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Enantioselective Conjugate Additions of Organolithiums to BHA Enoates Mediated By A Chiral Ligand

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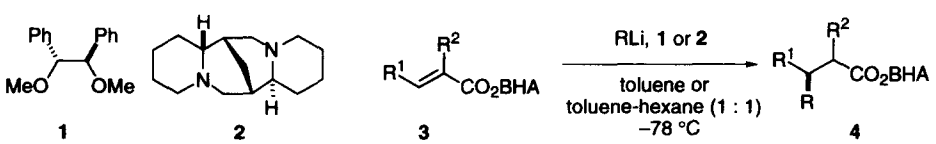
Abstract: The conjugate addition reactions of BHA alkenoates with organolithiums in toluene or toluene-hexane at –78 °C were mediated by the chiral ligands **1** and **2** to give the corresponding 3-substituted alkanoates in high ees and high yields. The two ligands are complementary each other, **1** is effective for phenyl- and vinyllithiums to give the adducts in 64-93% ee, while **2** is effective for butyl- and ethyllithiums to give the adducts in 91-99% ee.

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] The asymmetric addition to the olefin bonded covalently by a chiral activating group has well documented to give the adduct with high level of diastereoselectivity.[2,3] In spite of impressive progress made in the diastereoselective reactions, an external chiral ligand-controlled reaction has remained relatively undeveloped.[4] Excepting the prominent organocopper-based asymmetric conjugate addition reactions that produce chiral 3-substituted ketones in high enantioselectivities,[5] the organometallic way for conversion of alkenoates to chiral 3-substituted alkanoates has been still challenging. We describe herein that the reactions of organolithiums with alkenoates are mediated by an external chiral ligand to afford the corresponding conjugate addition products in reasonably high enantioselectivities.



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

On the basis of the asymmetric reactions of organolithiums or lithium ester enolates with imines,[6] oxides,[7] or naphthalenecarboxylates[8] under control of chiral ether or amino ether ligands, chiral compounds **1**,[6a,d] **2**,[9] BHA enoates **3**,[10] and butyl- and phenyllithiums were chosen as the representative chiral ligands, electrophiles, and organolithiums, respectively.

A hexane solution of 3.0 eq of butyllithium was added to 3.3 eq of **1** in toluene at –78 °C and the mixture was stirred for 20 min at the same temperature.[11] 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 was stirred at –78 °C for 1 h to afford, after protonation with MeOH and purification by silica gel column chromatography (hexane-diethyl

ether = 30 : 1), (*R*)-**4a** (R^1 = Me, R^2 = H, R = Bu) in 90% yield. The ee was determined to be 70% by chiral stationary phase HPLC (Daicel Chiralpak AD, hexane). 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.[12] On the other hand, addition of butyllithium to a mixture of **1** and **3** in toluene at –78 °C afforded (*R*)-**4a** in a decreased 54% ee, clearly indicating that the order of addition affects the efficiency. The quantity of **1** also affects the efficiency, both of 4.2 and 8.4 eq (1.4 and 2.8 eq against butyllithium) of **1** gave (*R*)-**4a** in the same ee of 85% (Table I). These results suggest that competitive formation of butyllithium-**1** and butyllithium-**3**[13] complexes is operative. The butyllithium-**1** chelate further forms butyllithium-**1**-**3** complex in advance to the reaction, affording chiral **4a**. The butyllithium-**3** complex affords racemic **4a** without aid of **1**. It is not surprising, therefore, to observe that 2.9 eq (0.98 eq against butyllithium) of **1** gave **4a** in 55% ee.

These results clearly indicate that preferential formation of the chelated complex with butyllithium and a chiral ligand is necessary for the reaction of high efficiency. The chiral diamine **2** was selected for such ligand to satisfy the above requirement, because nitrogen atom has higher coordinating ability to lithium. The reaction was mediated by 4.2 eq (1.4 eq against butyllithium) of **2** in toluene at –78 °C for 70 min to afford (*R*)-**4a** in 96% ee and 73% yield. The enantioselectivity improved to 99% (77% yield) by performing the reaction in toluene-hexane (1 : 1) at –78 °C for 40 min.

We have also examined the reaction of phenyllithium as a carbonucleophile with **3**. The reaction was mediated by 3.3 eq of **1** in toluene at –78 °C for 45 min to afford (*S*)-**4b**[14] in 84% ee. On the other hand, the reaction in the presence of 4.2 eq of **2** in toluene-hexane at –78 °C for 40 min gave (*S*)-**4b** in 42% ee.

It became apparent that **1** and **2** are complementary each other, and effective for sp^2 and sp^3 carbanions, respectively, as shown in Table I. The reactions of vinyl- and phenyllithiums were mediated by **1** to give **4** in 64-93% ee, whereas rather poor ee of 44% was observed in the reaction of butyllithium (entry 7). The reactions of ethyl- and butyllithiums were mediated by **2** to give **4** in 91-99% ee, whereas the poor 43% ee was observed in the reaction of phenyllithium (entry 10).

