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Chiral Ligand-Controlled Asymmetric Conjugate Addition of Lithium Amides to Enoates

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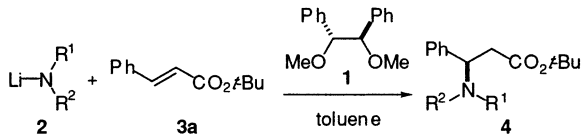
The conjugate addition of nucleophiles to α,β-unsaturated carbonyl compounds is one of the most powerful bond forming reactions and has been widely utilized as a key reaction in organic synthesis.[1] We have been engaged in the chiral ligand-controlled[2] asymmetric reactions of various types of nucleophiles such as organolithiums,[3] organocoppers,[4] organoboranes,[5] and arylthiols.[6] Asymmetric conjugate addition of nitrogen nucleophiles to enoates provides chiral β-amino acid equivalents that, although less abundant than their α-analogues,[7] occur in nature as components of peptidic natural products with potent pharmacological activities.[8] The most well-known, medicinally important class of nonpeptidic β-amino acids is found in β-lactams.[9] Among several strategies for the synthesis of optically active β-amino acid derivatives,[10] the conjugate addition of nitrogen nucleophiles to α,β-unsaturated carboxylic acid derivatives is one of the most attractive and versatile methods. Three major ways have been described to achieve asymmetric conjugate addition of nitrogen nucleophiles by using chiral acceptors,[11] chiral amines,[12] and chiral catalysts.[13] We describe herein that the conjugate addition reaction of lithium *N*-benzyltrimethylsilylamide with enoates is controlled or catalyzed by an external chiral ligand **1**[14] to produce β-amino esters in high enantioselectivities up to 99% ee and high yields. To the best of our knowledge, this is the first success in an external chiral ligand-controlled asymmetric conjugate addition of lithium amides to enoates.

At the outset of our study, we examined the reaction efficiency of lithium amides **2a**−**d** with *tert*-butyl cinnamate **3a**. The reaction of lithium diisopropylamide **2a** with **3a** under the mediation of a slight excess of **1** in toluene at −20 °C for 1 h gave β-amino ester **4a** ($R^1 = R^2 =$ *i*-Pr) with 68% ee in 45% yield (Table 1, entry 1). Delighted by this promising result, we next examined lithium dibenzylamide **2b**, which is an ammonia equivalent convertible by hydrogenolysis, to afford, after 3 h at −78 °C, **4b** ($R^1 = R^2 =$ Bn) with a disappointing 4% ee in 48% yield. Fortunately, lithium *N*-benzyltrimethylsilylamide **2c**[15] was an ammonia equivalent of choice, after 0.7 h at −78 °C, producing protodesilylated **4c** ($R^1 =$ H, $R^2 =$ Bn) with an excellent 93% ee in 92% yield (entry 3). Unfortunately, **2d** gave no conjugate addition product **4d**, recovering **3a** unchanged (entry 6). (−)-Sparteine[16] was not the choice as a chiral ligand to give **4c** from **2c** with a miserable 3% ee in 25% yield.

The amount of **2c** is one of the critical factors affecting the reaction efficiency. The reduced amount of **2c** to 1.5 equiv from 3.0 equiv gave **4c** with a diminished 82% ee in 81% yield (entry 4). Because the lithium ester enolate, generated by the reaction of **2c** with **3a**, could possibly interfere with the reaction efficiency of **1**−**2c** by forming a ternary complex,[17] conversion of a lithium ester enolate into an inert silyl enol ether may improve the efficiency. Thus, trimethylchlorosilane (TMSCl) was added together with **3a** to a solution of **1** and **2c** in toluene, giving **4c** with a satisfactorily high 97% ee in 97% yield (5 h at −78 °C) (entry 5). The reaction

Table 1. Chiral Ligand **1**-Controlled Asymmetric Addition of **2** to **3a**

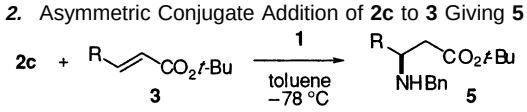


2 **3a** **4**

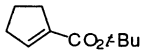
entry	**2**[a]	R^1	R^2	**1** (equiv)	*T* (°C)	*t* (h)	yield (%)	ee[b] (%)
1	**a** (2.2)	*i*-Pr	*i*-Pr	2.6	−20	1.0	45	68
2	**b** (3.0)	Bn	Bn	3.6	−20	0.2	48	4
3	**c** (3.0)	TMS	Bn	3.6	−78	0.7	92[c]	93
4	**c** (1.5)	TMS	Bn	1.8	−78	2.0	81[c]	82
5[d]	**c** (1.5)	TMS	Bn	1.8	−78	5.0	97[c]	97
6	**d** (3.0)	TMS	TMS	3.6	−20	12.0	0	

[a] Numbers in parentheses represent the equivalents of **2**. [b] The ee was determined by a chiral stationary phase HPLC. [c] The isolated product was a protodesilylated **4c** ($R^1 =$ H, $R^2 =$ Bn). [d] Five equivalents of TMSCl was added together with **3a**.

