Lewis Acid-Promoted 1,4-Addition to Chiral Imide Derivatives in the Synthesis of β-Amino Acids

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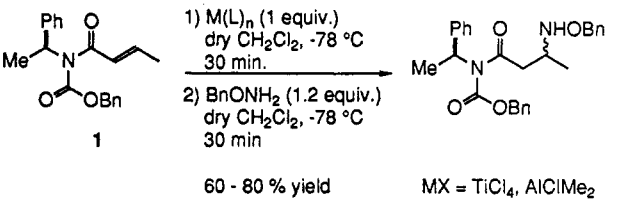
The 1,4-addition of *O*-benzylhydroxylamine to imides **3** in the presence of various Lewis acids is described. The reaction is performed in CH_2Cl_2 at −78 °C and affords derivatives **4** and **5** in good chemical yields and in different diastereomeric ratios, depending on the Lewis acid employed. $TiCl_4$ and Me_2AlCl give opposite diastereoselectivities. Furthermore, enantiomerically pure β-amino acid **9** is obtained in good yield from compound **4a**.

Recently, we have been interested in methods for the synthesis of polyfunctionalized sequences with high regio- and stereocontrol[1] and in the use of these methods for preparing enantiomerically pure polyols, amino alcohols, and diamines, which are useful intermediates in the synthesis of complex molecules. In our last few papers, we disclosed our results on the synthesis of α- and β-hydroxy acids[2] and α- and β-amino acids.[3] The synthesis of β-amino acids has been receiving more and more attention because these compounds represent useful starting materials for the preparation of naturally occurring macrolides[4] and β-lactam antibiotics.[5]

Among the strategies for the synthesis of enantiomerically pure β-amino acids,[6] diastereoselective 1,4-additions of chiral amines to α,β-unsaturated esters[7] and additions of amines to chiral α,β-unsaturated acyl derivatives[8] have attracted much interest. Recently, the lithium amide derived from (*R*)-*N*-(α-methylbenzyl)benzylamine has been used as a synthetic equivalent in a Michael addition to benzyl crotonate; the addition occurs with 95% de and gives after debenzylation, the (−)-(*R*)-3-aminobutanoic acid.[9]

To introduce the C–N bond, instead of increasing the nucleophilicity of the amine by utilizing the corresponding metal amide,[10] we sought to enhance the reactivity of the electrophilic substrate by using a Lewis acid as an activating agent and the *O*-benzylhydroxylamine as a nucleophile. Lewis acids promote numerous reactions, including Diels–Alder reactions, ene reactions, alkylations, aldol condensations, Michael addition, Claisen rearrangements, and the reactions of acetals and unsaturated ethers.[11] Furthermore hydroxylamines have been found to be efficient nucleophiles for additions to α,β-unsaturated acids in refluxing alcohol for the synthesis of racemic β-amino acids.[12]

In a modification of this reaction, we added *O*-benzylhydroxylamine to the crotonimide of (*S*)-phenylethylamine **1** in the presence of a Lewis acid. The reaction occurred smoothly in CH_2Cl_2 at −78 °C in 30 min and in good yield. On the contrary, when the reaction was performed in the absence of a Lewis acid, no addition product was observed.



1 60 - 80 % yield MX = $TiCl_4$, $AlClMe_2$

Unfortunately, upon reaction of **1** with various Lewis acids and *O*-benzylhydroxylamine in CH_2Cl_2, a 1:1 diastereomeric mixture of (*S*,*S*)- and (*S*,*R*)-derivatives was obtained.

It is well known that the use of chiral heterocycles in diastereoselective synthesis leads to significant levels of asymmetric induction.[13] Accordingly, the use of the