Solvent effects may be dramatic, 80% ee goes up to 91% in the reaction of ethyllithium with **3** (R^1 = Bu, R^2 = H) by changing solvent from toluene to diethyl ether (entry 11). Generally, higher selectivities were obtained in toluene-hexane than those in toluene for the reaction of butyllithium with acyclic enoates by the mediation of **2** (entry 3, 4, 8).

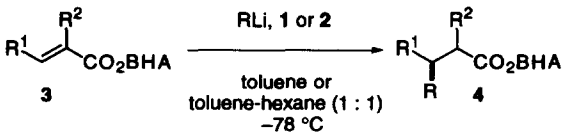
The reaction of cyclic enoates in toluene preferentially gave the *cis*-products in 92-95% ee (entry 14-17). However, direct protonation of the resulting lithium enolate by methanol at –78 °C provided a mixture of *cis* and *trans* esters in a ratio of 59:28 (entry 16). In advance to protonation by methanol, it is necessary to add THF for the *cis* selective protonation, probably attributable to the removal of the chiral ligand from the lithium enolate-chelate by ligand exchange with THF. It is also noteworthy that 1.3 eq of organolithium and 1.4 or 1.8 eq of the ligand are enough to obtain cyclic **4** in high ee and yield, due to the relatively low reactivity of the resulting enolate toward further Michael reaction with cyclic **3**.

The sense of asymmetric induction mediated by **1** and **2** is same, attacking organolithium from the top face of **3** regardless to acyclic and cyclic enoates.

The chiral ligands **1** and **2** were recoverable for reuse in high yield.

Furthr studies toward catalytic process of the reaction are in progress in our laboratories.

Table I. Enantioselective Conjugate Additions of Organolithiums to BHA Enoates



entry	R^1	R^2	R	eq	1/2	eq	solvent	time (min)	4	yield (%)	ee[a] (%)	*R/S*[b]
1	Me	H	Bu	3.0	1	4.2	toluene	40	**a**	78	85	*R*
2	Me	H	Bu	3.0	1	4.2	toluene/ hexane	40	**a**	86	77	*R*
3	Me	H	Bu	3.0	2	4.2	toluene	70	**a**	73	96	*R*
4	Me	H	Bu	3.0	2	4.2	toluene/ hexane	40	**a**	77	99	*R*
5	Me	H	Ph	3.0	1	3.3	toluene	45	**b**	62	84	*S*
6	Me	H	Ph	3.0	2	4.2	toluene/ hexane		**b**	89	42	*S*
7	Et	H	Bu	3.0	1	4.2	toluene	40	**c**	89	44	*R*
8	Et	H	Bu	3.0	2	4.2	toluene/ hexane	40	**c**	89	99	*R*
9	Et	H	Ph	3.0	1	4.2	toluene	40	**d**	77	88	*S*
10	Et	H	Ph	3.0	2	4.2	toluene	40	**d**	98	43	*S*
11	Bu	H	Et	3.0	2	4.2	$_2$O	40	**c**	79	91	*S*
12	Bu	H	Vinyl	3.0	1	4.2	toluene	40	**e**	90	64	*S*
13	Bu	H	Ph	3.0	1	4.2	toluene	45	**f**	77	86	*S*
14	$(CH_2)_3$		Bu	1.3	2	1.8	toluene	70	**g**	78/8[c]	95/95	1*R*,2*S*
15	$(CH_2)_3$		Ph	1.3	1	1.4	toluene	60	**h**	97/2[c]	93	1*R*,2*S*
16	$(CH_2)_4$		Bu	1.3	2	1.8	toluene	60	**i**	87/2[c]	94	1*R*,2*S*
17	$(CH_2)_4$		Ph	1.3	1	1.4	toluene	180	**j**	83/1[c]	92	1*R*,2*S*

a) Ee was determined by chiral stationary phase HPLC (Daicel Chiralpak AD for **4a**, Chiralcel OD or OD-H for the corresponding alcohols of **4b**, **4d**, **4f**, **4h**, and **4j**), NMR for the MTPA ester of the alcohol of **4i**, and specific rotation for **4c**, **4e**, **4g**, **4i**. b) The absolute configuration was determined by converting to the corresponding carboxylic acid for **4a**,[12] **4c**,[15] **4d**,[14] **4f**,[16] **4j**[17,18] and alcohol for **4b**,[13] **4g**,[17] **4h**,[17] and **4j**,[16,17] and interconversion from **4j** for **4i**.[19] Hydrogenation of **4e** with Raney Ni W-3 correlated with **4c**. c) The major product is the *cis*-isomer.[16,17]

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