Table 2. Asymmetric Conjugate Addition of **2c** to **3** Giving **5**



3 **5**

entry	method	**3**	R	*t* (h)	yield (%)	ee (%)[a]
1	A	**b**	Me	0.25	92	97
2	B			0.25	90	96
3[b]	A	**c**	*i*-Pr	2.0	70	99
4	B			0.5	68	61
5	A	**d**	(*E*)-MeCH=CH	3.0	73	98
6	B			3.0	85	90
7	A	**e**	1-naphthyl	3.0	99	91
8	B			1.0	97	92
9	A	**f**	2-naphthyl	3.0	90	94
10	B			1.0	98	91
11	A	**g**		1.0	*cis* 61	92
					trans 9	97
12	B			2.0	*cis* 87	85
					trans 6	73

[a] The ee was determined by a chiral stationary phase HPLC. [b] Three equivalents of **2c** was used.

of **2c** with methyl crotonate gave the corresponding aminated product with 82% ee (85%) and 49% ee (78%), depending on the presence and absence of TMSCl, respectively, indicating the advantageous generality of the simultaneous addition of TMSCl.

We then examined the reaction of **2c** with a variety of enoates **3**. To a toluene solution of 1.8 equiv of **1** and 1.5 equiv of **2c** was added a mixture of **3** and 5.0 equiv of TMSCl (method A). For comparison, the reaction of 3.0 equiv of **2c** with **3** in the presence of 3.6 equiv of **1** was examined without addition of TMSCl (method B). With *tert*-butyl crotonate **3b**, which has deprotonatable methyl protons at the β-position, the reaction gave **5b** with 97% ee in 92% yield under method A (Table 2, entry 1). In the absence of TMSCl (method B), comparable selectivity and yield (96% ee, 90%) were

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obtained (entry 2). The reaction of **3c**, having an isopropyl group, gave **5c** with an excellent high 99% ee in 70% yield by method A (entry 3). The reaction of *tert*-butyl sorbate **3d**, having a propenyl group at the β-position, regioselectively gave a 1,4-addition product **5d** with 98% ee in 73% yield (entry 5). In the reactions of **3c** and **3d** without TMSCl (method B), **5c** and **5d** were obtained with lower 61 and 90% ee, respectively (entries 4 and 6). The reaction of **3e** and **3f**, having a 1- or 2-naphthyl group at the β-position, under method A, gave **5e** and **5f** with 91 and 94% ee in 99 and 90% yields, respectively (entries 7 and 9). The reaction of cyclic enoate **3g** under method A gave *cis*-**5g** with 92% ee in 61% yield along with *trans*-**5g** with 97% ee in 9% yield (entry 11). Without TMSCl, the selectivity of the reaction was lower, giving *cis*-**5g** with 85% ee in 87% yield and *trans*-**5g** in 6% yield (entry 12).

The stereochemistry of the asymmetric reaction was determined by hydrogenolytic debenzylation of (+)-**4c** (R^1 = H, R^2 = Bn) with Pearlman's catalyst under hydrogen in methanol at room temperature to furnish (+)-*R*-**4** (R^1, R^2 = H) of the established absolute configuration[18] in 94% yield. The cyclic (−)-*cis*-**5g** undertook isomerization with potassium *tert*-butoxide in THF at room temperature for **5d** to afford (+)-*trans*-**5g** in 60% yield, and then debenzylated to the corresponding (−)-(1*R*,2*S*)-*tert*-butyl 2-aminocyclohexanecarboxylate[19] in 77% yield. Thus, the same sense of the stereochemical approach of **2c** to acyclic and cyclic **3** was operative in the reaction.

The reaction of (*Z*)-*tert*-butyl cinnamate[20] instead of (*E*)-**3a** (method A) is interesting to note in that (+)-**4c** (R^1 = H, R^2 = Bn) of the same absolute configuration was obtained in 98% ee and 50% yield, along with α-trimethylsilylated *trans*-cinnamate[21] in 44% yield. With method B, (+)-**4c** was again obtained in 95% ee and 91% yield. These indicate that *Z*- to *E*-isomerization[22] takes place by the action of **2c** as a base, supplying (*E*)-**3a** as a final substrate of the conjugate addition reaction.

The reaction of **2c** in the absence of **1** in a toluene solvent was sluggish, producing racemic **4c** in 40% yield at −78 °C after 17 h. Taking advantage of the accelerating effect by a chiral ligand **1**, we conducted the catalytic reaction of 1.5 equiv of **2c** with **3a** at −78 °C for 17 h in the presence of 5.0 equiv of TMSCl and 0.3 equiv of **1** in toluene to afford **4c** with 70% ee in 75% yield. This preliminary result shows that the catalytic reaction is promising.

In summary, we have developed the highly efficient external chiral ligand-mediated asymmetric conjugate addition of lithium amides to enoates, which provides a powerful new methodology for the construction of chiral β-amino carbonyl moieties. Currently, our focus is on the development of the catalytic asymmetric version.

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Supporting Information Available: The general procedure, characterization data, NMR spectra, and HPLC traces (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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