Norketoyobirine (7a). (a) Hydrogenolysis of 7c. From **7c** (26 mg, 0.0721 mmol), NaOH (100 mg, 2.5 mmol), 10% Pd–C (10 mg), CH_2Cl_2 (3 mL), MeOH (40 mL), and H_2 (3 h) was obtained **7a**[17] (20 mg, 98% yield): mp 299–300 °C (MeOH) (Lit.[17] mp 299–300 °C).

(b) Hydrogenolysis of 7d. From **7d** (13 mg, 0.0405 mmol), NaOH (50 mg, 1.25 mmol), Pd–C (30 mg), CH_2Cl_2 (3 mL), MeOH (40 mL), and H_2 (balloon, 3 h) was obtained **7a**[17] (11 mg, 95% yield).

Decarbomethoxydehydrogambirtannine (6a). A solution of **7a** (15 mg, 0.05 mmol) in $POCl_3$ (2 mL) was refluxed for 2 h. Volatile materials were evaporated in vacuo, the residue was dissolved in MeOH (5 mL), and the solution was treated with $NaBH_4$ (150 mg, 3.95 mmol) at 0 °C. The mixture was stirred for a further 30 min at rt and then concentrated in vacuo. The residue was dissolved in H_2O and CH_2Cl_2, the organic phase was decanted and dried with Na_2SO_4, and the solvent was evaporated. Chromatography of the residue (20:1, CH_2Cl_2–ether) afforded (±)-decarbomethoxydihydrogambirtannine (**6a**) (10 mg, 70%), which was crystallized from MeOH–H_2O as white crystals: mp 191–192 °C (lit.[18] mp 193–195 °C).

(17) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003.
(18) Chaterjee, A.; Ghosh, S. *Synthesis* **1981**, 818.

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Registry No. **2b**, 91494-65-4; **3a**, 102421-38-5; **3b**, 119219-84-0; **3c**, 119219-85-1; **4a**, 462-80-6; **4b**, 54632-05-2; **5a**, 32255-47-3; **5b**, 119219-83-9; **5c**, 119219-86-2; **5d**, 15495-36-0; **5e**, 119219-88-4; **5f**, 10211-78-6; **5g**, 144181-88-4; (±)-**6a**, 61825-78-3; **7a**, 51598-75-5; **7b**, 144181-84-0; **7c**, 144181-85-1; **7d**, 144181-87-3; **7e**, 144181-86-2; **8a**, 96165-61-6; **8b**, 144181-81-7; **8c**, 144181-82-8; **8d**, 144181-83-9; **9a**, 525-41-7; **9b**, 68796-67-8; **11**, 144181-80-6; EtCOCl, 141-75-3; ClCOCOCl, 79-37-8; ClCOCOOMe, 5781-53-3; *N*-[2-(indol-3-yl)-ethyl]butyramide, 76049-36-0; tryptamine, 61-54-1; benzenediazonium 2-carboxylate, 1608-42-0; 4,5-dimethoxybenzenediazonium 2-carboxylate, 119219-87-3.

Supplementary Material Available: HRMS for compounds **3b**, **3c**, **5a**, **5d**, **5e**, **5g**, **7b**, **7d**, **7e**, and **8d** and elemental analyses for compounds **3b**, **3c**, **5b**, **5d**, **5g**, **7b**, **7c**, **7d**, **7e**, **8b**, **8c**, **8d**, **9b**, *N*-[2-(indol-3-yl)ethyl]butyrylamide, and **11** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of Racemic α-Amino Carboxamides via Lewis Acid-Mediated Reactions of α-Methoxyglycinamide Derivatives with Allylsilanes: Enzymatic Resolution to Optically Active α-Amino Acids

