Asymmetric titanium-catalysed Michael addition of *O*-benzylhydroxylamine to α,β-unsaturated carbonyl compounds: synthesis of β-amino acid precursors

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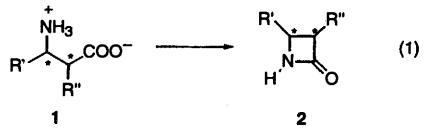
A new titanium-catalysed Michael type addition of *O*-benzylhydroxylamine to α,β-unsaturated *N*-acylated 1,3-oxazolidinones giving β-amino acid precursors has been developed. The reaction is catalysed by TiX_2–TADDOLate and $TiCl_2$–BINOLate complexes and good conversions with enantiomeric excesses up to 42% were obtained with the application of 10 mol% of the catalyst. In order to determine the absolute stereochemistry of the enriched enantiomer one of the products, 3-(3-benzyloxyaminobutanoyl)-1,3-oxazolidin-2-one, was converted into methyl 3-benzoylaminobutanoate. Based on the absolute stereochemistry of the Michael type addition product the mechanism for the addition step is discussed, as well as the structure of the active intermediate.

Introduction

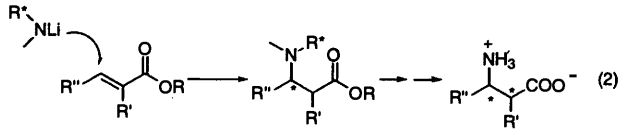
During the last half decade, interest in the synthesis of enantiomerically pure β-amino acids **1** has markedly increased.[1,2] The presence of optically active β-amino acids in peptides and the interesting pharmacological activity in their free form, including their easy conversion into the analogous β-lactams **2** [eqn. (1)],[3–5] make these molecules good targets for the organic chemist.



(1)

1 **2**

Among the most usual approaches to the enantioselective synthesis of asymmetric β-amino acids **1** is the Michael type addition of optically active lithium amides to α,β-unsaturated esters **3** [eqn. (2)]. These procedures, which especially have been



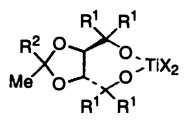
(2)

3 **1**

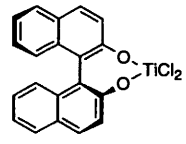
developed by Davies *et al.*, give high diastereoisomeric excesses.[6]

Enders *et al.* have developed a related reaction where (*S*)-2-methoxymethyl-1-trimethylsilylaminopyrrolidine (TMS-SAMP) is used as a chiral ammonia equivalent. After deprotection, the β-amino acid analogous with diastereoisomeric excesses of 90–98% were obtained.[7–9] Other approaches include the Michael addition of achiral amines or amides to asymmetric α,β-unsaturated acid derivatives.[10–12] Achiral Lewis acid-catalysed Michael addition of benzyloxyamine to chiral α,β-unsaturated carbonyl-containing compounds (imides) has recently been described by Cardillo *et al.*[13] The Lewis acids tested were mainly $TiCl_4$ and $AlCl(Me)_2$ and the two diastereomeric products were formed in ratios ranging from 55:45 to 89:11.

All the previously mentioned procedures require at least 1 molar equivalent of the enantiopure reagent. This paper presents an attempt to perform enantioselective addition of an amino functionality to an α,β-unsaturated carbonyl compound using the chiral Lewis acids such as the TiX_2–TADDOLates **4a–f** and $TiCl_2$–BINOLate **5** as the catalyst. The use of these titanium complexes as asymmetric catalysts have previously shown excellent properties for cycloadditions such as the Diels–Alder reactions[14] and the 1,3-dipolar cycloaddition of alkenes with nitrones.[15,16]



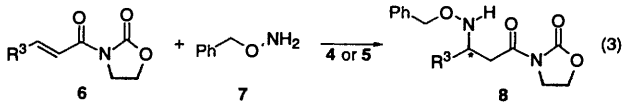
4 (TiX_2-TADDOL)