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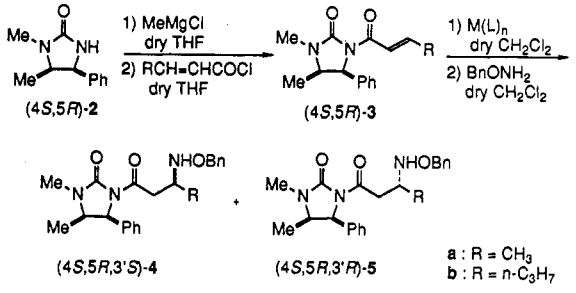
Table I. Ratios of the Diastereomeric Products of the 1,4-Addition of *O*-Benzylhydroxylamine to the Imides 3a and 3b

entry	R	$M(L)_n$ (no. equiv)	total yield (%)	diastereomer percent[a] 4	5
1	CH_3	$ZnCl_2$ (1)	92	55	45
2	CH_3	$TiCl_4$ (1)	80	80	20
3	n-C_3H_7	$TiCl_4$ (1)	90	77	23
4	n-C_3H_7	$TiCl_2(O\text{-}iPr)_2$ (1)	38	50	50
5	CH_3	$AlCl(Me)_2$ (1)	65	26	74
6	CH_3	$AlCl(Me)_2$ (1.4)	65	19	81
7	CH_3	$AlCl(Me)_2$ (2)	70	20	80
8	n-C_3H_7	$AlCl(Me)_2$ (1.4)	81	13	87
9	n-C_3H_7	$AlCl(Me)_2$ (2)	83	11	89

[a] Product ratios were determined on crude product mixtures by means of ^1H and ^{13}C NMR.

N-crotonyl derivatives of (*S*)-4-benzyloxazolidin-2-one and of (4*S*,5*R*)-4-methyl-5-phenyloxazolidin-4-one[14] as starting materials was explored. These chiral heterocycles were treated with *O*-benzylhydroxylamine in the presence of a Lewis acid. In all the cases tested, good yields of 1,4-addition products were obtained, but the diastereoselectivity of the reaction proved to be low. Better results were achieved with (4*S*,5*R*)-1,5-dimethyl-3-alkenyl-4-phenylimidazolidin-2-ones **3a** and **3b**, prepared in 89% yield from the magnesium salt of (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one[15] and the corresponding α,β-unsaturated acyl chlorides.

Treatment of (4*S*,5*R*)-3-alkenylimidazolidin-2-one **3** with *O*-benzylhydroxylamine in dry CH_2Cl_2 in the presence of the Lewis acid furnished an easily separable diastereomeric mixture of **4** and **5** in good chemical yield.



Representative results of the additions of *O*-benzylhydroxylamine to **3a** and **3b** in CH_2Cl_2 at −78 °C in the presence of various Lewis acids are listed in Table I.

As shown in Table I, the overall yields of the 1,4-additions are generally good, although the stereoselectivity strongly depends upon the Lewis acid. Zinc chloride gives a 92% yield with very low diastereoselectivity (entry 1). With $TiCl_2(i\text{-}OPr)_2$, the reaction occurs in very low yield and selectivity (entry 4). With $TiCl_4$,[16] both conjugate addition and reaction diastereoselectivity increase, and an 80:20 ratio of **4a**/**4b** (entry 2) and a 77:23 ratio of **5a**/**5b** (entry 3) are obtained. Major product **4a** was separated and crystallized from ethanol, and its X-ray crystal structure determination is shown in Figure 1.

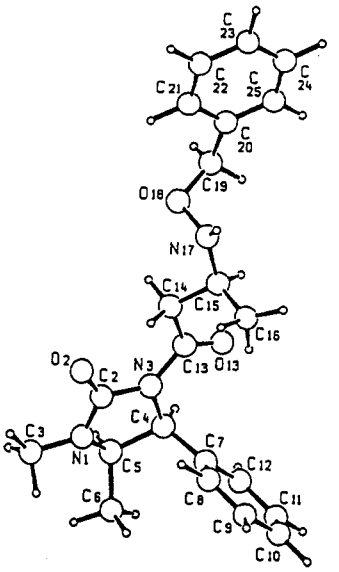


Figure 1. The molecular structure of **4a** showing the atom-numbering scheme.