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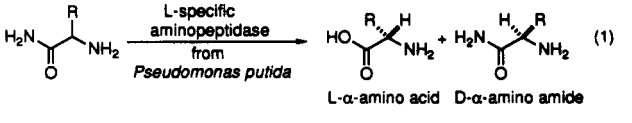
A short and expedient synthetic route to optically active, saturated and γ,δ-unsaturated α-amino acids is reported. The key step is a $BF_3{\cdot}OEt_2$-mediated reaction of allylsilanes with *N*-(alkoxycarbonyl)-α-methoxyglycinamides **11–15**, leading to the corresponding γ,δ-unsaturated α-aminocarboxamides. The genuine S_N1-character of this process with iminium ion **6** as intermediate is proven in the case of the glycine ester **10**. Thus, reaction of enzymatically resolved **10** with π-nucleophiles leads to racemic products. The most useful iminium precursors are the *N*-methoxyamides **12–14** providing good yields of coupling products. The most convenient N-protective group is the allyloxycarbonyl group. Deprotection proceeds via a Pd(0)-catalyzed transprotection to the corresponding BOC-protected analogues. Four examples of the enzymatic resolution of α-amino carboxamides, by using an L-specific aminopeptidase from *Pseudomonas putida*, are described in detail. Most notably, secondary *N*-methoxyamides are good substrates for the enzyme to provide the desired α-amino acids in high optical purity.

Introduction

The synthesis of α-amino acids remains a topic of considerable interest because of the ever growing importance of both natural and unnatural amino acids.[1] It is crucial that such compounds are available in enantiomerically pure form due to the divergent biological activities of the enantiomers.

Of the several methods known to obtain α-amino acids as pure enantiomers,[2] a particularly attractive method involves the use of an L-specific aminopeptidase to perform an enzymatic kinetic resolution of a racemic mixture of α-amino amides (eq 1).[3] This enzymatic reaction has been



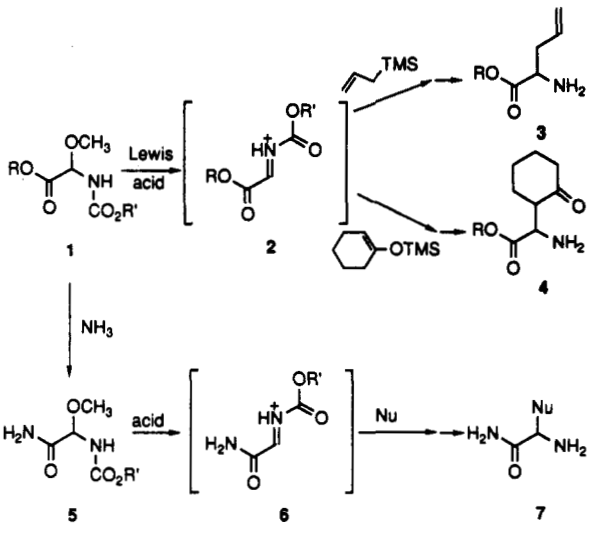
(1)

(1) (a) Barrett, G. C., Ed. *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985. (b) O'Donnell, M. J., Ed. *α-Amino Acid Synthesis*; *Tetrahedron Symposia-in-Print number 33*; Pergamon: Oxford, 1988; pp 5253–5614.

(2) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989.

0022-3263/92/1957-6769$03.00/0

Scheme I



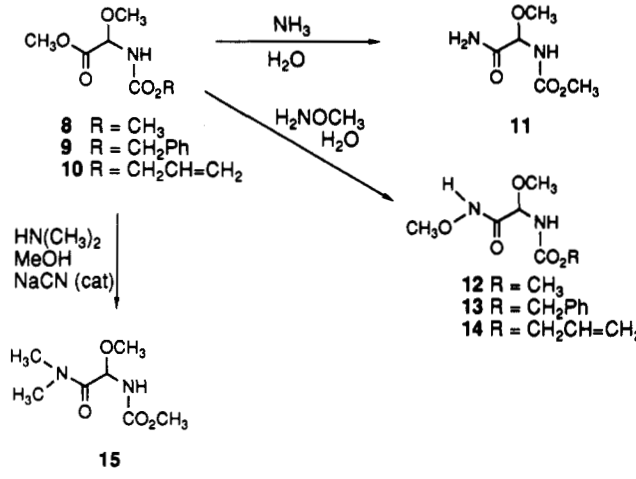
shown to proceed successfully with the primary amide functionality in the substrates as well as with dipeptides and with alkyl, alkenyl, and aromatic groups as the α-substituent.

