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Michael synthesis of esters of β-amino acids: Stereochemical aspects

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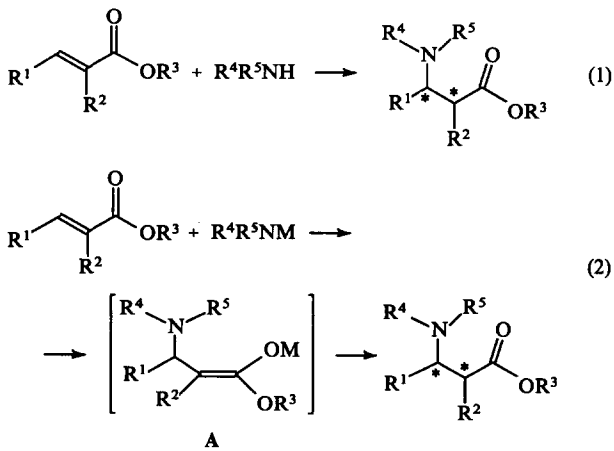
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Abstract. Published data dealing with the synthesis of esters of β-amino acids by nucleophilic addition of amines and metal amides to esters of α,β-unsaturated carboxylic acids are considered. Information on the influence of various factors on the chemical yield and diastereoselectivity of the Michael reaction is discussed systematically. The bibliography includes 70 references.

I. Introduction

During recent years, extensive studies on the synthesis and stereochemistry of β-lactams, which are fragments of numerous natural biomolecules, have been carried out. Since the biological activity of β-lactams is associated with only one of all possible diastereomers,[1,2] the attention of researchers is focused on the problem of asymmetric synthesis of homochiral β-lactams.[3–5] Chiral β-amino acids[6] or their esters, which are difficult to obtain, are precursors of these compounds.

The simplest method for the synthesis of β-amino esters is the conjugate addition of primary or secondary amines (reaction 1) or the corresponding metal amides (reaction 2) to esters of α,β-unsaturated carboxylic acids.



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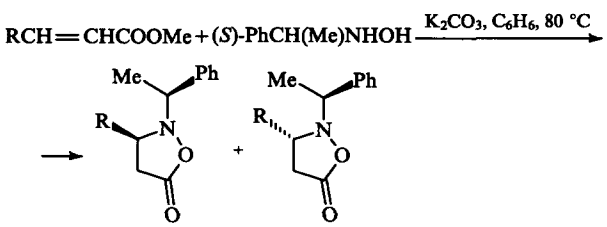
These reactions (if R^1 and/or $R^2 \neq H$) result in the formation of a chiral centre at the C_β (and/or C_α) atom and, in some cases, if certain conditions are satisfied, asymmetric synthesis of esters of β-amino acids becomes possible.

II. Nucleophilic addition of amines to esters of α,β-unsaturated acids

The conditions of the syntheses of β-amino esters from primary amines and α,β-unsaturated carboxylates are presented in Table 1. Polar solvents such as alcohols or carboxylic acids are usually employed as the reaction medium. Aprotic solvents, in particular THF, are also used; in some cases, the addition occurs only in a polar medium.[7]

Primary amines do not react with esters of α,β-unsaturated carboxylic acids under ordinary conditions, except for some individual cases (Table 1, entries 1, 2, 6, and 41); therefore, to prepare β-amino esters, the process of addition must be activated.[17]

Thermal activation of this reaction leads to satisfactory results; primary amines react most readily with methyl hydroxybenzylacrylate (yields 92% – 95%, see entries 3 and 4 in Table 1). With crotonates (entries 12 – 15, 17, and 18) and cinnamates (entries 38 and 39), the yields of β-amino esters are as low as 14% – 47%. It can be seen that an increase in the size of the substituent at the β-carbon atom decreases the chemical yields of the resulting β-amino esters from 26% – 47% to 14% – 16%. Similar results were also obtained for the addition of (*S*)-α-phenylethylhydroxylamine to methyl esters of α,β-unsaturated carboxylic acids.[18]



The yields of isoxazolidinones, which are formed in this reaction and can be readily reduced to β-amino acids, decrease from 91% (in the case of 4-methylpentenoic acid) to 54% (in the case of cinnamic acid).

The Michael reaction can also be activated by high pressure.[19] This can be illustrated by the addition of benzylamine and α-methylbenzylamine to substituted menthyl crotonates (cf.

Table 1. Conditions of reactions of primary amines with esters of α,β-unsaturated carboxylic acids.

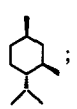
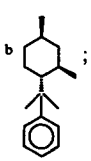
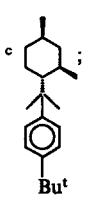
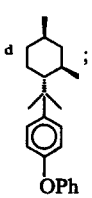
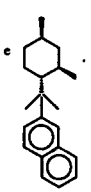
$$R^1CH=C(R^2)COOR^3 + R^4NH_2 \longrightarrow \underset{\mathbf{1}}{R^1CH(NHR^4)CH(R^2)COOR^3}$$