The *S* configuration at C(15) follows the known configurations at C(4) and C(5), *S* and *R*, respectively, of the heterocycle. The imidazolidin-2-one ring shows puckering with the "envelope" conformation [C(5) ca. 0.33 Å above the least-squares plane passing through the remaining four atoms]. The five-membered ring lies almost coplanar with the phenyl ring bound to C(19) and approximately perpendicular to the phenyl ring bound to C(4) [the dihedral angles between the two pairs of fragments are 6.5° and 82.7°, respectively].[17]

With dimethylaluminum chloride as the Lewis acid and **3a** as the Michael acceptor, the diastereoselectivity of the reaction increases when the amount of Lewis acid is increased from 1 equiv to an excess (26:74 *versus* 19:81) (entries 5 and 6); a further enhancement of selectivity (11:89 **4b**/**5b** ratio) is observed with **3b** (entry 9). The stereochemistry of compounds **4b** and **5b** was assigned by comparison of the ^1H and ^{13}C NMR spectra of compounds **4a**, **4b**, **5a**, and **5b**. These results show that $TiCl_4$ affords facial selectivity opposite to that afforded by Me_2AlCl.

The results obtained with 1.4 or 2 equiv of Me_2AlCl are in agreement with the intermediacy of chelated salt **6**, which is analogous to a chelate proposed by Evans[18a] and Snider.[18b] Nucleophilic attack on aluminum-chelated crotonyl imide derivative **6** would preferably occur from the Cβ-re face of the *S*-cis conformation, resulting in the formation of (4*S*,5*R*,3′*R*)-**5** as the major product.

In an effort to find an explanation for the unexpected reversal of selectivity with $TiCl_4$, we compared the ^1H NMR spectrum of **3a** with the spectra of its complexes with $AlMe_2Cl$ (2 equiv) **6** and $TiCl_4$ (1 equiv) **7**. (The spectra were measured at room temperature and at −60 °C in

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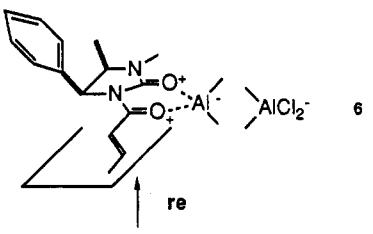

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Figure 2. Diastereofacial selectivity in the 1,4-addition in the presence of $AlMe_2Cl$ (2 equiv).

CD_2Cl_2 (Figure 3)). The ^1H NMR of the complexes, identical at −60 °C and at room temperature, suggest that both metals strongly chelate the two carbonyls of the imide. In fact, the reported preferred conformation of **3a**[19] is in agreement with the value of the chemical shift of H_α (δ 7.5 ppm), which is deshielded by the carbonyl of the heterocycle. On the contrary, both complexes **6** and **7** show H_α to be more shielded (δ 6.0 and 6.2 ppm, respectively); in this conformation, H_α does not appear to suffer the deshielding effect of the heterocyclic carbonyl group.

The ^1H NMR spectrum of the complex of **3a** with only 1 equiv of $AlMe_2Cl$ in CD_2Cl_2 is poorly resolved and shows a complex pattern that changes with temperature (+20 °C to −60 °C). This result establishes that more than 1 equiv of $AlMe_2Cl$ is needed to form a stable complex.

From these data it is difficult to rationalize the inversion of the observed selectivity. This inversion might be ascribed to the differences in metal–oxygen bond lengths and bond angles between the titanium and aluminum complexes. The C–O–Ti bonds in the $TiCl_4$–ethyl *O*-acryloyllactate complex[20] have recently been reported to have bond lengths of 2.109 and 2.13 Å, respectively. Moreover, the chelation of $TiCl_4$ to the ester carbonyls places Ti 48° and 64° out of the carbonyl planes and gives Ti–O–C angles of 132° and 134°, respectively. If these parameters are applied to complex **7** (Figure 4), then the titanium is forced to lie under the plane because of the presence of the bulky phenyl group. This situation forces the acyl chain above the plane, so that the si face is exposed to nucleophilic attack (as shown by structure **7a**).