In recent years, our group has investigated the Lewis acid-mediated reactions of α-methoxyglycine esters **1** with different types of π-nucleophiles, in particular allylsilanes[4] and silyl enol ethers (Scheme I).[5] These methods constitute versatile routes to racemic (protected) γ,δ-unsaturated α-amino acids (e.g., **3**)[4] and γ-oxo α-amino acids (e.g., **4**),[5] respectively. An essential feature of this methodology is the intermediacy of iminium ion **2**, which is a highly electrophilic species due to the presence of carbonyl substituents on both carbon and nitrogen.[6]

Continuing the work in this area we set about to investigate the use of carboxamide **5** as the starting material for a similar acid-mediated coupling via **6**. In this way rapid access would be gained to racemic α-amino amides **7**, which are the substrates required for the above-mentioned enzymatic route to enantiomerically pure α-amino acids. As we were interested to know the influence of the amide moiety on the course of these coupling reactions, we also wished to test N-substituted amides in these reactions. Furthermore, there was considerable interest in screening the influence of substituents on the amide nitrogen on the activity and selectivity of the enzymatic resolution process.[3a]

In this paper we wish to describe a short and efficient synthetic route toward optically active saturated and γ,δ-unsaturated α-amino acids by way of Lewis acid-induced reactions of a series of α-methoxyglycine amide derivatives with allylsilanes, followed by deprotection of these products and enzymatic resolution. The use of several different protective groups and deprotection methods, such as the recently developed palladium-catalyzed transprotection reaction, will be discussed. Moreover, we will show that not only primary but also α-amino *N*-methoxy-carboxamides are good substrates for the aminopeptidase.

Scheme II



Results and Discussion

Synthesis of Precursors. Starting from the readily available α-methoxyglycine esters **8–10**[7] (Scheme II), the amides **11–15** were synthesized by using straightforward aminolysis reactions.[8] While **12–14** were rapidly formed with aqueous *O*-methylhydroxylamine, the formation of **15** was efficiently catalyzed by a small amount of sodium cyanide.[8b] The precursors, synthesized in this way, were subjected to Lewis acid-mediated coupling reactions with allylsilanes.[9]

Mechanism. Substitution reactions of *N,O*-acetals like **8–10** with π-nucleophiles, mediated by Lewis acids, are usually supposed to proceed via an S_N1-type mechanism (Scheme I), involving the *N*-acyl- or *N*-(alkoxycarbonyl)-iminium ion as the intermediate. However, this assumption has only been proven for a few cases.[10] Moreover, reactions of a similar type have been shown to proceed partly or completely via an S_N2-mechanism, either by the formation of an intermediate complex between the starting material and the Lewis acid, allowing the attack of the nucleophile from only one side,[11] or by using a very good leaving group, which enhances the reaction rate significantly and therefore allows a one-step substitution reaction.[12] The subtle details of the mechanism will depend on the choice of the Lewis acid, the solvent, and the leaving group. We were interested to know whether the α-methoxyglycine derivatives, used in this paper, react entirely in an S_N1-type manner or whether some S_N2-character might be observed.

That compounds of type **8–10** indeed react via cationic intermediates in a genuine S_N1-type reaction when sub-

(3) See, e.g.: (a) Hermes, H. F. M. Ph.D. Thesis, University of Groningen, The Netherlands, 1992. (b) Kamphuis, J.; Boesten, W. H. J.; Broxterman, Q. B.; Hermes, H. F. M.; Van Balken, J. A. M.; Meijer, E. M.; Schoemaker, H. E. In *Advances in Biochemical Engineering/Biotechnology*; Fiechter, A., Ed.; Springer-Verlag: Berlin, 1990; Vol. 42, pp 133–186. (c) Sheldon, R. A.; Schoemaker, H. E.; Kamphuis, J.; Boesten, W. H. J.; Meijer, E. M. In *Stereoselectivity of Pesticides*; Elsevier: Amsterdam, 1988; pp 409–451. (d) Boesten, W. H. J. (DSM/Stamicarbon). U.S. Patent 3,961,700.

