arylimines that we believe has considerable potential in future organic synthesis.<sup>1-3</sup> We have previously described the asymmetric addition of organolithiums to the imines derived from  $\alpha,\beta$ -unsaturated or naphthalenecarbaldehydes by using a stoichiometric amount of a chiral ligand.<sup>4,5</sup> Regioselectivity in the addition reactions was highly dependent on the amine moiety of the imines; giving 1,4-conjugate addition products as aldehydes from the cyclohexylimines<sup>4</sup> and 1,2-addition products as secondary amines from the arylimines (for example, 1 to 3),<sup>5</sup> respectively.

It thus seemed to us that the possibility of asymmetric C-C bond formation catalyzed by a substoichiometric amount of a chiral ligand deserved to be explored. This appeared particularly true because such a process would result in the catalytic asymmetric C-C bond formation in that versatile organolithiums are applicable as carbon nucleophiles.



The procedure is exemplified by the reaction of methyllithium with benzaldehyde 4methoxyphenylimine (1,  $R^1 = Ph$ ) in the presence of 0.05 equivalent of a chiral aminoether (S)-2<sup>5</sup> (molar ratio of 1 :  $R^2Li$  : 2 = 1 : 2 : 0.05) (Table I, entry 4). A solution of methyllithium ( $R^2 = Me$ ) in ether (low halide)<sup>6</sup> (1.64 mL, 2.0 mmol) was added over a period of 5 min to a mixture of 1 ( $R^1 = Ph$ ) (211 mg, 1.0 mmol) and 2 (14 mg, 0.05 mmol) in toluene (20 mL) at -42 °C. The mixture was stirred at -42 °C for 3 h. Usual workup and purification by silica gel column chromatography (benzene) afforded 3 ( $R^1 = Ph$ ,  $R^2 = Me$ ) (218 mg, 96% yield) with 40% ee.<sup>7,8</sup> The enantiomeric excess (ee) was determined by HPLC analysis (Waters Optipak-XC, hexane-isopropanol = 9:1, 0.3 ml/min, 254 nm). The ligand 2 was recovered quantitatively for reuse without any loss of optical purity.

Some of other results are summarized in Table I. The reaction of methyllithium with 1  $(R^1 = Ph)$  at -42 °C was effected by the presence of 2.6 equivalent of 2 to give 3 in 66% ee (entry 1). Ee of 3 was slightly decreased to 62, 58, and 47% as the amount of 2 decreased to 0.5, 0.2, and 0.1 equivalent, respectively (entries 1-3). However, the chiral catalyst 2 of 0.05 equivalent still exhibited remarkable catalytic effect on asymmetric induction to give 3 with 40% ee (entry 4). Asymmetric catalysis turnover number (entry 4) was calculated to be 12 (theoretical maximum catalytic turnover number is 20 in the asymmetric induction) on the basis of 66% ee obtained in the stoichiometric reaction (2.6 equivalent of 2).

On the contrary to the stoichiometric asymmetric reaction<sup>5</sup> which proceeded at -78 °C to provide 3 ( $\mathbb{R}^1 = \mathbb{Ph}$ ,  $\mathbb{R}^2 = \mathbb{M}e$ ) in nearly quantitative yield, the catalytic reaction in which 0.05 equivalent of 2 was used as a catalyst did not proceed smoothly at -78 °C. However, the reaction proceeded even in the absence of 2 at -42 °C for 3 h to give the racemic 3 in 91% yield. Judging from these experimental results it may be supposed that the reaction rate of methyllithium probably complexed with 2 obviously overwhelmed that of the non-catalytic reaction.

It is also noteworthy that in the reaction of butyllithium the choice of the reaction solvent is critical to realized the catalytic asymmetric induction. Addition of butyllithium ( $R^2 = Bu$ ) to 1 ( $R^1 = Ph$ ) in diisopropyl ether provided 3 ( $R^1 = Ph$ ,  $R^2 = Bu$ ) of 60% ee with regardless to the amount of 2 (0.3 and 2.6 equivalents) used in the reaction (entry 7). However, significant decrease of enantioselectivity was observed in toluene (25 vs 58% ee, entry 5) and in ether (45 vs 67% ee, entry 6). A 0.05 equivalent of 2 in diisopropyl ether as a reaction solvent provided 3 ( $R^1 = Ph$ ,  $R^2 = Bu$ ) with 40% ee. A catalytic turnover number in the asymmetric induction was calculated to be 13 (theoretical maximum catalytic turnover number is 20 in the asymmetric induction) (entry 8).<sup>9</sup>

Addition of vinyllithium to 1 ( $\mathbb{R}^1 = \mathbb{P}h$ ) was also catalyzed by 0.3 equivalent of 2 to provide the product 3 ( $\mathbb{R}^1 = \mathbb{P}h$ ,  $\mathbb{R}^2 = \mathbb{C}H_2 = \mathbb{C}H$ ) with 64% ee (entry 9).