As an example of the use of **4** and **5** for the synthesis of enantiomerically pure β-amino acids, (+)-(*S*)-3-butanoic acid **9** was obtained by reduction of the N–O bond of **4a** with Zn/Cu couple in acetic acid[21] and subsequent hydrolysis of imidazolidin-4-one **8** under the reaction conditions reported by Evans ($LiOH/H_2O_2$ in THF/water).[22] β-Amino acid **9** was purified on BIORAD AG 50W-X2 cation exchange resin (NH_4OH 1.5 M as eluant) ($[\alpha]_D$ +37.8° (*c* 0.1, H_2O), lit.[23] $[\alpha]_D$ +38.8° (*c* 0.48, H_2O)) and transformed into its *N*-benzoyl methyl ester derivative **10** ($[\alpha]_D$ = −40.8° (*c* 1, $CHCl_3$), lit.[7b] $[\alpha]_D$ = −42.0° (*c* 0.77, $CHCl_3$)).

At present, further work is in progress in order to increase the diastereoselectivity of the 1,4-addition and to accomplish the diastereoselective synthesis of polyfunctionalized acid derivatives.[24]

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts are reported in ppm relative to the solvent peak of $CHCl_3$, defined to be δ 7.27. Infrared spectra were recorded with an FT-IR spectrometer. Melting points were determined in open capillaries and are uncorrected. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh). THF was distilled from sodium benzophenone ketyl. Dry methylene chloride was purchased from Fluka. *O*-Benzylhydroxylamine was obtained from *O*-benzylhydroxylamine hydrochloride and aqueous sodium hydroxide and extracted into methylene chloride.

(4*S*,5*R*)-1,5-Dimethyl-3-alkenoyl-4-phenylimidazolidin-2-one (3). To a stirred solution of imidazolidin-2-one **2**[15] (20 mmol, 3.8 g) in dry THF (40 mL) at 0 °C was added methylmagnesium chloride (20 mmol, 1 M in THF, 20 mL). After 30 min, 2-butenoyl (or 2-hexenoyl) chloride (20 mmol) was added at 0 °C, and the mixture was stirred for 1 h at 25 °C. Water was added, the THF was evaporated, and the mixture was extracted twice with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel with cyclohexane/ethyl acetate 9:1 to afford **3a** (**3b**) in 89% yield.

(4*S*,5*R*)-3a: IR (film) 1721, 1681, 1623 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, 3H, *J* = 6.6 Hz, PhCHCHC*H*$_3$), 1.90 (dd, 3H, *J* = 1.6 Hz, 6.9 Hz, CH=CHC*H*$_3$), 2.84 (s, 3H, NCH_3), 3.91 (dq, 1H, *J* = 6.6 Hz, 8.5 Hz, PhCHC*H*CH$_3$), 5.36 (d, 1H, *J* = 8.5 Hz, PhC*H*CHCH$_3$), 7.01 (dq, 1H, CH=C*H*CH$_3$, *J* = 6.9 Hz, 15.2 Hz), 7.28 (m, 5H, Ph), 7.48 (dd, 1H, *J* = 15.2 Hz, 1.6 Hz, C*H*=CHCH$_3$); ^{13}C NMR ($CDCl_3$) δ 14.9, 18.3, 28.1, 53.9, 59.4, 123.1, 126.9, 127.9, 128.4, 136.7, 144.4, 155.9, 164.7; $[\alpha]_D$ = +67.8° (*c* 1.5, $CHCl_3$); mp 170–172 °C. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.64; H, 7.07; N, 10.78.

(4*S*,5*R*)-3b: IR (film) 1721, 1679, 1623 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, 3H, *J* = 6.6 Hz, PhCHCHC*H*$_3$), 0.92 (t, 3H, *J* = 7.3 Hz, $CH_2CH_2CH_3$), 1.49 (m, 2H, $CH_2CH_2CH_3$), 2.21 (m, 2H, $CH_2CH_2CH_3$), 2.84 (s, 3H, NCH_3), 3.91 (dq, 1H, *J* = 6.6 Hz, 8.5 Hz, PhCHC*H*CH$_3$), 5.35 (d, 1H, *J* = 8.5 Hz, PhC*H*CHCH$_3$), 6.99 (dt, 1H, OCCH=C*H*, *J* = 9.6 Hz, 15.4 Hz), 7.24 (m, 5H, Ph), 7.47 (dt, 1H, *J* = 1.5 Hz, 15.4 Hz, OCC*H*=CH); ^{13}C NMR ($CDCl_3$) δ 13.7, 15.0, 21.4, 28.2, 34.6, 54.0, 59.5, 121.8, 127.0, 128.0, 128.5, 136.7, 149.2; $[\alpha]_D$ = +87.1° (*c* 1.2, $CHCl_3$); mp 130–133 °C. Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.3; H, 7.74; N, 9.78. Found: C, 71.22; H, 7.77; N, 9.84.