(4) Mooiweer, H. H.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1989**, *45*, 4627.

(5) Mooiweer, H. H.; Ettema, K. W. A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1990**, *46*, 2991.

(6) For a review, see: Heimstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol 2, Chapter 4.5.

(7) (a) Ben-Ishai, D.; Zoller, U. *Tetrahedron* **1975**, *31*, 863. (b) Ben-Ishai, D.; Bernstein, Z. *Tetrahedron* **1977**, *33*, 881.

(8) (a) Kenner, G. W.; Mendive, J. J.; Sheppard, R. C. *J. Chem. Soc. C* **1968**, 761. (b) Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 2033.

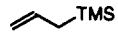
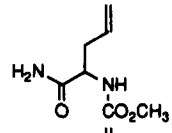
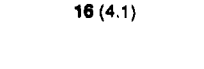
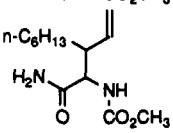
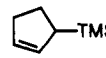
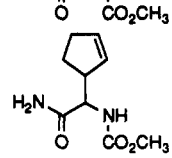
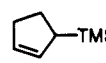
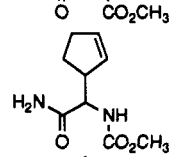
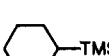
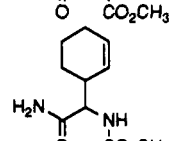
(9) For coupling reactions with silyl enol ethers, see: Roos, E. C.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Kamphuis, J.; Schoemaker, H. E. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 360.

(10) Yamamoto, Y.; Nakada, T.; Nemoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 121 and references cited therein.

(11) Piccolo, O.; Azzena, U.; Melloni, G.; Delogu, G.; Valoti, E. *J. Org. Chem.* **1991**, *56*, 183.

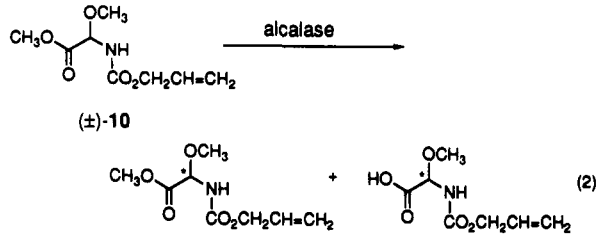
(12) (a) Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 11. (b) Reference 2, p 107.

Table I. Coupling of α-Methoxyglycine Amide (11) with Allylsilanes

entry	allylsilane (equiv, Z/E ratio)	condns[1]	product (yield, diastereomeric ratio)
1	 16 (4.1)	HCOOH (neat)	 20 (91%)
2	 17 (1.0, 18:82)	$BF_3{\cdot}OEt_2$ (3.7) CH_3CN 0 °C→rt, 48 h	 21 (64%, 28:72)
3	 18 (2.0)	$BF_3{\cdot}OEt_2$ (2.0) CH_3CN 0 °C→rt, 3 h	 22 (57%, 50:50)
4[1]	 18 (1.8)	$BF_3{\cdot}OEt_2$ (1.8) CH_2Cl_2 0 °C→rt, 3 h	 22 (82%, 50:50)
5[1]	 19 (1.9)	$BF_3{\cdot}OEt_2$ (1.9) CH_2Cl_2 0 °C→rt, 3 h	 23 (70%, 55:45)