5 ($TiCl_2$-BINOL)

a R^1 = 3,5-$Me_2C_6H_3$, R^2 = Me X = Cl
b R^1 = Ph, R^2 = Me X = Cl
c R^1 = Et, R^2 = Me X = Cl
d R^1 = C_6H_4Ph, R^2 = Me X = Cl
e R^1 = Ph, R^2 = Ph X = Cl
f R^1 = Ph, R^2 = Me X = OTf

The substrates for these Michael type additions catalysed by complexes **4a–f** and **5** are the alkenoyl-1,3-oxazolidin-2-ones **6a–c** which react with *O*-benzylhydroxylamine **7** to form the Michael-addition product **8** [eqn. (3)]; this can be converted easily into the corresponding β-amino acid.



(3)

6 **7** **8**

a R^3 = Me
b R^3 = Pr
c R^3 = Ph

a R^3 = Me
b R^3 = Pr
c R^3 = Ph

Results and discussion

The results for the reaction of 3-[(*E*)-but-2-enoyl]-1,3-oxazolidin-2-one **6a** with *O*-benzylhydroxylamine **7** in the presence of complexes **4a–f** and **5** are presented in Table 1 (for experimental details see Experimental section).

The results in Table 1 show that the complexes **4a–e** and **5** in general catalyse the reaction of 3-[(*E*)-but-2-enoyl]-1,3-

Table 1 The results for the reaction of 3-[(*E*)-but-2-enoyl]-1,3-oxazolidin-2-one **6a** with *O*-benzylhydroxylamine **7** in the presence of the complexes **4a–f** and **5** as catalysts

Entry	Catalyst (mol%)	Temp. (°C)	Conv.[a,b] (%)	Ee[a] (%)
1[c]		0	5	—
2	**4a** (10)	0	54	31
3	**4b** (10)	0	69	29
4	**4c** (10)	0	36	0
5	**4d** (10)	0	59	22
6	**4e** (10)	0	35	16
7	**4f** (10)	0	100	28
8	**4f** (10)	−20	100	28
9	**5** (10)	0	9	35

[a] All values are based on at least two experiments. The uncertainties of the ee values are less than ±3. [b] The conversions were determined from ^{1}H NMR spectra of the crude products. [c] This reaction was performed at RT in 24 h.

oxazolidin-2-one **6a** with *O*-benzylhydroxylamine **7** at 0 °C giving the addition product **8a** at a conversion of 35–70% (entries 2–6, 9); note that the uncatalysed reaction leads to a product yield of only 5% after 24 h at room temperature (RT) (entry 1). The enantiomeric excesses (ee's) are generally *ca.* 20–35%, with the exception of the reaction performed in the presence of the catalyst **4c** which gives an ee of 0% (entry 4). The latter catalyst has an alkyl substituent (ethyl) in the α-positions to the alkoxy-oxygen atoms whilst the former has an α-aromatic substituent. It should be noted that similar reduction in ee has been observed in TiX_2–TADDOLate catalysed cycloadditions when the aromatic substituent is exchanged with an alkyl substituent.[15] By the replacement of the chloride ligands on the titanium atom in catalyst **4b** with triflate ligands, **4f**, an increase in reactivity is observed. The reaction in the presence of 10 mol% of **4f** at 0 °C and −20 °C gives 100% conversion according to ^{1}H NMR spectroscopy of the crude reaction mixture with an ee of 28% in both cases (entries 7,8). In all the reactions a high conversion is observed immediately after the addition of **7**, after which the catalytic effect either decreases or vanishes, presumably due to a competing reaction in which **7** inhibits the catalyst. This proposed competing reaction is defeated when the chloride ligands are replaced by triflates. Furthermore, a small amount (<5%) of a by-product shown by analysis to be the product of the replacement of the oxazolidinone in **8a** with a benzyloxyamine is observed. The fact that the Michael addition does proceed to some degree in the absence of a catalyst raises the question as to whether the catalysed reaction product will be contaminated with some product formed without catalysis and thereby reducing the enantiomeric induction. Particularly during the work-up, the unchanged starting materials might react upon evaporation of solvent. If this is so, in practice, a slight increase in reaction yield and a slight decrease in the ee's compared to the pure catalysed reaction will be observed.