No	R^1	R^2	R^3	R^4	t/ h	T/°C	Solvent	P/ atm	Catalyst	Yield (%)	d.e.[a] (%)	Ref.
1	H	CH(OH)Me	Me	CH_2Ph	48	20	MeOH	1	None	99	64	8
2	H	CH(Me)OSiMe$_2$Bu^t	Me	CH_2Ph	48	25	MeOH	1	"	90	91	8
3	H	CH(OH)Ph	Me	CH_2Ph	2	70	MeOH	1	"	95	54	8
4	H	CH(OH)Ph	Me	CH_2Ph	40	67	THF	1	"	92	57	8
5	H	CH(OH)Me	Me	CH_2Ph	40	67	THF	1	"	77	49	8
6	H	CH(OH)Ph	Me	CH_2Ph	46	0	MeOH	1	"	98	61	8
7	H	H	Me		–	118	AcOH	1	"	90	–	9
8	H	Me	Me	Bu^t	24	30	MeCN	1	"	0	–	10
9	H	Me	Me	Bu^t	24	30	MeCN	1	Yb(OTf)$_3$	4	–	10
10	H	Me	Me	Bu^t	24	30	MeCN	3000	None	11	–	10
11	H	Me	Me	Bu^t	24	30	MeCN	3000	Yb(OTf)$_3$	47	–	10
12	Me	H	Me	(*R*)-CH(Me)Ph	12	78	EtOH	1	None	40	7	11
13	Me	H	Me	(*S*)-CH(Me)Ph	12	78	EtOH	1	"	47	7	11
14	Me	H	Et	(*S*)-CH(Me)Ph	6	78	EtOH	1	"	28	13	12
15	Me	H	Me	(*R*)-CH(Me)Ph	4	78	EtOH	1	"	35	<4	13
16	Me	H	Me	CH(Me)Ph	120	20	CH_2Cl_2	13817	"	60	5	14
17	Me	H	*l*-Menthyl[b]	CH_2Ph	12	78	EtOH	1	"	26	2	11
18	Me	H	*l*-Menthyl[b]	(*R*)-CH(Me)Ph	12	78	EtOH	1	"	28	5	11
19	Me	H	*l*-Menthyl[b]	(*S*)-CH(Me)Ph	12	78	EtOH	1	"	25	15	11
20	Me	H	*l*-Menthyl[b]	CH_2Ph	72	20	MeOH	4935	"	35	10	14
21	Me	H	8-Ph-*l*-menthyl[c]	(*R*)-CH(Me)Ph	24	50	CH_2Cl_2	13817	"	60	50	14
22	Me	H	8-Ph-*l*-menthyl[c]	(*S*)-CH(Me)Ph	24	50	CH_2Cl_2	13817	"	60	60	14
23	Me	H	8-Ph-*l*-menthyl[c]	CH_2Ph	96	50	MeOH	14804	"	90	60	14
24	Me	H	8-*p*-Bu^{t}C$_6$H$_4$-*l*-menthyl[d]	CH_2Ph	24	25	MeOH	14804	"	65	75	14
25	Me	H	8-*p*-PhOC$_6$H$_4$-*l*-menthyl[e]	CH_2Ph	24	25	MeOH	14804	"	90	95	14
26	Me	H	8-Naphth-*l*-menthyl[f]	CH_2Ph	24	25	MeOH	14804	"	50	>99	14

Table 1 (continued).

No	R^1	R^2	R^3	R^4	t/ h	T/°C	Solvent	P/ atm	Catalyst	Yield (%)	d.e.[a] (%)	Ref.
27	Me	H	Et	CH_2Ph	6	20	CH_2Cl_2	1	$La(OTf)_3$	95	–	15
28	Me	H	Et	CH_2Ph	6	20	CH_2Cl_2	1	$Sm(OTf)_3$	95	–	15
29	Me	H	Et	CH_2Ph	25	20	CH_2Cl_2	1	$Yb(OTf)_3$	92	–	15
30	Me	H	Et	CH_2Ph	6	20	THF	1	$Yb(OTf)_3$	97	–	15
31	Me	H	Et	CH_2Ph	6	20	EtOH	1	$Yb(OTf)_3$	95	–	15
32	Me	H	Et	CH_2Ph	6	20	MePh	1	$Yb(OTf)_3$	92	–	15
33	Me	H	Et	CH_2Ph	4.5	20	CH_2Cl_2	1	$TiCl_4$	28	–	15
34	Me	H	Et	CH_2Ph	17	20	THF	1	$YbCl_3$	28	–	15
35	Me	H	Et	CH(Me)Ph	12	20	THF	1	$Yb(OTf)_3$	26	32	15
36	Me	H	Et	CH_2Ph	15	20	CH_2Cl_2	1	$Yb(OTf)_3$	42	–	10
37	Me	H	Et	CH_2Ph	24	30	MeCN	1	$Yb(OTf)_3$	100	–	10
38	Ph	H	Et	(*R*)-CH(Me)Ph	12	78	EtOH	1	None	16	17	11
39	Ph	H	Et	(*S*)-CH(Me)Ph	12	78	EtOH	1	"	14	19	11
40	$CH_2CH(OMe)_2$	H	8-Ph-*l*-Menthyl[c]	CH_2Ph	24	20	MeOH	12830	"	85	60	14
41		H	Me	CH_2Ph	50	−50	None	1	"	85	100	16

[a] In Tables 1 – 4, d.e. stands for diastereomeric excess;

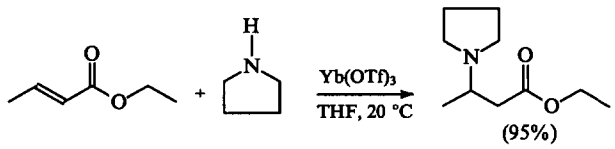
a  ; b  ; c  ; d  ; e  .

entries 17–19 and 20–26 in Table 1). The chemical yields vary between 50% and 90% and depend on the nature of the substituent in the substrate.

The use of titanium tetrachloride (Table 1, entry 33) or of ytterbium chloride (entry 34) as catalysts of the conjugate addition does not favour an increase in the yield of β-amino esters (yield ~28%); in addition, the amide of the initial α,β-unsaturated carboxylic acid is formed in these reactions as a side product in approximately the same yield (26%).

When various 2-chloro-2-cyclopropylideneacetates react with (4*S*,5*R*)-4,5-diphenyloxazolidin-2-one in THF in the presence of 10 mol.% of sodium hydride and a small amount of DB-18-C-6 crown ether, the corresponding 1,4-addition products are formed in chemical yields of 57%–88%.[20]

Recently it has been shown[15] that highly oxophilic lanthanide triflates, which are currently widely used in organic catalysis,[21] accelerate the Michael reaction, in particular the addition of benzylamine to ethyl crotonate (Table 1, entries 27–32). The yields of the target products in these reactions are 92%–97%, and no side products are formed. In the presence of ytterbium triflate, pyrrolidine easily adds to ethyl crotonate giving the corresponding product in 95% yield; however, α-phenylethylamine, which is sterically more hindered, does not react so readily: the yield of the corresponding product is only 26% (see Table 1, entry 35).