1,4-Addition of *O*-Benzylhydroxylamine to (4*S*,5*R*)-1,5-Dimethyl-3-alkenoyl-4-phenylimidazolidin-2-ones 3a and 3b. A solution of 3-acylimidazolidin-2-one **3** (0.3 mmol) in dry CH_2Cl_2 (10 mL) was stirred at −78 °C under argon. The Lewis acid (0.3 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred at −78 °C for 30 min. Then *O*-benzylhydroxylamine (0.36 mmol, 0.12 M solution in CH_2Cl_2, 3 mL) was added dropwise, and the mixture was stirred for an additional 1 h at −78 °C. Then 1 M NaOH solution (20 mL) was added, the mixture was allowed to warm to rt, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate 9:1 for **4a**/**5a** and 95:5 for **4b**/**5b**) and products **4** and **5** were easily separated. (Product **5** was the more-polar one.)

(4*S*,5*R*,3′*S*)-4a: IR (Nujol) 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (d, 3H, *J* = 6.6 Hz, PhCHCHC*H*$_3$), 1.15 (d, 3H, *J* = 6.5 Hz,ONCHC*H*$_3$), 2.80 (s, 3H, NCH_3), 3.04 (dd, 1H, *J* = 4.4 Hz, 16.6 Hz, OCC*H*HCHN), 3.29 (dd, 1H, *J* = 8.2 Hz, 16.6 Hz, OCCH*H*CHN), 3.54 (m 1H, OCCHHC*H*N), 3.76 (dd, 1H, *J* = 6.6 Hz, 8.5 Hz, PhCHC*H*CH$_3$), 4.64 (s, 2H, OCH_2Ph), 5.23 (d, 1H, *J* = 8.5 Hz, PhC*H*CHCH$_3$), 7.31 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.8, 18.3, 28.0, 39.5, 52.8, 53.7, 59.1, 76.4, 126.8, 127.5, 127.9, 128.1, 128.4, 136.5, 137.9, 155.7, 171.2; $[\alpha]_D$ = +70.6° (*c* 1,

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(24) During the course of our work, an independent investigation of the 1,4-asymmetric additions of allyltrimethylsilanes to α,β-unsaturated *N*-acyloxazolidin-4-ones or *N*-enoyl sultams was reported by Wu, M.-J.; Wu, C.-C.; Lee, P.-C. *Tetrahedron Lett.* **1992**, *33*, 2547–2548.