Replacement of chloride ligands with triflates increases the reaction rate and, thereby, the conversion remarkably. This must be due to an increase in the Lewis acidity of the catalyst. Nevertheless, the ee is independent of the temperature in the temperature interval explored, and the ee is similar to the ee obtained with the catalyst bearing the chloride ligands (Table 1, entries 3, 8, 9), indicating that the triflate ligands do not change the steric environments at the reaction site in the transition state.

In Table 2 the results of the reaction of the alkenes **6b** and **6c** with *O*-benzylhydroxylamine **7** in the presence of **4b** or **4f** as the catalyst are presented. A high degree of conversion is generally observed. For the alkene **6b** two experiments at RT and −20 °C, respectively were performed. Similar to the experiments described above, no significant change in enantioselectivity was observed when the reaction temperature was lowered (entries 2, 3). This was also observed for reactions using **6c** as the alkene.

Table 2 The results for the reactions of 3-[(*E*)-hex-2-enoyl]-1,3-oxazolidin-2-one **6b** and 3-(*E*)-cinnamoyl-1,3-oxazolidin-2-one **6c** with *O*-benzylhydroxylamine **7**, in the absence and presence of the catalysts **4b** and **4f**

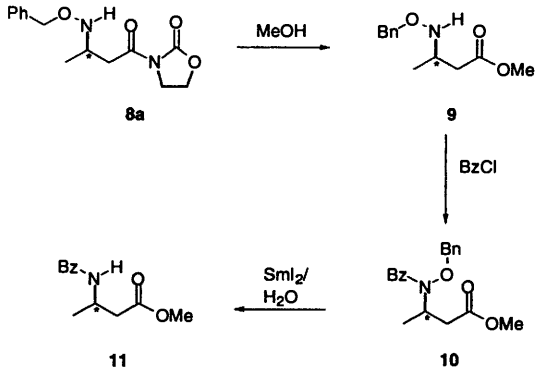
Entry	Alkene	Catalyst (mol%)	Temp. (°C)	Conv.[a,b] (%)	Ee[a,c,e] (%)
1[d]	**6b**	—	RT	5	—
2	**6b**	**4f** (10)	RT	94	35
3	**6b**	**4f** (10)	−20	90	30
4[d]	**6c**	—	RT	0	—
5	**6c**	**4b** (10)	RT	10	Nd
6	**6c**	**4f** (10)	RT	69	42
7	**6c**	**4f** (10)	0	63	37
8	**6c**	**4f** (10)	−20	<5	Nd

[a] All values are based on at least two experiments. The uncertainties of the ee values are less than ±6. [b] The conversions were determined from ^{1}H NMR spectra of the crude products. [c] The ee's of the rections for entries 5 and 8 were not determined. [d] This reaction was performed at RT in 24 h. [e] Nd = not determined.

Reactions performed at RT and 0 °C gave comparable ee's 42 and 37%, respectively. Of special interest is the fact that the treatment of **6c** with **7** at RT in the absence of a catalyst afforded no product and that the same reaction in the presence of catalyst **4b** gave only 10% conversion (entries 4, 5), while using **4f** as a catalyst gave 69% conversion (entry 6). This also indicates that the replacement of chloride ligands with triflate increases the Lewis acidity of the titanium complex.

The replacement of the methyl substituent in **6a** with a propyl substituent, **6b**, did not alter the reactivity or stereoselectivity of the reaction, whereas substitution with a phenyl substituent, **6c**, decreases the reactivity, but gives rise to a slight increase in ee (entries 6, 7).

In an attempt to obtain information about the mechanism for the addition step the absolute stereochemistry of the enriched enantiomer in the reaction product **8a** was achieved by its transformation to methyl 3-benzoylaminobutanoate **11**. In all the reactions leading to **8a** with ee, the dominant enantiomer was the same. The first step in this transformation is treatment of **8a** with MeOH giving the methyl ester **9** (64%). In the next reaction the nitrogen atom is benzoylated with BzCl giving **10** (65%). Methyl 3-benzoylaminobutanoate **11** is obtained in good yield by reduction with SmI_2.[17,18] The transformations are outlined in Scheme 1.