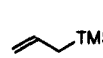
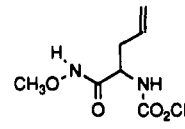
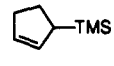
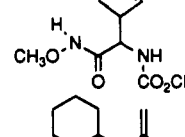
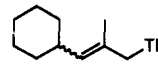
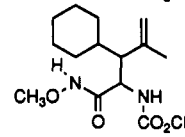
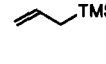
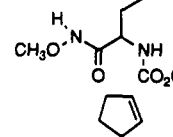
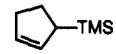
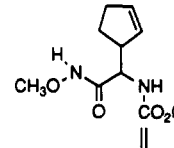
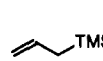
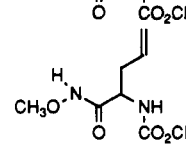
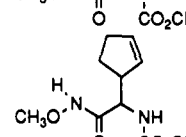
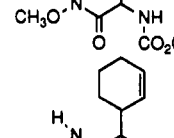
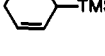
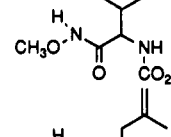
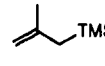
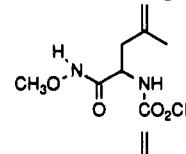
[1] In entries 4 and 5, 11 was first silylated using the following conditions: Et_3N (2.2 equiv), $ClSi(CH_3)_2CH_2CH_2Si(CH_3)_2Cl$ (2.0 equiv), benzene, reflux, 17 h; see also ref 9.

jected to Lewis acid-mediated substitutions was proven in the following way. Methyl 2-methoxy-2-((allyloxycarbonyl)amino)acetate **10** was resolved enzymatically using an alcalase (NOVO batch PMN 4211, activity 2.5 AU/g). In this way, compound **10** could be obtained in optically active form. The enantiomeric excess was 82 (±5)%, as determined by NMR measurements using Eu(hfc)$_3$ as chiral shift reagent (eq 2).



When this (+)-**10** was reacted with three π-carbon nucleophiles of different type, namely allyltrimethylsilane, 1-phenyl-1-(trimethylsiloxy)ethene, and furan, mediated by different Lewis acids, in all cases *completely racemized products* were obtained after the reaction. This clearly indicates that these reactions proceed via the postulated mechanism, shown in Scheme I. That no S_N2-reaction was found whatsoever can be explained by the fact that the methoxy group is a relatively poor leaving group. Therefore, a single-step substitution of this group is not expected. In some of the attempts, a certain amount of starting material was recovered after the reaction, having still a small positive rotation. When (+)-**10** was mixed with boron trifluoride etherate without the presence of a carbon nucleophile, it appeared to racemize rather slowly; after stirring the mixture of 24 h at room temperature, the starting material, recovered in nearly quantitative yield, had almost completely racemized ($[\alpha]^{25}_D$ +1.0 (*c* 2.5, MeOH).

Table II. Coupling of N-Substituted α-Methoxyglycinamide Derivatives with Allylsilanes

entry	precursor	allylsilane (equiv, Z/E ratio)	product (yield, diastereomeric ratio)
1	13	 16 (2.0)	 26 (85%)
2	13	 18 (1.5)	 27 (63%, 50:50)
3	13	 24 (1.5, 33:67)	 28 (68%, 50:50)
4	12	 16 (2.0)	 29 (80%)
5	12	 18 (2.0)	 30 (77%, 50:50)
6	14	 16 (1.5)	 31 (90%)
7	14	18 (2.0)	 32 (70%, 50:50)
8	14	19 (2.0)	 33 (73%, 60:40)
9	14	 25 (2.2)	 34 (41%)
10	15	 16 (1.5)	 35 (90%)

Coupling Reactions. First, primary amide **11** was investigated as starting material. The usefulness of this compound appeared to be limited because of its poor solubility in many organic solvents. With allyltrimethylsilane (4 equiv) as the nucleophile, the reaction proceeded well if carried out in neat formic acid (Table I, entry 1). This led to coupling product **20** in high yield. Other allylsilanes, however, did not react satisfactorily under these conditions. As an alternative we studied the use of acetonitrile as solvent, and boron trifluoride etherate as Lewis acid. In this way, a number of coupling reactions could be successfully performed, leading to the desired products in reasonable yields (entries 2, 3).