Remarkable catalytic asymmetric induction was also observed in the reactions of 1 derived from cinnamaldehyde, 1- and 2-naphthalenecarbaldehydes with methyl-, butyl-, and vinyllithiums in toluene or disopropyl ether as a solvent to provide the corresponding optically active amines 3 (entries 10-15).

Enantioselectivity described here is moderate, however, we believe that further efforts aiming to clarify the catalytic mechanism of the reaction and to improve the enantioselectivity by developing more efficient chiral catalysts will open the new frontier of the catalytic asymmetric reactions in which organolithium can be used as a carbon nucleophile.<sup>10.11</sup>

	PhCH <sub>2</sub>	
RI. N. A	Me <sub>2</sub> N O	H B <sup>1</sup> . * N
+ R <sup>2</sup> Li	2 MeO	R <sup>2</sup>
1 - Ome		3 UMe

Table I. Catalytic Asymmetric Addition of Organolithiums to Imines (1) producing 3<sup>a</sup>

entry	<b>R</b> <sup>1</sup>	R <sup>2</sup> Li <sup>b</sup>	2/eq	solvent	temp/°C	ee/%c	yield/%d
1	Ph	Me	0.5	toluene	-42	62(66)	96(95)
2	Ph	Me	0.2	toluene	-42	58	85
3	Ph	Me	0.1	toluene	-42	47	90
4	Ph	Me	0.05	toluene	-42	40	96
5	Ph	Bu	0.3	toluene	-78	25(58)	99(89)
6	Ph	Bu	0.3	Et <sub>2</sub> O	-78	45(67)	90(88)
7	Ph	Bu	0.3	i-Pr2O	-78	60(60)	<del>9</del> 9(99)
8	Ph	Bu	0.05	i-Pr2O	-78	40	97
9	Ph	CH2=CH	0.3	toluene	-42	64(72)	70(96)
10	PhCH=CH	Me	0.3	toluene	-42	40(48)	81(90)
11	1-Naph	Me	0.3	toluene	-42	55(57)	99(99)
12	1-Naph	Bu	0.3	i-Pr <sub>2</sub> O	-78	50(65)	99(99)
13	1-Naph	CH2=CH	0.3	toluene	-42	49(60)	98(99)
14	2-Naph	Me	0.2	toluene	-42	51(62)	99(94)
15	2-Naph	Bu	0.3	i-Pr <sub>2</sub> O	-42	59(68°)	98(95°)

a) Reaction procedure was described in the text (molar ratio of  $1 : R^2Li : 2 = 1 : 2 : 0.05 \sim 2.6$ ; reaction time: 20-300 min). b) MeLi (low halide) in ether and BuLi in hexane were used. Vinyllithium in ether was prepared from tetravinyltin and PhLi. c) Determined by HPLC analysis using chiral column (Waters Optipak-XC and -TC). Numbers in parentheses represent % ee obtained by using 2.6 equivalent of 2. d) Yields referred to isolated pure compounds (3). Numbers in parentheses represent yields obtained by using 2.6 equivalent of 2. e) Yield obtained in ether solvent.

## References and Notes

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- (6) Methyllithium complexed with LiBr (Aldrich) did not afford satisfactory %ee in the catalytic reaction.
- (7) All new compounds described in this paper provided satisfactory analytical and spectroscopic data.
- (8) 4-Methoxyphenyl group in 3 can be oxidatively removed to liberate an optically active primary amine.<sup>5</sup>
- (9) The presence or absence of diethyl ether in organolithium solution is probably responsible for the catalytic activity dependence on solvent. Detail is not clear at the present time.
- (10) Possibility in the catalytic asymmetric addition of butyllithium to benzaldehyde has been suggested by using 0.0077 equivalent of a binaphthyl-based chiral diamine to butyllithium providing a product with 7% ee. Mazaleyrat, J.-P.; Cram, D. J. J. Am. Chem. Soc. 1981, 103, 4585.
- (11) Authors are grateful to partial financial support from the Hoan-sha Foundation, the Japan Foundation for Optically Active Compounds, and Ministry of Education, Science and Culture, Japan (Grant in Aid for Scientific Research).

(Received in Japan 1 March 1991)