Scheme 1

The configuration at the β-carbon atom of the most abundant enantiomer of **11** was by comparison with the literature found to be *S*.[13] This means that the *O*-benzylhydroxylamine **7** is predominantly approaching the alkene β-carbon atom in **6a** from the *si*-face.

The catalytic effect is presumed to rise from the bidentate coordination of the *N*-acyloxazolidinone to the titanium centre which will then be hexacoordinated. Theoretically one can imagine five different complexes in one of which the two chlor-

ide ligands are *trans* and in four of which the chloride ligands are *cis*. In recent publications the nature of the active intermediate is discussed.[16,19–21] With the relatively low ee's described in this paper it is hard to draw any conclusion as to whether the reaction proceeds *via* one of the five intermediate complexes or *via* some of them or all of them.

Conclusion

A new Michael type addition of *O*-benzylhydroxylamine to α,β-unsaturated *N*-acylated-1,3-oxazolidinones catalysed by TiX_2–TADDOLate **4** and TiX_2–BINOLate **5** complexes has been developed. The reaction proceeds well with high conversions, especially with the $Ti(OTf)_2$–TADDOLate complexes as the catalyst, and affords moderate ee. The α,β-unsaturated *N*-acylated 1,3-oxazolidinone substrates can have both alkyl and aromatic substituents. The addition product can easily be transformed into the corresponding *N*-benzoylated β-amino acid methyl ester by treatment with first MeOH, followed by reaction with benzoyl chloride and reduction with SmI_2. The absolute stereochemistry of the *N*-benzoylated β-amino acid methyl ester indicates an attack of the *O*-benzylhydroxylamine on the β-carbon atom from the *si*-face of the alkene which is coordinated to the asymmetric titanium catalyst. The moderate ee can, to a certain extent, be accounted for by the relatively small size of the attacking nucleophile.

Experimental

General methods

The ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively on a Varian Gemini 300 instrument, IR spectra on a Perkin-Elmer FT-IR spectrometer PARAGON 1000 and mass spectra on a Micromass 7070F mass spectrometer and GC-MS on a Trio-2 spectrometer. Chemical shifts for ^1H NMR and ^{13}C NMR are reported in ppm downfield from tetramethylsilane (TMS). HPLC analysis was performed using 4.6 mm × 25 cm DAICEL CHIRALCEL OD and DAICEL CHIRALPAK AD columns. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Flash chromatography was performed using silica gel 60 (particle size 0.040–0.063 mm, Merck). Solvents were dried using standard procedures. The 4 Å molecular sieves were activated by heating to 250 °C for 3 h in high vacuum. All glass equipment and syringes were dried in an oven at 130 °C prior to use.

The starting materials **6a–c** and the chiral TADDOL ligands in the catalysts **4a,c–e** were synthesized according to the literature.[22] The BINOL and the TADDOL ligands in catalysts **4b,f** and **5** were obtained from Aldrich. *O*-Benzylhydroxylamine was obtained from the hydrochloride salt (Aldrich) by dissolving this in 2 M aqueous NaOH, extracting the solution with CH_2Cl_2 and drying ($MgSO_4$) the extract.

General procedure for the reaction of alkenoyl-1,3-oxazolidin-2-ones 6a-c and *O*-benzylhydroxylamine 7 in the presence of the TiX_2–TADDOLates 4a–f and $TiCl_2$–BINOLate 5 catalysts