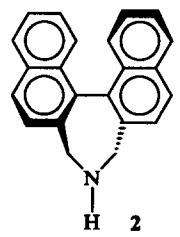


The catalytic addition of amines to esters of α,β-unsaturated acids occurs at room temperature over a period of several hours. Both polar (ethanol) and non-polar (toluene) solvents have been used as the reaction media. The best results were achieved with THF as the solvent and ytterbium triflate as the catalyst. Variation of the polarity of the reaction medium or the use of triflates of other lanthanides do not lead to any substantial changes in the yield of the reaction product (Table 1, entries 30–32, 27–29).

More recent studies[10,22,23] have confirmed that lanthanide triflates are preferred as catalysts in the Michael conjugate addition over other Lewis acids, since the latter are more prone to form complexes with amines thus decreasing their reactivity. The use of acetonitrile as the solvent increases the chemical yield of β-amino esters to 100% (Table 1, entries 36 and 37). In the case of sterically more hindered *tert*-butylamine, a considerable increase in the chemical yield can be achieved by using a combination of activating factors, such as high pressure and a catalyst (ytterbium triflate). Under these conditions, even secondary amines (for example, diisopropylamine and diisobutylamine) enter into the reaction with esters of α,β-unsaturated carboxylic acids. The main contribution to the increase in the chemical yields of the reaction products is made by pressure (Table 1, entries 8–11).

The addition of primary amines and cyclic secondary amines to esters of α,β-unsaturated carboxylic acids also led to satisfactory yields of products (39%–72%), when baker yeast was used as the catalyst.[24]

Acyclic secondary amines do not usually react with esters of α,β-unsaturated carboxylic acids,[14,15] whereas cyclic secondary amines, for example, piperidine[15,22,23,25] react to give products in very high chemical yields (up to 100%). For example, 2,7-dihydro-1*H*-dinaphtho[2,1-*c* : 1′,2′-*e*]azepine **2** adds to methyl crotonate to afford the corresponding product in 68% yield.[26]



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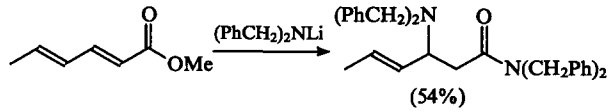
The reaction is carried out with excess methyl crotonate, with boiling, and without a solvent.

Analysis of the data presented in Table 1 indicates that when sterically less hindered reactants are used and when the optimal reaction conditions (solvent, temperature, pressure, and catalyst) are chosen, esters of β-amino acids can be synthesised in high yields.

III. Nucleophilic addition of metal amides to esters of α,β-unsaturated carboxylic acids

In recent years, metal amides, which have found wide application in asymmetric synthesis, have been used with increasing frequency for the nucleophilic addition to esters of α,β-unsaturated carboxylic acids.[27]

Primary and some secondary lithium amides react with esters of α,β-unsaturated carboxylic acids as strong bases. Therefore, apart from the target esters of β-amino acids **3**, which are formed in relatively low yields, these reactions afford the corresponding amides **4** or esters of β,γ-unsaturated carboxylic acids **5** (Table 2), these compounds being the main reaction products. In some cases, β-aminoamides have also been detected among the products.[34]



Side products **5** are also formed when sterically hindered secondary lithium amides react with esters of α,β-unsaturated carboxylic acids (Table 2, entries 9 and 10). For example, the formation of esters **5** in this reaction has been explained[33] by the fact that in the six-membered transition state, the amide attacks

Table 2. Products of the interaction of lithium amides with esters of α,β-unsaturated carboxylic acids.

$$R^1CH_2CH=CHCOOR^2 + R^3R^4NLi \longrightarrow$$
$$\longrightarrow \underset{\mathbf{3}}{R^1CH_2CH(NR^3R^4)CH_2COOR^2} +$$
$$+ \underset{\mathbf{4}}{R^1CH_2CH=CHCONR^3R^4} + \underset{\mathbf{5}}{R^1CH=CHCH_2COOR^2}$$

No	R^1	R^2	R^3	R^4	Yield (%)			Ref.
					3	**4**	**5**	
1	H	Me	(*R*)-CH(Me)Ph	H	28	35	–	13
2	H	Me	CH_2Ph	H	20	60	–	28
3	H	Me	Pr^i	Pr^i	44	–	14	28
4	H	Et	Pr^i	Pr^i	–	–	92	29
5	H	Me	$SiMe_3$	$SiMe_3$	–	–	9	28
6	H	Et	Pr^i	Pr^i	–	–	23	30
7	Br	Me	Pr^i	Pr^i	–	–	<5	31
8	Ph(*Z*)[a]	Me	CH_2Ph	$SiMe_3$	–	–	95	32
9	Ph(*E*)[a]	Bu^t	(*R*)-CH(Me)Ph	CH_2Ph	69	–	20	33
10	Ph(*Z*)[a]	Bu^t	(*R*)-CH(Me)Ph	CH_2Ph	–	–	92	33

[a] The configuration of the initial ester is given in parentheses.

the protons of the methylene group, located in the γ-position with respect to the carbonyl group in the substrate, and thus induces the rearrangement of the double bond to the β,γ-position. This process is markedly facilitated if the initial ester has the *cis*-configuration.

The nucleophilic properties of secondary lithium amides, which are more bulky, dominate over their basic properties. Therefore, they preferentially add to the β-position with respect to the carbonyl group, which results in the formation of β-amino esters as the main (and practically the only) reaction products (Table 3). The reaction is usually carried out at a low temperature for 15–30 min. Varying the temperature conditions (from −78 to +20 °C) exerts no substantial influence on the chemical yield of β-amino esters.[13,29,45] The best results have been achieved by using a 1.5-fold excess of the amide.[44] Lithium benzyl(α-phenylethyl)amide **7** is used most often in these conjugate addition reactions.

