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Lanthanoid Triflate Catalyzed Conjugate Addition of Amines to α, β-Unsaturated Esters. A Facile Route to Optically Active β-Lactam

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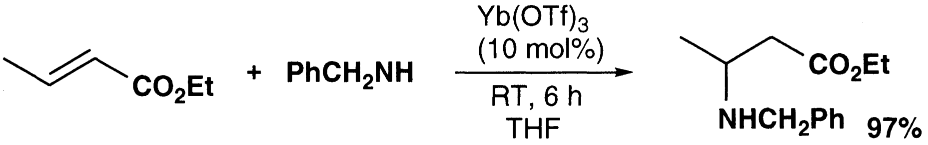
Catalytic amount of lanthanoid(III) triflates promoted the conjugate addition of amines to 2-alkenoic acid esters to give β-amino esters. The reaction of benzylamine with α,β-unsaturated esters containing a stereogenic center at γ-position proceeded diastereoselectivity to yield optically active β-lactam precursors.

The conjugate addition of amines to α,β-unsaturated esters[1] yielding β-amino esters[2] requires drastic reaction condition[3] except a case of acrylate derivatives.[4,5] Although application to the synthesis of optically active products was recently reported by using lithium silylamide,[6] simple addition of amine is still challenging. Lewis acid such as $BF_3 \cdot OEt_2$ or $TiCl_4$ could not catalyze the conjugate addition of amines to α,β-unsaturated esters by preferential complex formation with amines. After several trials, we have found that highly oxophilic lanthanoid salts give satisfactory results.[7] We describe here the conjugate addition of benzylamine to α,β-unsaturated esters yielding β-amino esters under the catalytic action of lanthanoid triflates.[8,9] A treatment of ethyl (*E*)-2-butenoate in THF with amines in the presence of lanthanoid(III) salts afforded β-amino esters in high yields (Scheme 1).

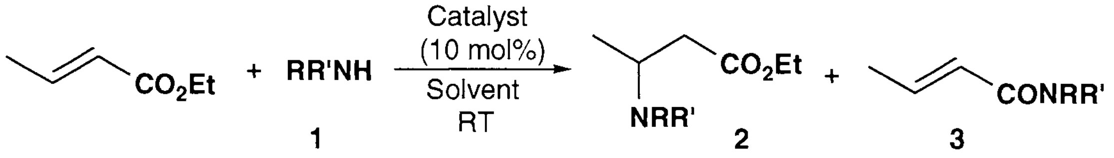


Scheme 1.

Among lanthanoid(III) salts examined, ytterbium triflate gave the best result. A typical procedure of the reaction; a solution of benzylamine (0.16 g, 1.5 mmol) in THF (1.0 ml) was added to a solution of ethyl (*E*)-2-butenoate (0.11 g, 1.0 mmol) and $Yb(OTf)_3$ (0.062 g, 0.1 mmol) in THF (1.0 ml) at room temperature and the reaction mixture was stirred for 6 h. The resulting mixture was diluted with a mixture of hexane and ethyl acetate (2/1, 30 ml) and filtered through celite. After the filtrate was concentrated in vacuo, chromatography on a silica gel column gave ethyl 3-benzylaminobutanoate in 97% yield (0.21 g). The reaction catalyzed by ytterbium chloride proceeded sluggishly. The combination of catalyst, solvent, and amines are summarized in Table 1.

In the absence of catalyst, the addition did not occur under this reaction condition (run 1). Lewis acids such as $BF_3 \cdot OEt_2$ and $TiCl_4$ did not show efficient activation for the conjugate addition, but amide was formed (run 3). On the contrary, the use of lanthanoid(III) triflates promoted the conjugate addition of amine

Table 1. Conjugate Addition of Amines to Ethyl (*E*)-2-Butenoate in the Presence of Various Metal Salts[a]



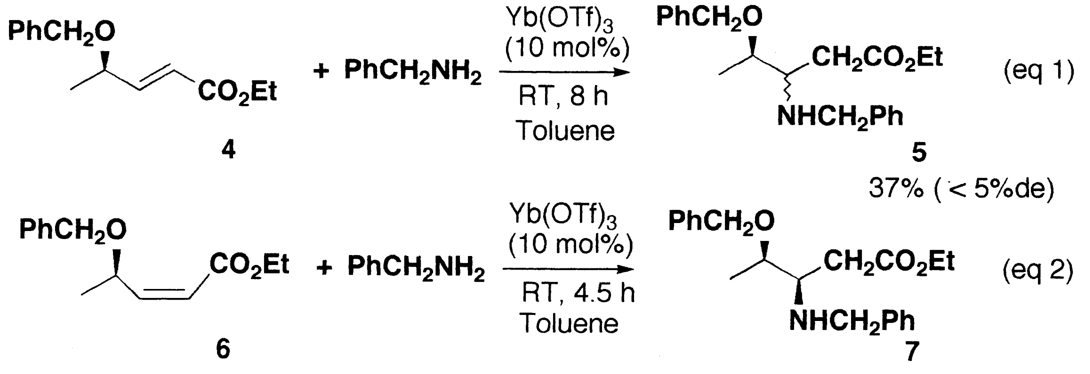
Run	Amine (**1**)	Catalyst	Solvent	Time	**2** (%)[b]	**3** (%)[b]
1	$PhCH_2NH_2$	-	CH_2Cl_2	12	0[c]	0
2	"	$BF_3 \cdot OEt_2$	"	12	0[c]	0
3	"	$TiCl_4$	"	4.5	28	26
4	"	$La(OTf)_3$	"	6	95	0
5	"	$Sm(OTf)_3$	"	6	95	0
6	"	$Yb(OTf)_3$	"	2.5	92	0
7	"	$YbCl_3$	THF	17	28	26
8	"	$Yb(OTf)_3$	"	6	97	0
9	"	"	Ethanol	6	95	0
10	"	"	Toluene	6	92	0
11	$PhCH(NH_2)CH_3$	"	THF	12	26 (32%de)[d]	0
12	Pyrrolidine	"	"	6	95	0