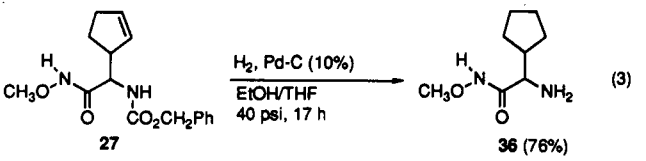
The procedure was further improved by treating 11 with a silylating agent prior to reaction with the allylsilane. Both trimethylsilyl chloride[13] and 1,2-bis(chlorodimethylsilyl)ethane[14] were used in these silylations. After refluxing overnight in benzene a thick suspension was formed due to the formation of insoluble triethylamine hydrochloride salts. The removal of these salts by filtration appeared to be a troublesome operation due to the moisture-sensitivity of the N–Si bond in these products. In both cases only monosilylation of the primary amide functionality could be effected, as was inferred from the ^{1}H-NMR spectrum.[15] Because of their lability, the silylated amides were used immediately without further purification. They reacted well with allylsilanes, leading to the desired primary amides after workup (cf. entries 4 and 5). The yields were slightly higher with the stabase-adduct than with the TMS-adduct. The success of the silylation route is probably merely due to the increased solubility of the starting materials, so that the reactions with allylsilanes could now be performed in dichloromethane as the solvent. The somewhat inconvenient procedure and the moisture-sensitivity of the precursors, however, render the silylation route not so attractive.

Table II contains the results of allylsilane coupling reactions of *N*-methoxyamides 12–14 and *N,N*-dimethylamide 15. The following standard procedure was used for these reactions. Boron trifluoride etherate (2 equiv) was added to a mixture of the α-methoxyglycinamide derivative and the allylsilane in dichloromethane at −78 °C. After being stirred for 15 min at this temperature, the mixture was allowed to warm to room temperature and stirring was continued for another 3–6 h.

Table II clearly shows that the reactions of secondary and tertiary amides with allylsilanes generally provide good yields of coupling products (except for entry 9, where the yield is modest). The presence of a substituent on the amide nitrogen enhances the solubility, and therefore the usefulness of these compounds. Furthermore, the reactions of the amide precursors proceeded much faster than the same reactions of the corresponding esters.[4] Compared to an ester carbonyl, the amide carbonyl function is less electron-withdrawing. Therefore, the intermediate cation is less destabilized and thus formed more easily, causing a higher reaction rate. Boron trifluoride etherate proved to be the best Lewis acid. When, instead of boron trifluoride etherate, tin tetrachloride was used in the reaction in entry 1, a somewhat lower yield was found (73%). The use of titanium tetrachloride led to a very poor yield of 26. Diastereomer ratios were usually close to 50:50. In this reaction series, three different alkoxycarbonyl groups were used as protective groups for the amine, namely the methoxycarbonyl (MeOC), benzyloxycarbonyl (Cbz), and allyloxycarbonyl (Alloc) group. As can be seen in Table II, yields of coupling reactions lie in the same range for different protective groups (cf. entries 1, 4, and 6 and entries 2, 5, and 7), indicating that this variation has little or no effect on the outcome of these reactions.

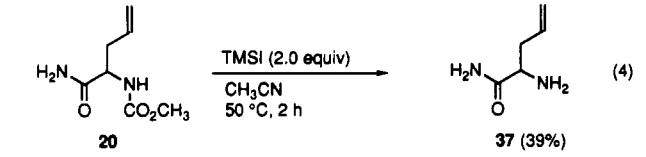
We became particularly interested in the *N*-methoxyamide derivatives, because these compounds showed good solubilities and reactivities and were therefore easier to handle than the silylamides. Moreover, we were interested to test the *N*-methoxyamides in the enzymatic resolution process.

Deprotection. While the choice of different N-protective groups had almost no effect on the coupling reaction, marked influences on the deprotection efficiency were observed. Deprotection of the obtained coupling products may lead either to saturated or γ,δ-unsaturated α-amino amides. As an example of the first category, compound 27, bearing the benzyloxycarbonyl group on nitrogen, was deprotected using catalytic hydrogenation to give 2-amino-2-cyclopentyl-*N*-methoxyacetamide 36 in good yield (eq 3).