Good results have also been obtained when the lithium derivative of the above-mentioned dihydro-4*H*-dinaphthoazepine and lithium benzyl(trimethylsilyl)amide have been used as nucleophiles (chemical yields of up to 88% and of 77%–99%, respectively). When symmetrical lithium bis(α-phenylethyl)amide is used, the yield of the corresponding β-amino esters decreases to 23% due to the steric hindrance arising in the amide itself during the nucleophilic attack.[48] The introduction of substituents in one of the benzene rings in lithium benzyl(α-phenylethyl)amide exerts no influence on the final result of the reaction (Table 3, entries 60–62).

The introduction of a methyl group in the α-position with respect to the carbonyl group of the ester also decreases the yields of the corresponding β-amino esters from 77%–92% to 21%–61% (cf. entries 1, 2 and 7, 8 as well as entries 17, 18 and 21, 22, etc. in Table 3). The nature of the radical located in the β-position with respect to the carboxyl group of the substrate and the nature of the ester group exert as a rule no substantial influence on the chemical yield in the nucleophilic addition of metal amides to the double bond. The yield of β-amino ester increases somewhat if the initial ester contains a silyl group[46,49] (Table 3, entries 51–53 and 54).

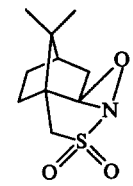
The conjugate addition of lithium amides occurs more successfully with the *trans*-isomers of α,β-unsaturated esters. In those cases where the corresponding *cis*-isomers are used, the chemical yield decreases from 80% to 39% (see Table 3, entries 42 and 43). However the *cis*-configuration of cyclic esters does not influence the yield of the final β-amino ester (Table 3, entries 14, 15, and 26, 30–32).

The solvent exerts substantial influence on the addition. The reaction is usually carried out in polar aprotic solvents such as THF or 1,2-dimethoxyethane (DME). Less polar solvents, for example, toluene or its mixtures with THF, are also used sometimes. The addition of an excess of a crown ether (12-crown-4) increases the chemical yield of β-amino esters by a factor of 1.5–2 (cf. entries 36 and 41 as well as 47 and 48 in Table 3), whereas the addition of polar solvents (in particular, HMPTA) considerably decreases the yield (from 44% to 18%–28%) (Table 3, entries 36, 38, and 39).[44,50] Since the basic properties of amides are enhanced in a polar medium, the interaction of ethyl crotonate with lithium diisopropylamide in THF containing some HMPTA affords the isomeric β,γ-unsaturated ester **5** as the only product (see Table 2, entry 4), whereas in the absence of HMPTA, the reaction occurs as a 1,4-addition in nearly quantitative yield (90%).[29]

Various protonating agents have been used to decompose the β-aminoenolates **A** formed upon 1,4-addition (see reaction 2); a saturated aqueous solution of ammonium chloride, alcohols, or a buffer solution with pH 7 are employed most frequently. The best result has been achieved by using sterically hindered 2,6-di-*tert*-butylphenol. The use of acetic acid as the protonating agent leads to a decrease in the chemical yield of β-amino ester from 40% to 21% (cf. entries 6 and 8 in Table 3), and when aqueous acetic acid is used, the final product may polymerise.[51]

If an alkyl halide is added to the reaction mixture instead of a protonating agent, the β-aminoenolate **A** is alkylated at the α-carbon atom (the so-called tandem reaction) resulting in the formation of α-alkyl-β-amino ester **8** (Table 4). An increase in the size of the radical R^5 in the alkylating agent usually deteriorates the chemical yield of the product **8** (see entries 10 and 11; 12 and 13; and 15 and 16 in Table 4). The nature of the substituents in the amide and in the ester is not crucial for the occurrence of the tandem reaction.

When (+)-(camphorsulfonyl)oxaziridine **9**



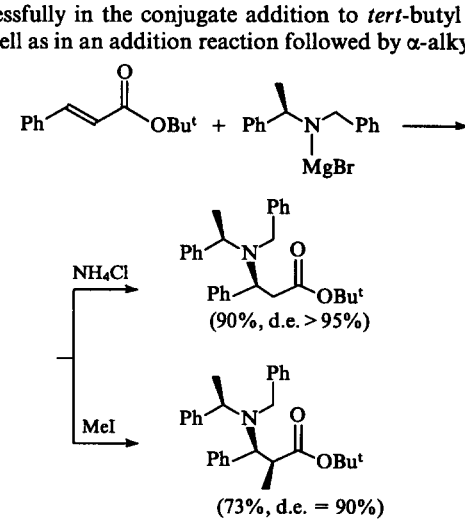
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is used as a hydroxylating agent, α-hydroxy-β-amino esters **10** can be prepared (Table 5). If a phenyl substituent occurs in the β-position with respect to the carbonyl group, the yield of the final product is higher than those obtained with compounds containing aliphatic substituents (entries 2, 3, and 5–8 in Table 5). However, replacement of the phenyl group by a benzyl group leads to a sharp decrease in the product yields (entries 2 and 9; 3 and 10). It is of interest that when lithium (*S*)-benzyl(α-phenylethyl)amide is used, the yield of the product **10** is higher than with the (*R*)-isomer (Table 5, entries 7–10). The nature of the alkyl radical in the ester group exerts an ambiguous influence on the yield of the α-hydroxy-β-amino esters.