To a 0.1 M solution in toluene of $TiCl_2(OPr^i)_2$ (0.1 ml, 0.01 mmol) was added the ligand (TADDOL or BINOL; 0.012 mmol). The mixture was stirred for 30 min and then diluted with toluene (0.4 ml). [For catalysts bearing triflate groups, AgOTf (2 equiv.) was added at this point, and the slurry was filtered after 5 min of stirring]. Molecular sieves and the alkene **6a–c** (0.1 mmol) were added and the mixture was brought to the desired temperature. A 0.3 M solution of *O*-benzylhydroxylamine in toluene (0.5 ml, 0.15 mmol) was added over 30 min. The mixture was kept at the desired temperature for 2 h after which the mixture was directly transferred to a pipette column (silica gel) for filtration and elution with Et_2O. The product was purified on a small pipette column with gradient elution system; 100% CH_2Cl_2–0.5% MeOH in CH_2Cl_2. The following HPLC conditions were applied: **8a**: AD column, 15% Pr^iOH in hexane, **8b**: AD column, 10% EtOH in hexane, and **8c**: OD column, 10% Pr^iOH in hexane.

3-(3-Benzyloxyaminobutanoyl)-1,3-oxazolidin-2-one, 8a. ν_{max}(film)/cm^{-1} 1698 and 1778; δ_H 1.16 (d, *J* 6.6, 3 H, CH_3), 2.87 (dd, *J* 4.4, 16.5, 1 H, CHCH*H*), 3.21 (dd, *J* 7.7, 16.5, 1 H, CHC*H*H), 3.6 (m, 1 H, CH), 3.75 (m, 2 H, NCH_2CH_2O), 4.16 (m, 2 H, NCH_2CH_2O), 4.65 (s, 2 H, $PhCH_2$), 5.80 (s, 1 H, NH) and 7.13–7.32 (m, 5 H, Ph); δ_C 18.0, 39.2, 42.0, 52.7, 61.6, 76.2, 127.5, 128.0, 128.1, 137.5, 153.3 and 171.7; *m/z* 278.127 ($C_{14}H_{18}N_2O_4$ requires 278.1266), 191 (49%) and 150 (100%).

3-(3-Benzyloxyaminohexanoyl)-1,3-oxazolidin-2-one, 8b. ν_{max}(film)/cm^{-1} 1695 and 1780; δ_H 0.85 (t, *J* 6.9, 3 H, CH_3), 1.28–1.52 (m, 4 H, $CH_3CH_2CH_2$), 2.85 (dd, *J* 3.9, 16.0, 1 H, CHCH*H*), 3.18 (dd, *J* 8.6, 16.0, 1 H, CHC*H*H), 3.37–3.45 (m, 1 H, CH), 3.64–3.80 (m, 2 H, NCH_2CH_2O), 4.09–4.23 (m, 2 H, NCH_2CH_2O), 4.57 (s, 2 H, $PhCH_2$), 5.8 (br s, 1 H, NH) and 7.21–7.31 (5, Ph); δ_C 14.1, 19.3, 34.4, 38.1, 42.4, 57.5, 61.8, 76.3, 127.7, 128.2, 128.5, 137.7, 153.6 and 172.5; *m/z* 306.158 ($C_{16}H_{22}N_2O_4$ requires 306.1579), 264 (16%), 220 (98%) and 205 (100%).

3-(3-Benzyloxyamino-3-phenylpropanoyl)-1,3-oxazolidin-2-one, 8c. ν_{max}(film)/cm^{-1} 1699, 1780; δ_H 3.30 (dd, *J* 4.9, 16.5, 1 H, CHCH*H*), 3.58 (dd, *J* 8.5, 16.5, 1 H, CHC*H*H), 3.80–3.87 (m, 2 H, NCH_2CH_2O), 4.24–4.31 (m, 2 H, NCH_2CH_2O), 4.61–4.66 (m, 3 H, CH and $PhCH_2$), 6.2 (br s, 1 H, NH), 7.25–7.43 (10, Ph and $PhCH_2$); δ_C 39.4, 42.4, 61.5, 62.0, 76.5, 127.7, 127.8, 128.0, 128.3, 128.5, 137.4, 139.8, 153.5 and 171.3; *m/z* 341 (11%), 254 (9%), 218 (72%) and 212 (100%).