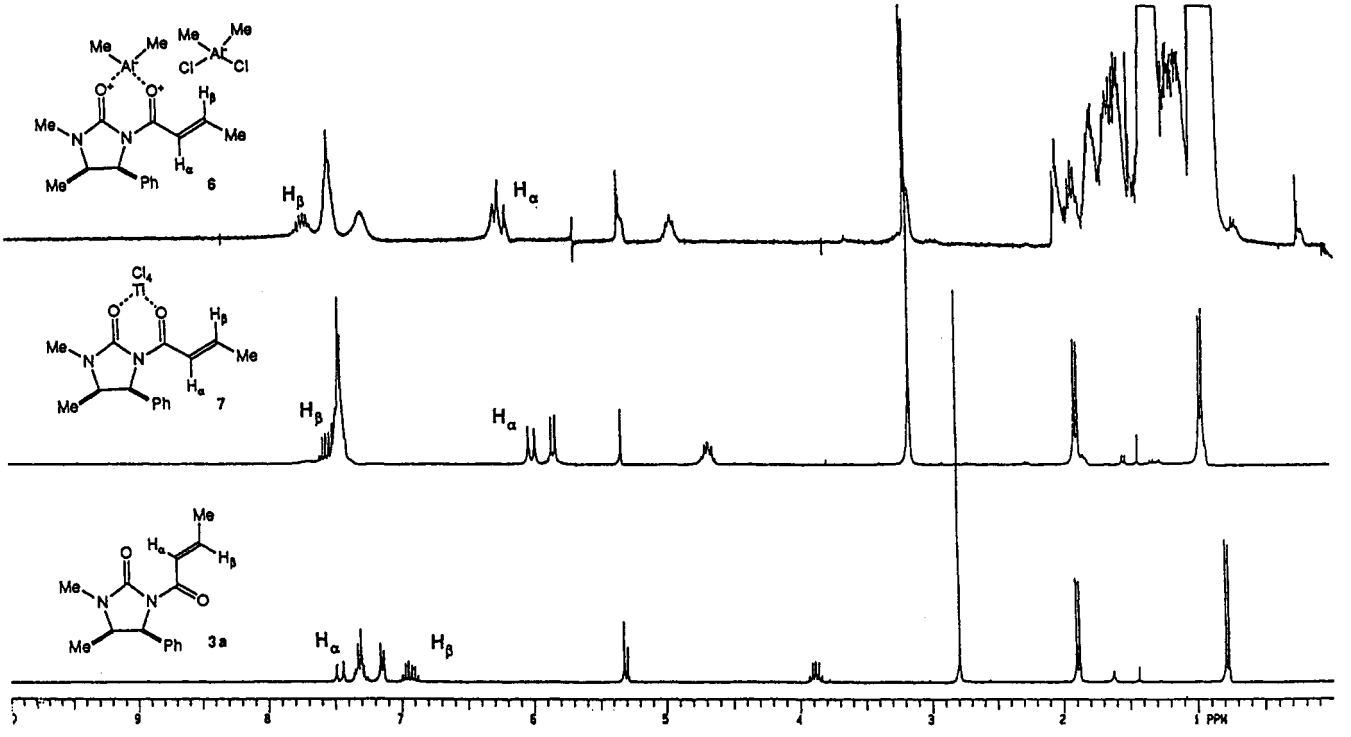


Figure 3. ^1H NMR of **3a** and of its complexes with $AlMe_2Cl$ (2 equiv) **6** and $TiCl_4$ (1 equiv) (**7**) performed at 300 MHz in CD_2Cl_2 at rt under an inert atmosphere. A 1 M solution of $AlMe_2Cl$ in hexanes was used.

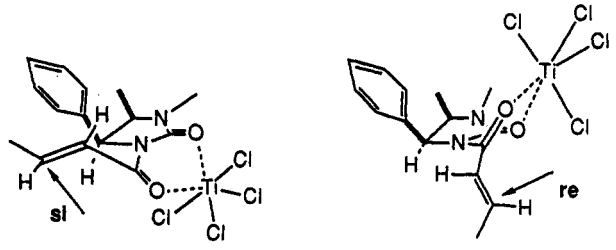
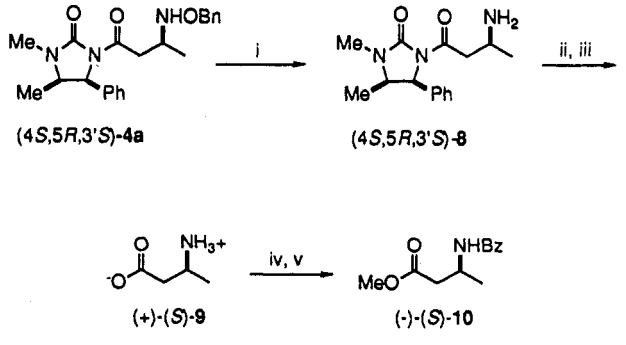


Figure 4. Diastereofacial selectivity in the 1,4-addition in the presence of $TiCl_4$ (1 equiv).

Scheme I[a]



[a] (i) $Zn/Cu(OAc)_2/AcOH$, H_2O, 70 °C, 2 h; (ii) $LiOH/H_2O_2$ THF/H_2O, rt, 15 h; (iii) cation-exchange resin, 1.5 M NH_4OH; (iv) BzCl, aqueous NaOH/acetone; (v) $ClSiMe_3$, dry MeOH, rt 12 h.

