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A ternary complex reagent for an asymmetric Michael reaction of lithium ester enolates with enoates

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ABSTRACT

A lithium ester enolate was activated by both a chiral etheral ligand and a lithium amide to form a ternary complex reagent that reacted with enoates giving the corresponding Michael addition products in reasonably high enantioselectivity of up to 97% ee.

The activation of nucleophilic reagents[1] has been the major challenge of organic chemistry. Lewis basic chiral ethereal or amino molecules are used as external ligands for preparation of active nucleophiles in asymmetric reaction.[2] We have developed a variety of chiral organic ligands for the activation of organometallics.[3] Among these organoligands a chiral diether **1** has been shown to mediate an asymmetric Mannich reaction of lithium ester enolate with imines by forming a ternary complex reagent comprised of lithium enolate-**1**-lithium amide.[4] Since the successful enantioselective asymmetric Michael reactions of unstabilized lithium enolates are quite limited in the number,[5] we applied the ternary complex reagent into the Michael reaction of lithium ester enolates with unactivated simple enoates.[6] We describe herein the highly enantioselective Michael reaction of a ternary complex reagent of a lithium ester enolate with enoates affording the Michael adducts in high enantioselectivity of up to 97% ee.

We began our studies with the Michael reaction of isobutyrate **2** with crotonate **3a** in the presence of a chiral etheral ligand **1** in toluene (Table 1). The lithium enolate **4**,[7] generated from **2** by treating with an equivalent of lithium diisopropylamide (LDA), reacted at −78 °C for 0.5 h to give the desired Michael adduct **5a** with 60% ee quantitatively (entry 1). The same level of enantioselectivity, 65% and 63% ee, obtained by using lithium isopropylcyclohexylamide (LICA) and dicyclohexylamide (LDCA) as a lithiating base, suggests that the presence of an amine does not affect the enantioselectivity.

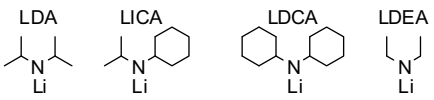
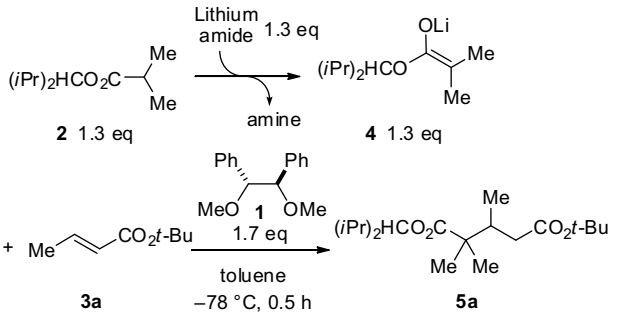


Table 1
Chiral ligand control in asymmetric Michael addition



Entry	Lithium amide	Yield (%)	ee (%)
1	LDA	99	60
2	LICA	93	65
3	LDCA	94	63

Dramatic improvement in enantioselectivity was observed by using 2 equiv of LDA as a lithiating agent to give **5a** with 94% ee in 78% yield (Table 2, entry 1). The enantioselectivity was highly dependent on a lithium amide used ranging from 94% ee to 68% ee (entries 1–4). It is worthy to note that the existence of an equimolar amount of a lithium amide afforded **5a** with higher enantioselectivity relative to those obtained in the absence of a lithium amide.

The higher reactivity of a ternary complex of lithium enolate, **4**–**1**-lithium amide, became apparent from the reaction with cinnamate **3b** at −78 °C for 0.5 h to give **5b** with 78% ee in 81% yield (Scheme 1). The absence of LDA resulted in the poorer reactivity to give 4% yield of **5b** with 12% ee. A LDA assisted lithium enolate **4** was also powerful to give racemic **5b** in 72% yield.[8]

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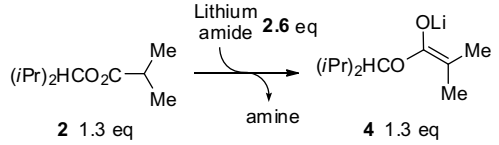
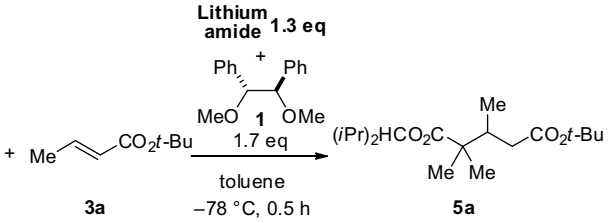
Table 2
Both of chiral ligand and lithium amide control in asymmetric Michael reaction of lithium enolate