Methyl 3-benzyloxyaminobutanoate 9. 3-(3-Benzyloxyaminobutanoyl)-1,3-oxazolidin-2-one **8a** (195.5 mg, 0.574 mmol) with an ee of 30% was refluxed in MeOH for 3 d. Purification on silica-gel flash column with 80% Et_2O in light petroleum afforded the methyl ester as a thick oil (64%, 81.5 mg, 0.365 mmol). The ee of the product was analysed by HPLC on the OD column with 8% Pr^iOH in hexane as the eluent and was found to be maintained (30%); ν_{max}(film)/cm^{-1} 1734; δ_H 1.12 (d, *J* 6.6, 3 H, CH_3CH), 2.37 (dd, *J* 5.8, 16.0, 1 H, CHCH*H*), 2.60 (dd, *J* 7.2, 16.0, 1 H, CHC*H*H), 3.48 (m, 1 H, CH), 3.64 (s, 3 H, CH_3O), 4.69 (s, 2 H, $PhCH_2$), 5.72 (s, 1 H, NH) and 7.25–7.35 (m, 5 H, Ph); δ_C 17.9, 38.5, 51.4, 52.9, 76.5, 127.7, 128.2, 137.7 and 172.5; *m/z* 223.121 ($C_{12}H_{17}NO_3$ requires 223.1208), 191 (60%) and 150 (71%).

Methyl 3-(*N*-benzoyl-*N*-benzyloxyamino)butanoate 10. Enantio-enriched (ee = 30%) ester **9** (81.4 mg, 0.37 mmol) was dissolved in THF at RT. Pyridine (2 equiv., 0.74 mmol, 59 μl) was added to the mixture followed by benzoyl chloride (1.5 equiv., 0.56 mmol, 70 μl), added dropwise. The mixture was stirred for 0.5 h to give, after flash chromatography, (50% Et_2O–light petroleum) the benzoylated product (77.2 mg, 65%). The ee of the product, analysed by HPLC on the OD column with 10% Pr^iOH in hexane as the eluent, was found to be maintained (30%); ν_{max}(film)/cm^{-1} 1652 and 1738; δ_H 1.33 (d, *J* 6.6, 3 H, CH_3), 2.52 (dd, *J* 6.0, 15.7, 1 H, CHCH*H*), 2.88 (dd, *J* 8.3, 15.7, 1 H, CHC*H*H), 3.66 (s, 3 H, OCH_3), 4.73–4.81 (m, 3 H, $PhCH_2$ and CH) and 7.19–7.66 (m, 10 H, $PhCH_2$ and Bz); δ_C 18.4, 38.1, 51.7, 53.0, 78.2, 127.9, 128.1, 128.3, 128.7, 129.4, 130.5, 134.5, 134.9, 171.3 and 171.3; *m/z* 327 (50%), 396 (100%) and 254 (100%).

Methyl 3-benzoylaminobutanoate 11.[13] To a solution of the enantio-enriched (ee = 30%) ester **10** (77.3 mg, 0.24 mmol) in THF was added water (1 equiv.). This was followed by a 0.1 M THF solution of SmI_2 (2 equiv., 0.48 mmol, 4.8 ml), prepared from the overnight reflux of I_2 and Sm in THF. After 2 min the reaction was complete and the ee of the product was analysed by HPLC on the OD column with 10% Pr^iOH in hexane as the eluent; the ee was found to be maintained (30%). The optical rotation was found to be negative; δ_H 1.34 (d, *J* 7.2, 3 H, CH_3), 2.61 (dd, *J* 4.4, 16.0, 1 H, CHCH*H*), 2.68 (dd, *J* 5.5, 16.0, 1 H, CHC*H*H), 3.72 (s, 3 H, OCH_3), 4.54–4.62 (m, 1 H, CH), 6.97

(d, J 8.3, 1 H, NH), 7.40–7.52 (m, 3 H, Ph-*m*, -*p*), 7.78 (d, J 6.6, 2 H, Ph-*o*); δ_C 20.0, 39.5, 42.2, 51.8, 126.9, 128.5, 131.4, 134.5, 166.5 and 172.5.

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