$CHCl_3$); mp 102 °C. Anal. Calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 69.22; H, 7.17; N, 10.94.

(4*S*,5*R*,3'*R*)-5a: IR (film) 1730, 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (d, 3H, J = 6.5 Hz, PhCHCHC*H*$_3$), 1.14 (d, 3H, J = 6.4 Hz, ONCHC*H*$_3$), 2.82 (s, 3H, NCH_3), 3.06 (dd, 1H, J = 5.4 Hz, 16.4 Hz, OCC*H*HCHN), 3.26 (dd, 1H, J = 7.4 Hz, J = 16.4 Hz, OCCH*H*), 3.51 (m, 1H, OCCHHC*H*N), 3.85 (dd, 1H, J = 6.5 Hz, 8.6 Hz, PhCHC*H*CH$_3$), 4.65 (s, 2H, OC*H*$_2$Ph), 5.26 (d, 1H, J = 8.6 Hz, PhC*H*CHCH$_3$), 7.32 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.9, 18.3, 28.1, 39.6, 52.9, 53.8, 59.2, 76.5, 126.8, 127.5, 128.0, 128.2, 128.4, 136.5, 138.0, 155.7, 171.2; $[\alpha]_D$ = +29.1° (*c* 2, $CHCl_3$). Anal. Calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 69.31; H, 7.07; N, 11.06.

(4*S*,5*R*,3'*S*)-4b: IR (film) 1729, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (d, 3H, J = 6.6 Hz, PhCHCHC*H*$_3$), 0.88 (t, 3H, J = 7.0 Hz, $CH_2CH_2CH_3$), 1.38 (m, 4H, $CH_2CH_2CH_3$), 2.80 (s, 3H, NCH_3), 3.04 (dd, 1H, J = 2.5 Hz, 15.2 Hz, OCC*H*HCHN), 3.34 (dd, 1H, J = 8.7 Hz, 15.2 Hz, OCCH*H*CHN), 3.37 (m, 1H, OCCHHC*H*N), 3.72 (dd, 1H, J = 6.6 Hz, 8.5 Hz, PhC*H*CHCH$_3$), 4.61 (s, 2H, OC*H*$_2$Ph), 5.20 (d, 1H, J = 8.5 Hz, PhC*H*CHCH$_3$), 7.21 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.7, 19.1, 27.9, 34.3, 37.7, 53.5, 57.1, 59.1, 76.0, 126.7, 127.8, 128.0, 128.1, 128.2, 136.5, 138.0, 155.7, 171.5; $[\alpha]_D$ = +32.3° (*c* 0.44, $CHCl_3$). Anal. Calcd for $C_{24}H_{31}N_3O_3$: C, 70.39; H, 7.63; N, 10.26. Found: C, 70.45; H, 7.71; N, 10.19.

(4*S*,5*R*,3'*R*)-5b: IR (film) 1729, 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (d, 3H, J = 6.6 Hz, PhCHCHC*H*$_3$), 0.88 (t, 3H, J = 7.1 Hz, $CH_2CH_2CH_3$), 1.37 (m, 4H, $CH_2CH_2CH_3$), 2.82 (s, 3H, NCH_3), 3.12 (dd, 1H, J = 3.8 Hz, 15.4 Hz, OCC*H*HCHN), 3.30 (dd, 1H, J = 7.6 Hz, 15.4 Hz, OCCH*H*CHN), 3.32 (m, 1H, OCCHHC*H*N), 3.83 (dd, 1H, J = 6.6 Hz, 8.6 Hz, PhC*H*CHCH$_3$), 4.62 (s, 2H, OC*H*$_2$Ph), 5.25 (d, 1H, J = 8.6 Hz, PhC*H*CHCH$_3$), 7.31 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.9, 19.2, 28.1, 34.3, 37.8, 53.8, 57.2, 59.2, 76.2, 126.9, 127.5, 128.0, 128.2, 128.3, 128.4, 136.6, 138.2, 155.9, 171.6; $[\alpha]_D$ = +53.5° (*c* 0.2, $CHCl_3$). Anal. Calcd for $C_{24}H_{31}N_3O_3$: C, 70.39; H, 7.63; N, 10.26. Found: C, 70.38; H, 7.66; N, 10.29.