a) Ester (1.0 mmol), amine (1.5 mmol), catalyst (0.1 mmol), and solvent (2.0 ml) were used. b) Isolated yields. c) Ethyl (*E*)-2-butenoate was recovered quantitatively. d) The ratio was determined by ^{1}H-NMR.

(run 4–6, 8–10). It should be noted that protic solvent such as ethanol can be used (run 9).[9] The conjugate addition of 1-phenylethylamine proceeded sluggishly and resulted in low diastereoselectivity (run 11).

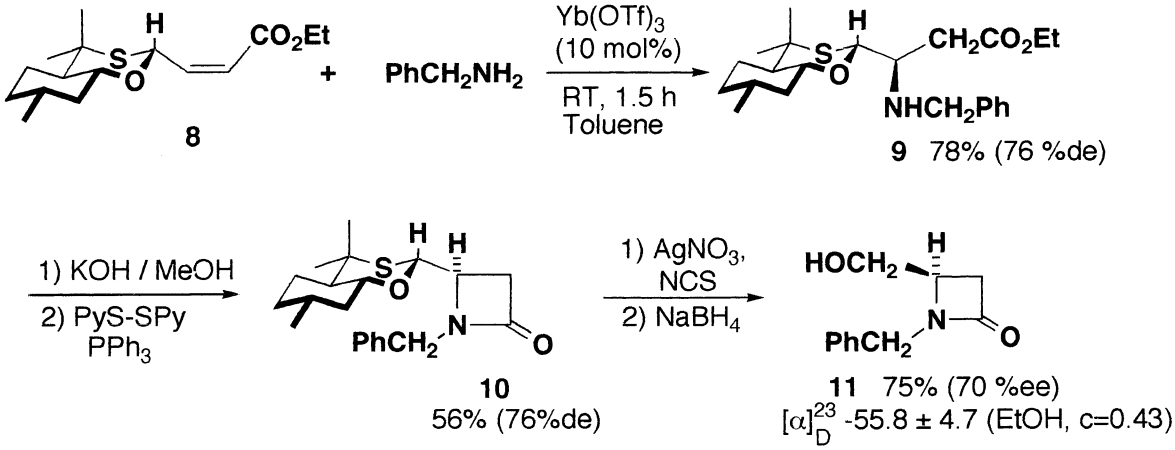
The conjugate additions of benzylamine to α,β-unsaturated esters, **4** and **6**, were tried under these reaction conditions. Although ethyl (*E*)-4-benzyloxy-2-pentenoate **4** did not proceed diastereoselectively, (*Z*)-isomer **6** showed high diastereoselectivity affording syn isomer **7** predominantly (Scheme 2).[10-12] ^{1}H-NMR of the reaction mixture in eq 2 did not show the isomerization of **6** into **4**. This fact implies that a reverse reaction from **7** to **4** or **6** did not occur under these reaction conditions.[13]

The ester **8** having the 1,3-oxathiane as a chiral auxiliary[14] reacted with benzylamine in the presence of catalytic amount of $Yb(OTf)_3$ to yield the adduct **9** in 78% with good diastereoselectivity (76%de) as shown in



Scheme 2.

Scheme 3. A hydrolysis of β-aminoester **9** followed by cyclization 6,15) gave the β-lactam **10** without racemization. The oxidative hydrolysis of hemithioacetal part in **10** followed by the reduction with NaBH$_4$ gave the chiral β-lactam **11**.16-18)



Scheme 3.

References

1) P. Perlmutter, "Conjugate Addition Reactions in Organic Synthesis," Pergamon Press, Oxford (1992), pp. 199-282.

2) Preparation of β-amino acid derivatives by homologation of α-amino acid: S. Matsubara, T. Kodama, and K. Utimoto, *Tetrahedron Lett.*, **31**, 6379 (1990), and references cited therein; by condensation of ester enolate with imine: T. Mukaiyama, H. Akamatsu, and J. S. Han, *Chem. Lett.*, **1990**, 889; see also E. F. Kleinman, "Comprehensive Organic Synthesis," ed by C. H. Heathcock, B. M. Trost, and I. Fleming, Pergamon Press, Oxford (1991), Vol. 2, pp. 893-952.

