THE CHIRAL LIGAND-CATALYZED ENANTIOSELECTIVE CONJUGATE ADDITION OF ORGANOLITHIUM TO BHA ENOATE

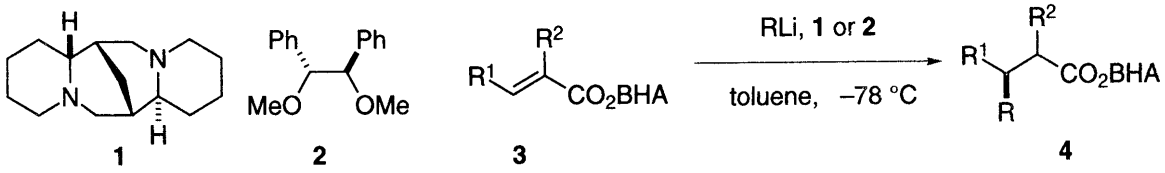
Yasutomi ASANO, Akira IIDA, and Kiyoshi TOMIOKA*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-01, Japan.

The conjugate addition reaction of BHA alkenoates with butyl- and phenyllithiums in toluene at –78 °C were catalyzed by a substoichiometric amount of chiral ligands **1** and **2** to give the corresponding 3-substituted alkanoates in good to modest ees.

KEYWORDS organolithium; chiral ligand; catalyst; addition

The asymmetric conjugate addition reaction of an organometal with an activated olefin is a rapidly developing area in synthetic chemistry of carbon-carbon bond formation.[1] Except for the prominent organocopper-based asymmetric conjugate addition reactions that produce chiral 3-substituted ketones with high enantioselectivities,[2] the organometallic method for catalytic conversion of alkenoates to chiral 3-substituted alkanoates remains challenging.[3] Recently we have shown that stoichiometric amounts of diamine sparteine **1**[4] and chiral diether **2**[5] are highly efficient chiral controllers for butyl- and phenyllithiums in asymmetric conjugate addition to enoates, respectively.[6] We describe herein that the reactions of organolithiums with alkenoates are catalyzed by a substoichiometric amount of **1** and **2** to afford the corresponding conjugate addition products with modest to good enantioselectivities.



1 **2** **3** **4**

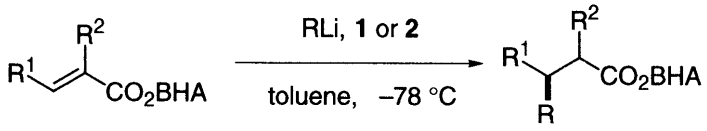
A hexane solution of 3.0 eq[7] of butyllithium was added to 0.3 eq of **1** in toluene at –78 °C and the mixture was stirred for 20 min. A toluene solution of BHA (2,6-di-*tert*-butyl-4-methoxyphenyl)-crotonate **3** (R^1 = Me, R^2 = H) was added and the whole mixture was stirred at –78 °C for 40 min to afford, after protonation with MeOH, usual workup, and purification by silica gel column chromatography (hexane-diethyl ether = 30 : 1), (*R*)-**4a** (R^1 = Me, R^2 = H, R = Bu)[8] in 85% ee and 95% yield, as shown in Table 1. With 0.1 eq of **1**, (*R*)-**4a** was produced in 72% ee and 86% yield. It is surprisingly efficient that 0.3 eq of **1**, corresponding to 0.1 eq against butyllithium, gave (*R*)-**4a** in 85% ee, compared with 96% ee obtained under stoichiometric conditions where 3.0 eq of butyllithium is converted to the chiral butyllithium-**1** complex in the presence of 4.2 eq (corresponding to 1.4 eq for butyllithium) of **1**. Since the reaction of 3.0 eq of butyllithium with **3** in the absence of **1** at –78 °C for 40 min gave racemic **4a** in 20% yield and recovered **3** in 62% yield, the presence of **1** clearly promoted the conjugate addition of butyllithium.

* To whom correspondence should be addressed.

On the other hand, addition of 3.0 eq of phenyllithium to **3** (R^1 = Me, R^2 = H) in toluene at –78 °C afforded (*S*)-**4b** (R^1 = Me, R^2 = H, R = Ph)[9] in 70% ee and 99% yield with 1.0 eq (corresponding to 0.33 eq against phenyllithium) of **2**, and in 42% ee with 0.3 eq of **2**. Compared with 84% ee obtained under stoichiometric conditions, the ee of 42% with 0.3 eq of **2** indicates the poorer efficiency of **2**.

Generally, 0.3 eq of diamine **1** catalyzes the reactions of 3.0 eq of butyllithium with alkenoates suffcicently to afford the corresponding adducts in 53-85% ees, as shown in Table 1. The efficacy of 0.3 eq of **2** for phenyllithium was not suffcicently high to afford the adducts in 36-49% ees.