The conjugate addition of amides of other metals to esters of α,β-unsaturated carboxylic acids has not been studied in detail. It has been found that titanium amides like $Ti(NR_2)_4$, $ClTi(NR_2)_3$, and $Cl_2Ti(NR_2)_2$ (R = Me, Et) add to acrylates, crotonates, and cinnamates to give the corresponding β-amino esters in good chemical yields (34%–97%); however, amides of β,γ-unsaturated acids (21%–39%) are often formed as side products. The formation of the latter can be completely eliminated by using esters with bulky ester groups.[59]

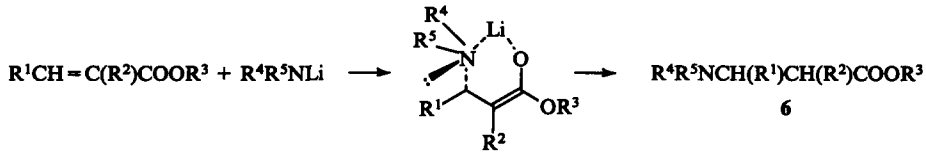
Lithium amidocuprates $(R_2N)_2CuLi$ add to esters of α,β-unsaturated carboxylic acids yielding β-amino esters as the main reaction products,[33,60,61] although in this case, too, small amounts of β,γ-unsaturated carboxamides are formed.[33]

Magnesium benzyl(α-phenylethyl)amide has been used successfully in the conjugate addition to *tert*-butyl cinnamate,[62] as well as in an addition reaction followed by α-alkylation.



The chemical yields of products in the latter reactions are comparable with the yields of the same products in the similar reactions involving the corresponding lithium amides (Table 3, entry 18; Table 4, entry 15).

Table 3. Conditions of the reactions of secondary lithium amides with esters of α,β-unsaturated carboxylic acids.



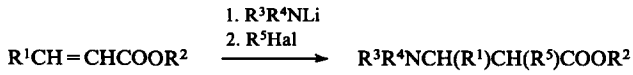
No	R^1 [a]	R^2	R^3	Solvent	Protonating agent	Yield of **6** (%)	d.e. (%)	Ref.
A. Lithium (*R*)-benzyl(α-phenylethyl)amide								
1	Me	H	Me	THF	NH_4Cl	75	>95	35
2	Me	H	Me	THF	NH_4Cl	85	95	13
3	Me	H	Bu^t	THF	NH_4Cl	75	>95	35
4	Me	H	Bu^t	THF	NH_4Cl	82	>99	13
5	Me	H	CH_2Ph	THF	NH_4Cl	88	95	13, 36
6	Me	Me	Me	THF	AcOH	21	71	37
7	Me	Me	Me	THF	pH 7	23	82	37
8	Me	Me	Me	THF	2,6-(Bu^t)$_2$C$_6$H$_3$OH	40	82	37
9	Me	Me	CH_2Ph	THF	pH 7	11	>82	37
10	Me	Me	Bu^t	THF	pH 7	43	88	37
11	Me	Me	Bu^t	MePh	Bu^{t}OH	78	20	37
12	Me	Me	Bu^t	MePh	pH 7	70	60	37
13	Me	Me	Bu^t	MePh/THF	pH 7	75	90	37
14	Me	Me	Bu^t	MePh/THF	2,6-(Bu^t)$_2$C$_6$H$_3$OH	72	>99	37
15	Et	Me	Bu^t	MePh/THF	2,6-(Bu^t)$_2$C$_6$H$_3$OH	65	>99	37, 38
16	Ph	H	Me	THF	NH_4Cl	77	>95	35
17	Ph	H	Bu^t	THF	2,6-(Bu^t)$_2$C$_6$H$_3$OH	92	95	39
18	Ph	H	Bu^t	THF	NH_4Cl	87	95	35
19	Ph	Me	Me	THF	pH 7	38	87	37
20	Ph	Me	Me	THF	2,6-(Bu^t)$_2$C$_6$H$_3$OH	37	93	37
21	Ph	Me	Bu^t	MePh/THF	2,6-(Bu^t)$_2$C$_6$H$_3$OH	61	>99	37
22	Ph	Me	Bu^t	MePh/THF	2,6-(Bu^t)$_2$C$_6$H$_3$OH	61	99	39
23	Ph	CH_2Ph	Bu^t	MePh/THF	2,6-(Bu^t)$_2$C$_6$H$_3$OH	45	>98	39
24	*p*-$C_6H_4CH_2OPh$	H	Me	THF	NH_4Cl	78	>99	13
25	C_7H_{15}	H	Bu^t	THF	NH_4Cl	91	>95	40
26	$-(CH_2)_4-$		Bu^t	THF	2,6-(Bu^t)$_2$C$_6$H$_3$OH	70	>95	41
B. Lithium (*S*)-benzyl(α-phenylethyl)amide								
27	CH=CHPh	H	Me	THF	NH_4Cl	81	100	42
28	CH=CHPh	H	Pr^i	THF	NH_4Cl	83	100	42
29	CH=CHPh	H	Bu^t	THF	NH_4Cl	98	100	42
30	$-(CH_2)_3-$		Bu^t	THF	2,6-(Bu^t)$_2$C$_6$H$_3$OH	85	71	41
31	$-(CH_2)_3-$		Bu^t	THF	2,6-(Bu^t)$_2$C$_6$H$_3$OH	65	>98	43
32	$-(CH_2)_4-$		Bu^t	THF	2,6-(Bu^t)$_2$C$_6$H$_3$OH	70	>95	41, 43
C. Lithium derivative of (*R*,*S*)-azepine **2**								
33	Me (*E*)	H	Bu^t	DME	NH_4Cl	83	97	44
34	Pr^i (*E*)	H	Bu^t	DME	NH_4Cl	69	94	44
35	Bu^i (*E*)	H	Bu^t	DME	NH_4Cl	74	97	44
36	C_7H_{15}	H	Me	THF	NH_4Cl	44	90	44
37	C_7H_{15}	H	Me	DME	NH_4Cl	32	91	44
38	C_7H_{15}	H	Me	THF/HMPA=4:1	NH_4Cl	18	50	44
39	C_7H_{15}	H	Me	THF/HMPA (20 eq.)	NH_4Cl	28	84	44
40	C_7H_{15}	H	Me	MePh	NH_4Cl	6	50	44
41	C_7H_{15}	H	Me	THF/12-C-4 (4 eq.)	NH_4Cl	60	95	44
42	C_7H_{15} (*E*)	H	Bu^t	DME	NH_4Cl	80	96	44
43	C_7H_{15} (*Z*)	H	Bu^t	DME	NH_4Cl	39	78	44
D. Lithium derivative of (*S*)-azepine **2**								
44	Me	Me	Bu^t	DME	NH_4Cl	63	>95	45
E. Lithium derivative of (*R*)-azepine **2**								
45	C_7H_{15}	H	Pr^i	DME	NH_4Cl	63	93	44
46	C_7H_{15}	H	Pr^i	THF/12-C-4 (8 eq.)	NH_4Cl	65	89	44
47	C_7H_{15}	H	Bu^t	THF/12-C-4 (4 eq.)	NH_4Cl	88	94	44
48	C_7H_{15}	H	Bu^t	THF/12-C-4 (1 eq.)	NH_4Cl	43	88	44
49	C_7H_{15}	H	Bu^t	DME	NH_4Cl	80	>97	44

Table 3 (continued).