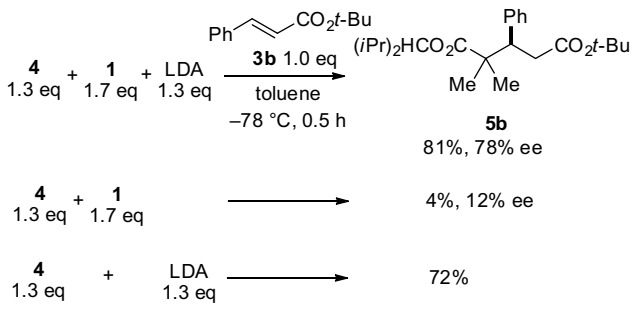
Entry	Lithium amide	Yield (%)	ee (%)
1	LDA	78	94
2	LICA	63	83
3	LDCA	74	71
4	LDEA	73	68

The selection of a lithium amide was also found to be important for the realization of high enantioselectivity (Table 3). A ternary complex reagent **4**–**1**-LDCA gave **5b** with 93% ee in 96% yield (entry 3).

The absolute configuration of **5b** was unambiguously determined by correlating **5b** and **6** with (*R*)-**7**[9] of the established configuration (Scheme 2). Other Michael products are assigned tentatively by analogy.

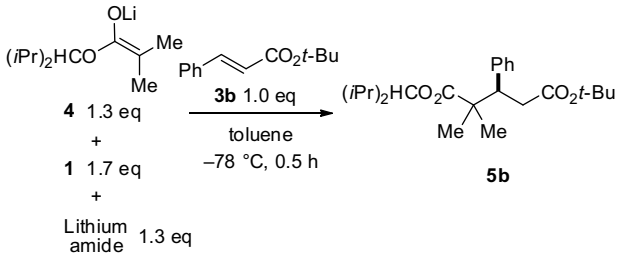
The promisingly high efficiency of the ternary complex of the lithium enolate was also confirmed by the reaction with **3d** to give the corresponding Michael adduct **5d** in high enantioselectivity of 97% ee (Table 4, entry 5). The Michael addition with α, β, γ, δ-unsaturated ester **3c** was 1,4-selective to give **5c** with 93% ee in 90% yield (entry 2).

A lithium enolate **8** derived from acetate, the most fundamental of alkanoates, was applicable in the Michael reaction as a ternary complex reagent (Table 5). The reaction with *tert*-butyl crotonate **3a** proceeded to give **10a** (R^1 = Me) with 62% ee in 20% yield (entry 1). A decreasing yield was attributable to the conjugate addition of LDA[3b] and γ-deprotonation of **3a**. Replacement of *tert*-butyl ester with a bulky and much more electron-withdrawing BHA (3,5-di-*tert*-butyl-4-hydroxyanisyl) ester **9** improved the reaction efficiency. The reaction with crotonate **9a** (R^1 = Me, R^2 = BHA) proceeded even in the absence of a lithium amide to give a quantitative yield of **11a** (R = Me), however, with only 19% ee (entry 2). A ternary reagent using LDA as a lithium amide gave **11a**

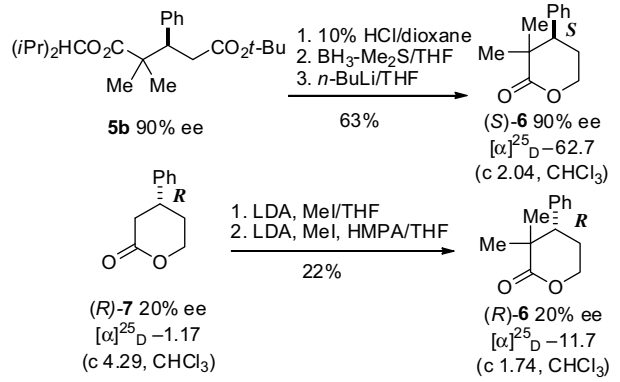


Scheme 1. Higher reactivity of lithium enolate assisted by chiral ligand and lithium amide.