3) Heating: M. Furukawa, T. Okawara, and Y. Terawaki, *Chem. Pharm. Bull. (Tokyo)*, **25**, 1319 (1977); High pressure: J. d'Angelo and J. Maddaluno, *J. Am. Chem. Soc.*, **108**, 8112 (1986).

4) For example see, P. Perlmutter and M. Tabone, *Tetrahedron Lett.*, **29**, 949 (1988); see also, R. C. Larock, "Comprehensive Organic Transformation," VCH Publishers, New York (1989),pp. 391-395.

5) Exceptionally, an addition of benzylamine to methyl 4,5-dihydroxy-2-pentenoate acetonide proceeds smoothly even at -50 °C. See, H. Matsunaga, T. Sakamaki, H. Nagao, and Y. Yamada, *Tetrahedron*

Lett., **24**, 3009 (1983).

6) N. Asao, T. Uyehara, and Y. Yamamoto, *Tetrahedron,* **44**, 4173 (1988); Y. Yamamoto, N. Asao, and T. Uyehara, *J. Am. Chem. Soc.*, **114**, 5427 (1992).

7) Lanthanoid(III) triflates promote the reaction between nitriles and amine, acting as Lewis acid: J. H. Forsberg, T. M. Balasubramanian, and V. T. Spaziano, *J. Chem. Soc., Chem. Commun.*, **1976**, 106; J. H. Forsberg, V. T. Spaziano, T. M. Balasubramanian, G. K. Liu, S. A. Kinsley, C. A. Duckworth, J. J. Poteruca, P. S. Brown, and J. L. Millwe, *J. Org. Chem.*, **52**, 1017 (1987).

8) General review for lanthanoid(III) triflate catalyst. See, G. A. Molandar, *Chem. Rev.*, **92**, 29 (1992).

9) Lanthanoid(III) triflates work as Lewis acid in water. See, S. Kobayashi, I. Hachiya, H. Ishitani, and M. Araki, *Synlett,* **1993**, 472; S. Kobayashi and I. Hachiya, *Tetrahedron Lett.*, **33**, 1625 (1992).

10) In the reaction of eq 1, starting material **4** was recovered in 63%. In the reaction of eq 2, **6** was recovered with stereoisomer **4** (**6** / **4** = 2 / 1) in 52% combined yield. An isomerization of the unchanged **6** to **4** occurred at work-up stage. The choice of solvent is important for the diastereoselective addition of benzylamine to **6**. The use of other solvents gave the following results: Cyclohexane 84%de (57% yield); Hexane 65%de (38% yield); THF 85%de (28% yield); THF / H_2O (10 / 1) 65%de (26% yield). The higher reaction temperature (40 °C) increased the yield of the adduct but resulted in the reducing of the diastereo-selectivity: Toluene 90%de (64% yield); Cyclohexane 82%de (74% yield).

11) A transition state model for diastereoselctive reaction of organocopper reagents with **4** and **6** were discussed in detail: See, Y. Yamamoto, Y. Chounan, S. Nishii, T. Ibuka, and H. Kitahara, *J. Am. Chem. Soc.*, **114**, 7652 (1992). The preparations of **4** and **6** are also shown.

12) The (*Z*)-configuration of the substrate is indispensable for the diastereoselective reaction. In the case of the reaction using (*E*)-isomer of **8** (Scheme 3) gave **9** in 80% yield only with 24%de. The unique coordination of hetero atoms in the substrate to lanthanoid metal controls the diastereoselectivities. See, also; S. Matsubara, T. Takai, and K. Utimoto, *Chem Lett.*, **1991**, 1447; K. Utimoto, A. Nakamura, and S. Matsubara, *J. Am. Chem. Soc.*, **112**, 8189 (1990). Mechanistic discussion are underway.

13) A treatment of **6** with benzylamine in toluene without catalyst resulted in isomerization into **4**: 53% yield of **4** and 39% yield of **6** were obtained after the treatment at room temperature for 6 h; 93% yield of **4** and 7% yield of **6** were obtained after the treatment at 60 ˚C for 6 h. In both cases, the conjugate adduct was produced in less than 5% yield.

14) E. L. Eliel, J. E. Lynch, and F. Kume, *Org. React.*, **65**, 215 (1987).

15) M. Ohno, S. Kobayashi, T. Iimori, and T. Izumi, *J. Am. Chem. Soc.*,**103**, 2406 (1981).

16) K.-Y. Ko, W. J. Frazee, and E. L. Eliel, *Tetrahedron,* **40**, 1333 (1984).

17) β-Lactam **11** is the enantiomer of common intermediate for natural (+)-thienamycin synthesis.[18]

18) The enantiomeric purity of **11** was determined by Chiralcel-OD (Daicel); for *S*-isomer: $[\alpha]^{23}{}_{D}$ +80.5 (EtOH, c=1.2), N. Ikota, H. Shibata, and K. Koga, *Chem. Pharm. Bull.*, **33**, 3299 (1985).

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