No	R^1 [a]	R^2	R^3	Solvent	Protonating agent	Yield of **6** (%)	d.e. (%)	Ref.
F. Lithium benzyl(trimethylsilyl)amide								
50	Me	H	Me	THF	AcOH/THF	88	–	28
51	$CH(Me)OSiMe_2Bu^t$	H	Bu^t	THF	MeOH	91	8	46
52	$CH(Me)OSiPh_2Bu^t$	H	Bu^t	THF	MeOH	99	78	46
53	$CH(Me)OSiPr^i_3$	H	Bu^t	THF	MeOH	95	80	46
54	(*S*)-$CH(Me)OCPh_3$	H	Bu^t	THF	MeOH	77	100	46
55	C_7H_{15}	H	Me	THF	MeOH	86	–	32
G. Lithium (*R*)-(α-phenylethyl)(trimethylsilyl)amide								
56		H	Et	THF	NH_4Cl	64	>99	47
H. Lithium (*R,R*)-bis(α-phenylethyl)amide								
57	Me	H	Me	THF	NH_4Cl	57	>99	13
58	Me	H	CH_2Ph	THF	NH_4Cl	23	98	13
59	Me	H	Bu^t	THF	NH_4Cl	27	>99	13
I. Lithium (*R*)-(3,4-dimethoxybenzyl)(α-phenylethyl)amide								
60	Me	H	Me	THF	NH_4Cl	68	95	13
61	Me	H	CH_2Ph	THF	NH_4Cl	74	96	13
62	Me	H	Bu^t	THF	NH_4Cl	83	>99	13
J. Lithium (*S*)-allyl(α-phenylethyl)amide								
63	Me	H	Bu^t	THF	NH_4Cl	92	>99	36
64	Et	H	Bu^t	THF	NH_4Cl	85	>99	36
65	Pr^i	H	Bu^t	THF	NH_4Cl	88	>99	36
66	Ph	H	Bu^t	THF	NH_4Cl	97	>99	36
67	CH=CHMe (*E*)	H	Bu^t	THF	NH_4Cl	78	>98	36

[a] Configuration of the initial ester is given in parentheses.

Table 4. Addition of lithium amides to esters of α,β-unsaturated carboxylic acids with simultaneous α-alkylation.



8

Number of reaction	R^1 [a]	R^2	R^3	R^4	R^5	Yield of **8** (%)	d.e. (%)	Ref.
1	Me	Bu^t	(*S*)-**2**		Me	71	85	45
2	Me	Me	Pr^i	Pr^i	C_8H_{17}	58	100	52
3	Ph	Bu^t	CH_2Ph	CH_2Ph	Me	71	>90	35
4	Me(*Z*)[a]	Me	$SiMe_3$	CH_2Ph	Me	88	6	53
5	Me(*E*)[a]	Me	$SiMe_3$	CH_2Ph	Me	68	38	53
6	Me(*Z*)[a]	Me	$SiMe_3$	CH_2Ph	C_8H_{17}	81	18	52, 53
7	Me(*E*)[a]	Me	$SiMe_3$	CH_2Ph	C_8H_{17}	60	80	53
8	Me	Me	(*R*)-CH(Me)Ph	CH_2Ph	Me	50	9	35
9	Me	Me	(*R*)-CH(Me)Ph	CH_2Ph	CH_2Ph	54	50	35
10	Me	Bu^t	(*R*)-CH(Me)Ph	CH_2Ph	Me	60	15	35
11	Me	Bu^t	(*R*)-CH(Me)Ph	CH_2Ph	CH_2Ph	42	0	35
12	Ph	Me	(*R*)-CH(Me)Ph	CH_2Ph	Me	61	85	35
13	Ph	Me	(*R*)-CH(Me)Ph	CH_2Ph	CH_2Ph	55	50	35
14	Ph	Me	(*R*)-CH(Me)Ph	CH_2Ph	$CH_2CH=CH_2$	79	50	35
15	Ph	Bu^t	(*R*)-CH(Me)Ph	CH_2Ph	Me	78	15	35
16	Ph	Bu^t	(*R*)-CH(Me)Ph	CH_2Ph	CH_2Ph	46	43	35

[a] Configuration of the initial ester is given in parentheses.

Table 5. Addition of lithium amides to esters of α,β-unsaturated carboxylic acids with simultaneous α-hydroxylation.

$$R^1CH{=}C(R^2)COOR^3 + (R)\text{-}Ph(Me)CHN(CH_2Ph)Li \xrightarrow{9} PhCH(Me)N(CH_2Ph)CH(R^1)CR^2(OH)COOR^3$$
7 10

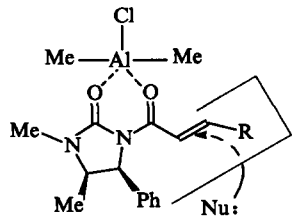
No	R^1	R^2	R^3	Yield of **10** (%)	d.e. (%)	Ref.
1	Ph	H	Me	43	>90	54
2	Ph	H	Bu^t	86	92	54, 55
3[a]	Ph	H	Bu^t	89	>98	54, 56
4	Me	H	Me	55	75	54
5	Et	H	Bu^t	53	>90	54
6	Me	H	Bu^t	36	>90	54
7	C_7H_{15}	H	Bu^t	63	88	40, 57
8[a]	C_7H_{15}	H	Bu^t	85	92	40
9	CH_2Ph	H	Bu^t	41	20	33, 58
10[a]	CH_2Ph	H	Bu^t	63	91	33
11	Me	Me	Bu^t	54	83	54

[a] The (*S*)-isomer of the amine was used.