Table 3
Lithium amide dependency of reaction efficiency

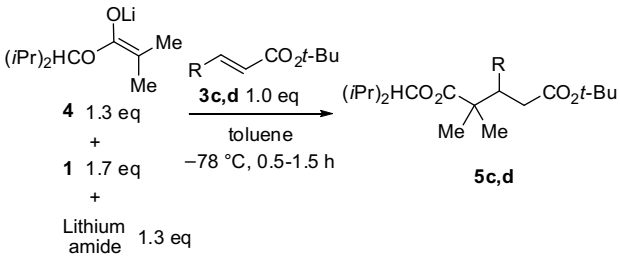


Entry	Lithium amide	Yield (%)	ee (%)
1	LDA	81	78
2	LICA	95	90
3	LDCA	96	93



Scheme 2. Correlation of **5b** and **6** with **7**.

Table 4
Asymmetric Michael reaction

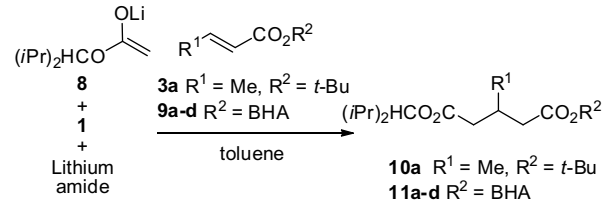


Entry	3	R	Lithium amide	5	Yield (%)	ee (%)
1	**3c**	MeCH=CH	LDA	**5c**	85	88
2	**3c**	MeCH=CH	LICA	**5c**	90	93
3	**3c**	MeCH=CH	LDCA	**5c**	83	91
4	**3d**	*i*Pr	LDA	**5d**	63	91
5	**3d**	*i*Pr	LICA	**5d**	82	97
6	**3d**	*i*Pr	LDCA	**5d**	62	88

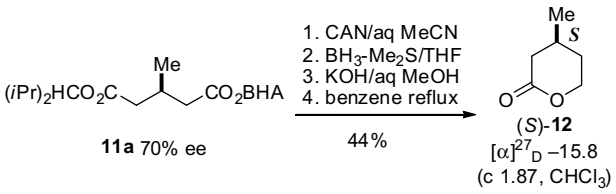
with 64% ee in unsatisfactory 31% yield, again due to the γ-deprotonation (entry 3). Finally, the use of LHMDS as a poor nucleophilic and basic lithium amide was found to improve the chemical yield to 94% of Michael adduct **11a** with 77% ee (entry 4). Other two enoates **9c, d** were converted to Michael adducts **11c, d** with 69% and 60% ee quantitatively (entries 5 and 6). For the reaction with cinnamate **9b** a bulky lithium amide was the best to give **11b** with 81% ee (entry 7).

The absolute configuration of **11a**(R^1 = Me) was unambiguously determined by correlating with (*S*)-**12**[10] of the established config-

Table 5
Asymmetric Michael reaction of acetate



Entry	3/9	R	Lithium amide	Temperature (°C)	Time (h)	Yield (%)	ee (%)
1	**3a**	Me	LDA	−78	0.5	20	62
2	**9a**	Me	None	−40	4	99	19
3	**9a**	Me	LDA	−78	16	31	64
4	**9a**	Me	LHMDS	−40	4	94	77
5	**9c**	MeCH=CH	LHMDS	−40	18	99	60
6	**9d**	*i*Pr	LHMDS	−40	16	99	69
7	**9b**	Ph	TMSBnNLi	−78	1	28	81



Scheme 3. Correlation of **11a** with (*S*)-**12**.

uration (Scheme 3). The same sense of enantiofacial differentiation of enolates **4** and **8** implies the operation of similar stereochemical control of ternary complex reagent.

In summary, the ternary complex reagent of a lithium ester enolate, comprised of a lithium ester enolate-chiral diether ligand–lithium amide, was found to be the most reactive than the binary reagent and to be the efficient Michael donor giving the corresponding adduct in reasonably high enantioselectivity of up to 97% ee.

Acknowledgments

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