Methyl (−)-(*S*)-*N*-Benzoyl-3-aminobutanoate (10). A solution of $Cu(OAc)_2$ (0.11 mmol, 20 mg) in glacial acetic acid (1 mL) was stirred until it became dark blue. After 10 min, zinc powder (5.2 mmol, 0.34 g) was added. Then a solution of **4a** (1.04 mmol, 0.2 g) in acetic acid (0.8 mL) and H_2O (0.2 mL) was added to the mixture, which was then heated at 70 °C for 2 h. After the mixture cooled, 1 M NaOH was added until pH = 10–11 and the mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. Product **8** was obtained nearly pure in 80% yield (0.42 mmol, 114 mg) and used without any further purification: ^1H NMR ($CDCl_3$) δ 0.72 (d, 3H, J = 6.6 Hz, PhCHCHC*H*$_3$), 1.07

(d, 3H, J = 6.3 Hz, CH_2CHNCH_3), 2.34 (bs, 2H, NH_2), 2.78 (s, 3H, NCH_3), 2.86 (dd, 1H, J = 9.3 Hz, 16.6 Hz, $OCCHHCHN$), 3.12 (dd, 1H, J = 1.7 Hz, 16.6 Hz, $OCCHHCHN$), 3.32 (m, 1H, $OCCH_2CHN$), 3.85 (dq, 1H, J = 6.6 Hz, 8.8 Hz, $PhCHCHCH_3$), 5.25 (d, 1H, J = 8.8 Hz, $PhCHCHCH_3$), 7.28 (m, 5H, Ph).

To a stirred solution of **8** (0.36 mmol, 100 mg) in THF (4 mL) and H_2O (1 mL) was added H_2O_2 (30% solution in water, 1.5 mmol, 0.15 mL), and then, after 5 min, a solution of LiOH (0.59 mmol, 14 mg) in H_2O (2 mL) was added. The mixture was stirred overnight at rt. Then Na_2SO_3 (1.44 mmol, 228 mg) in H_2O (3 mL) was added, and the mixture was concentrated under vacuum to evaporate the THF. Then water was added, and the aqueous mixture was washed twice with CH_2Cl_2 to eliminate imidazolidin-2-one **2**. 1 M HCl was added until the solution reached pH = 3. The solution was concentrated, and water was added. The mixture was adsorbed on cation-exchange resin BIORAD AG 50W-X2, and the resin was washed with distilled H_2O until the washes became neutral and then with NH_4OH 1.5 M to recover the β-amino acid. Evaporation of the aqueous solution afforded (*S*)-3-aminobutanoic acid **8** in the zwitterionic form (26 mg, 70% yield): ^1H NMR (D_2O + DCl) δ 1.24 (d, 3H, J = 6.7 Hz, $CHNCH_3$), 2.67 (d, 2H, J = 6.3 Hz, $OCCH_2$), 3.64 (m, 1H, CHN); mp 210–211 °C (lit.[23] 212 °C); $[\alpha]_D$ +37.8° (*c* 0.1, H_2O), lit.[23] $[\alpha]_D$ +38.8° (*c* 0.48, H_2O).

Amino acid **9** was fully characterized by transformation into its *N*-benzoyl methyl ester **10**:[7b] IR (film) 3300, 1730, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (d, 3H, J = 6.9 Hz, $CHNCH_3$), 2.66 (ABX, 2H, J = 4.9 Hz, 5.2 Hz, 15.9 Hz, $OCCH_2CHN$), 3.73 (s, 3H, OCH_3), 4.59, (m, 1H, CHN), 6.97 (d, 1H, J = 7.6 Hz, NH), 7.61 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 20.0, 39.5, 42.3, 51.7, 126.9, 128.5, 131.4, 133.4, 134.5, 166.5, 172.5; $[\alpha]_D$ = −40.8° (*c* 1, $CHCl_3$), lit.[7b] $[\alpha]_D$ = −42.0° (*c* 0.77, $CHCl_3$); mp 107–109 °C, lit.[7b] 108–109 °C. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.11; H, 6.75; N, 6.32.

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