IV. Stereochemistry of nucleophilic addition of amines and metal amides to esters of α,β-unsaturated carboxylic acids

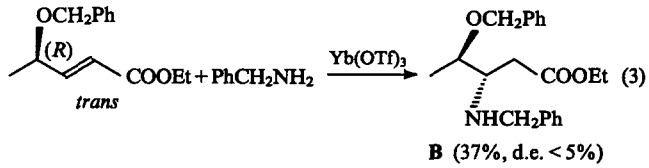
The reactions of chiral amines, in particular, of α-phenylethylamine, with esters of α,β-unsaturated carboxylic acids are characterised by relatively low stereoselectivities (d.e. = 0% – 19%, d.e. is diastereomeric excess), irrespective of the type of activation used: high temperature, high pressure, or a catalyst. The interaction of azepine **2** with methyl crotonate without a solvent is an exception; in this case, diastereomeric excess is 61%.[26]

When the conjugate addition of amines to esters of α,β-unsaturated carboxylic acids is carried out with the catalytic activation by lanthanide triflates, the diastereomeric excess is only 12% – 31%.[15, 22, 23] However, in the case where the substrate molecule can be fixed due to the coordination of the catalyst to the oxygen atoms of the carbonyl groups in the substituted amide of α,β-unsaturated acid, presented below, the steric restrictions thus arising cause the nucleophile to attack the substrate from the side that is sterically less hindered. Consequently, 1,4-addition occurs stereoselectively (d.e. up to 80%).[63, 64]

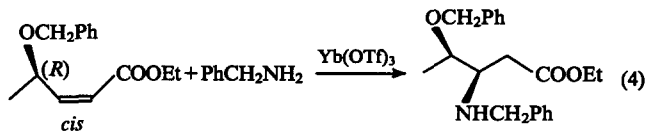


Reactions of benzylamine with acrylic acid derivatives having a chiral substituent in the α-position with respect to the carbonyl group are fairly stereoselective: d.e. is 49% – 91% (Table 1, entries 1 – 6). The presence of a bulky substituent in the β-position with respect to the carbonyl group of the ester is probably the main factor responsible for the stereospecific character of the addition (Table 1, entry 41), although the fact that this reaction was carried out at a negative temperature and without a solvent should apparently also be taken into account. The presence of a bulky ester group also increases the stereoselectivity of the reaction (entries 21 – 24) and, in some cases (entries 25 and 26), it even makes the reaction stereospecific.

However, the stereoselectivity of the conjugate 1,4-addition of amines to esters of α,β-unsaturated carboxylic acids is influenced most strongly by the geometric isomerism in the initial esters. It has been shown that, despite the fact that isomeric ethyl esters are characterised by the same (*R*)-configuration at the Cγ atoms, the *trans*-isomer reacts with benzylamine non-stereoselectively (reaction 3), whereas the reaction of the *cis*-isomer is highly stereoselective (reaction 4); the absolute configuration at the β-carbon atom in diastereomer **C**, formed as the major product, is opposite to that in diastereomer **B**.[15]



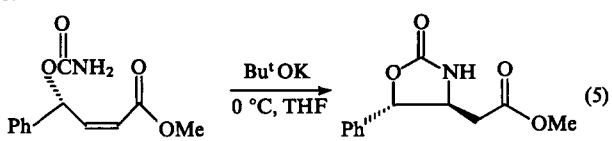
B (37%, d.e. < 5%)



C (48%, d.e. = 94%)

A similar picture has been observed when 1,4-addition has been carried out with lithium amides: the β-amino esters formed are characterised by the opposite configuration at the β-carbon atom.[44, 52, 53, 65] In this case, the stereoselectivity of the process depends to a lesser degree on the geometry of the initial ester (see Table 3, entries 42 and 43).

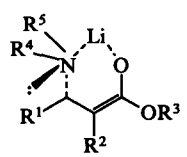
It should be specially noted that the intramolecular addition of the ω-amino-group, incorporated in the substituent at the asymmetric Cγ atom, to a double bond (reaction 5) is stereospecific.[66, 67]



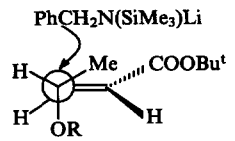
(75%, d.e. = 100%)

Apparently, the high degree of diastereoselectivity observed in reactions (4) and (5) is due to the appearance of steric restrictions hampering the attack of the nucleophile from one of the sides of the substrate.

Unlike amines, lithium amides react with α,β-unsaturated esters with high degrees of diastereoselectivity (see Table 3); only one of all the possible diastereomers is often formed. The stereoselectivity of these reactions can be accounted for by the fact that, due to the high ability of lithium cation to participate in coordination, the formation of a six-membered transition state is favourable and, consequently, the nucleophile adds predominantly from one side of the substrate.

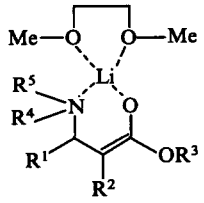


Bulky chiral substituents located in the γ-position with respect to the carbonyl group of the ester also increase the stereoselectivity of the addition. For example, it has been suggested[46] that the addition of lithium benzyl(trimethylsilyl)amide to butyl esters of silyl-substituted acrylic acids (entries 51 – 54 in Table 3) from the sterically hindered side is impossible.



However, neither the size of the group located in the β-position, nor the nature of the substituent in the α-position, nor the size of the ester group has a noticeable influence on the stereoselectivity of the addition of lithium amides to esters of α,β-unsaturated carboxylic acids.