Table 1. Catalytic Enantioselective Conjugate Additions of Organolithiums to BHA Enoates



3 **4**

Entry	R^1	R^2	R	eq	1/2	eq	Time/mi	4	Yield/%	ee/%[a]	*R*/*S*[b]
1	Me	H	Bu	3.0	**1**	0.3	50	**a**	95	85 (96)	*R*
2	Me	H	Bu	3.0	**1**	0.1	50	**a**	86	72	*R*
3	Me	H	Ph	3.0	**2**	1.0	40	**b**	99	70 (84)	*S*
4	Me	H	Ph	3.0	**2**	0.3	40	**b**	97	42	*S*
5	Et	H	Bu	3.0	**1**	0.3	40	**c**	94	83 (99)	*R*
6	Et	H	Ph	3.0	**2**	0.3	40	**d**	95	43 (88)	*S*
7	Bu	H	Ph	3.0	**2**	0.3	40	**e**	97	36 (86)	*S*
8	$(CH_2)_3$		Bu	3.0	**1**	0.3	60	**f**	82/4[c]	53 (95)	1*R*,2*S*
9	$(CH_2)_3$		Ph	3.0	**2**	0.3	70	**g**	88	49 (93)	1*R*,2*S*
10	$(CH_2)_4$		Bu	3.0	**1**	0.3	120	**h**	85/3[c]	81 (94)	1*R*,2*S*
11	$(CH_2)_4$		Ph	3.0	**2**	0.3	100	**i**	89[c]	47 (92)	1*R*,2*S*

a) Ees were determined by chiral stationary phase HPLC (Daicel Chiralpak AD for **4a**, Chiralcel OD or OD-H for the corresponding alcohols of **4b**, **4d**, **4e**, *cis*-**4g**, and *cis*-**4i**), NMR for the MTPA ester of the alcohol of *cis*-**4h**, and specific rotation for **4c**, *cis*-**4f**. The numbers in parentheses are ee % in the case of stoichiometric reaction (4.2 eq for **1** and **2**). *b)* The absolute configuration was determined by converting to the corresponding carboxylic acid for **4a**,[8] **4c**,[10] **4d**,[10] **4e**,[11] *cis*-**4h**[12,13] and alcohol for **4b**, *cis*-**4f**,[12] *cis*-**4g**,[12] and *cis*-**4i**,[12,13] and interconversion from *cis*-**4i** for *cis*-**4h**. *c)* The major product is the *cis*-isomer.[12,13]

These data suggest that the organolithium-chiral ligand complex is regenerated and reused in the present asymmetric reaction. The efficiency of regeneration of the expected reactive complex depends on the nature of the heteroatom of the ligand. The diamine **1** is superior to the diether **2** with respect to efficiency of regeneration, probably because of the higher coordinating ability of the nitrogen atom to lithium than that of the oxygen atom.

Although the enantioselectivity is not very high, the demonstrated chiral ligand-catalyzed reaction of organolithiums with enoates may become the basis for catalytic asymmetric carbon-carbon bond formation. Investigation seeking a much more powerful ligand is in progress in our laboratory.

Acknowledgment: We gratefully acknowledge financial support from Japan Society for Promotion of Science (RFTF-96P00302), the Ministry of Education, Science, Sports and Culture, Japan, and the Science and Technology Agency, Japan.

REFERENCES AND NOTES

1) Perlmutter P., "Conjugate Addition Reactions in Organic Synthesis, Tetrahedron Organic Chemistry Series," Vol. 9, Pergamon Press, Oxford, 1992.
2) Nakagawa Y., Kanai M., Nagaoka Y., Tomioka K., *Tetrahedron Lett.*, **37**, 7805-7808 (1996), and references cited therein.
3) For the catalytic enantioselective carbon-carbon bond formation with organometals in the conjugate addition reaction, see: Soai K., Hayasaka T., Ugajin S., *J. Chem. Soc., Chem. Commun.*, **1989**, 516-517.
4) Kretchmer was the first to use **1** as a chiral ligand in enantioselective conjugate addition. Kretchmer R. A., *J. Org. Chem.*, **37**, 2744-2747 (1972).
5) Tomioka K., Shindo M., Koga K., *J. Am. Chem. Soc.*, **111**, 8266-8268 (1989).
6) Asano Y., Iida A., Tomioka K., *Tetrahedron Lett.* **38**, 8973-8976 (1997).
For the asymmetric addition of aryllithiums to naphthalene BHA-esters, see: Tomioka K., Shindo M., Koga K., *Tetrahedron Lett.*, **34**, 681-682 (1993). For other stoichiometric reactions: Tomioka K., Sudani M., Shinmi Y., Koga K., *Chem. Lett.* **1985**, 329-332.
7) The excess (3 eq) of butyllithium prevents further Michael reaction of the initially formed lithium enolate with **3**.
8) The absolute configuration was determined to be *R* by converting (ceric ammonium nitrate in aq CH_3CN in 90% yield) to the corresponding carboxylic acid with the established configuration. Levene P. A., Marker R. E., *J. Biol. Chem.*, **95**, 1-24 (1932).
9) The absolute configuration was determined to be *S* by converting ($LiAlH_4$ in THF in 90% yield) to the corresponding alcohol with the established configuration. Paquette L. A., Gilday J. P., *J. Org. Chem.*, **53**, 4972-4978 (1988).
10) Meyers A. I., Smith R. K., Whitten C. E., *J. Org. Chem.*, **44**, 2250-2256 (1979).
11) Mukaiyama T., Takeda T., Fujimoto K., *Bull. Chem. Soc. Jpn*, **51**, 3368-3372 (1978).
12) Fang C.-L., Suemune H., Sakai K., *J. Org. Chem.*, **57**, 4300-4303 (1992).
13) Schultz A. G., Macielag M., Podhorez D. E., Suhadolnik J., C. *J. Org. Chem.*, **53**, 2456-2464 (1988).

(Received October 24, 1997; accepted December 2, 1997)