In solvents such as THF and DME, which are capable of forming chelates with the β-aminoenolate produced during the reaction, the selectivity of conjugate addition is higher (d.e. = 90% – 91%) than that in toluene (d.e. = 50%) (Table 3, entries 36, 37, and 40).[44]

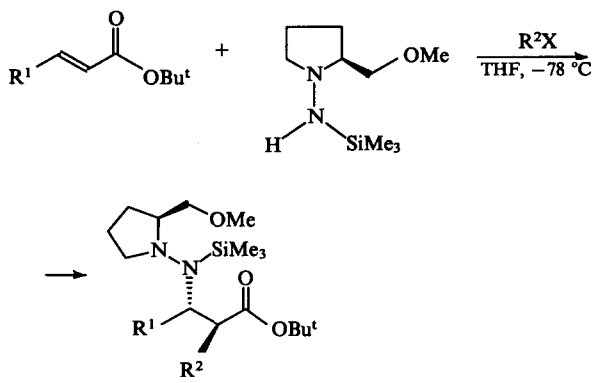


Unlike the products of simple addition of metal amides to a double bond, α-alkyl-β-amino esters resulting from the tandem 1,4-addition and simultaneous α-alkylation contain two asymmetrical centres at the α- and β-carbon atoms of the ester and are formed as mixtures of diastereomers with relatively low d.e. values. Only in some cases has stereospecific reaction been accomplished (Table 4, entries 2 and 3).

The reaction of lithium piperidide with *tert*-butyl α-naphthoate in the presence of methyl iodide as an alkylating agent occurs non-stereoselectively yielding a fairly large amount (32%) of a side product, α-naphthamide, whereas the similar reaction involving α- and β-naphthyloxazolines is stereospecific and affords no side products.[68] It is noteworthy that lithium benzyl(α-phenylethyl)amide does not react with *tert*-butyl α-naphthoate under these conditions.

High stereoselectivity in the tandem reaction can be achieved by using magnesium benzyl(α-phenylethyl)amide as the nucleophile. This leads not only to an increase in the diastereomeric excess (from 15% to 90%) compared to that attained with the corresponding lithium amide (see Table 4, entry 15), but also to the change in the absolute configuration of the asymmetric centre arising at the α-carbon atom in the ester.[62]

If the substituent R^1 at the β-carbon atom in the initial *tert*-butyl ester is an aliphatic group, the diastereomeric excesses obtained in the reactions of these esters with (*S*)-(–)-2-methoxymethyl-1-trimethylsilylaminopyrrolidine are 63%–96%. In the case where R^1 is an aromatic substituent, the interaction is stereospecific (d.e. >96%).[69]



The reactions of tandem addition with simultaneous α-hydroxylation occur with high diastereoselectivity (d.e. = 75%–99%), except for the interaction of (*R*)-benzyl(α-phenylethyl)amine with *tert*-butyl γ-phenylcrotonate (Table 5, entry 9). Apparently, this is due to the presence of steric restrictions hampering the interaction of the (*R*)-isomer with the above substrate.[33]

Thus, it follows from the analysis of the published data that the nature of the substituent in the substrate molecule is the main factor influencing the chemical yield in the conjugate addition of amines to esters of α,β-unsaturated carboxylic acids, whereas the geometry of the initial ester is the main factor determining the stereoselectivity of the process. The diastereomeric excess obtained in these reactions does not usually exceed 60% (Table 1). In the case where the reactions involve lithium amides, both the chemical yield and the stereoselectivity depend mostly on the geometry of the ester as well as on the solvent and the character of the protonating agent used.

In conclusion, it should be noted that at present, the addition of metal amides to esters of α,β-unsaturated carboxylic acids is the method of choice for the asymmetric synthesis of esters of β-amino acids. The most significant progress in this field of research has been achieved by a group of English scientists headed by S. Davies (Oxford).[13,35–41,43,48,49,54–58,62]

V. Mathematical modelling of structures of the transition states in the Michael nucleophilic addition

The stereochemical outcome of the conjugate addition of amines or lithium amides to esters of α,β-unsaturated carboxylic acids can be reliably predicted in some cases by virtue of molecular mechanics modelling of the structure of the transition state of the process.[48,70] In the modelling, the tetrahedral angle of the attack and the $N-C_\beta$ bond length in the transition state are taken fixed (it should be noted that variation of the angle of the attack by a nucleophile has no substantial influence on the final stereochemical outcome of the process[48]). It is believed that the $H-N...C_\beta-C_\alpha$ torsional angle is the main factor determining the stereochemistry of the reaction (if lithium amide is used, the position of the proton is occupied by the unshared electron pair at the nitrogen atom). The depths of the minima in the plot of the transition state energy versus the magnitude of the torsional angle are mostly determined by the spatial arrangement of the alkyl radicals in the nucleophile and by their structures. The natures of the substituents in the ester group and in the β-position with respect to the carbonyl group in the substrate and their mutual arrangement are also significant. In addition, in the reactions involving lithium amide, the possibility of chelate formation (the lithium atom can fix the structure of the transition state) should also be taken into account. A lower energy of the transition state corresponding to a particular minimum means that the probability of the formation of this transition state is greater.

The use of the energies of the transition states corresponding to minima in the calculation of Boltzmann distribution makes it possible to predict with high accuracy the ratio between the diastereomers of β-amino esters formed in the reaction; however, this is true only for kinetically controlled processes.[70] An increase in the difference between the energies of the transition states for the minima results in an increase in the stereoselectivity of conjugate addition. The absolute configuration of the reaction product depends on the structure of the most probable transition state.

The efficiency of this method has been demonstrated in relation to the reactions of azepine **2** and its lithium derivative with methyl crotonate[70] and the reaction of lithium benzyl(α-phenylethyl)amide with *tert*-butyl cinnamate.[48]

Thus, despite the fact that the systems in question are very complex and, therefore, the number of assumptions (based on analysis of empirical features) is large, mathematical modelling of transition states can be used to predict the stereochemical outcome of the conjugate addition of amines or lithium amides to esters of α,β-unsaturated carboxylic acids.

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