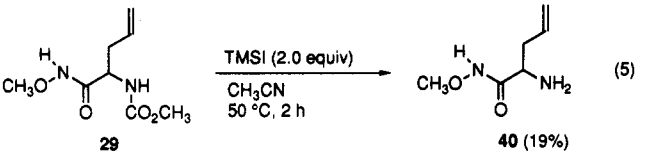


27 36 (76%) (3)

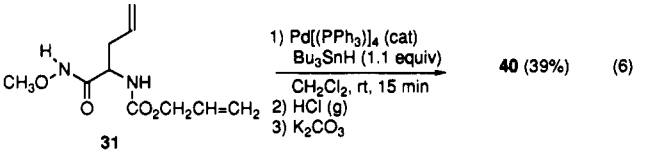
Deprotection to the γ,δ-unsaturated α-aminocarboxamides seemed at first to be more troublesome. This was mainly due to the poor solubilities of the deprotected compounds in organic solvents, thus making workup very difficult. Removal of the methoxycarbonyl group from 20 using iodotrimethylsilane gave, after normal workup, 2-amino-4-pentenamide (37) in a poor yield (39%; eq 4).



20 37 (39%) (4)



29 40 (19%) (5)



31 40 (39%) (6)

Using the same procedure for the deprotection of 29, 40 was obtained in an even lower yield (19%; eq 5). Therefore, we turned our attention to the use of the allyloxycarbonyl (Alloc) group as the protective group, as recent literature precedent reported the facile removal of this group with a catalytic amount of palladium(0).[16] Using this Alloc group, a series of protected *N*-methoxyamide derivatives was synthesized (Table II). However, the direct cleavage of this group under various conditions appeared to be again troublesome. With the conditions, analogous to those reported by Guibé et al.[16c] (Pd(0)/Bu_3SnH and then HCl(g)) only 39% of 40 could be obtained from 31, again merely due to isolation problems because of the poor solubility (eq 6).

With the development of the Pd(0)-catalyzed transprotection reaction, which was discovered recently in our

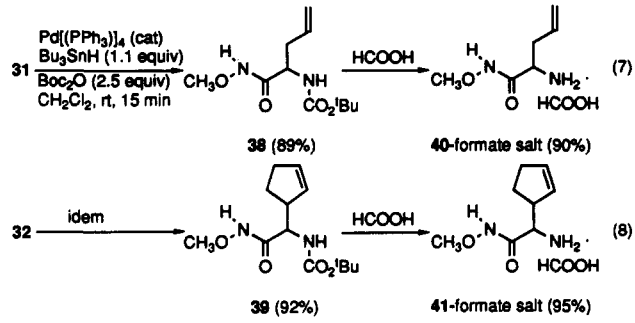
(13) (a) Klebe, J. F.; Finkbeiner, H.; White, D. M. *J. Am. Chem. Soc.* **1966**, *88*, 3390. (b) Yoder, C. H.; Copenhafer, W. C.; DuBeshter, B. *J. Am. Chem. Soc.* **1974**, *96*, 4283.

(14) 1,2-Bis(chlorodimethylsilyl)ethane has been used as a protective agent for amines to give the so-called stabase-adducts. See, e.g.: (a) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787. (b) Hudrlik, P. F.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 6251. (c) Guggenheim, T. L. *Tetrahedron Lett.* **1984**, *25*, 1253. (d) Cavelier-Frontin, F.; Jacquier, R.; Paladino, J.; Verducci, J. *Tetrahedron* **1991**, *47*, 9807.

(15) The ^{1}H-NMR spectra of all of these silylated amides clearly show two NH signals at 6.50–6.00 ppm and at 6.25–5.75 ppm, one of them assigned as the carbamate NH and the other one as the monosilylated, secondary amide NH. Also, the IR spectrum gives two NH bands, at 3440–3360 and 3320–3240 cm^{-1}. See also ref 9.

(16) See, e.g.: (a) Minami, I.; Ohashi, Y.; Shimizu, I.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 2449. (b) Hayakawa, Y.; Kato, H.; Uchiyama, M.; Kajino, H.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 2400. (c) Dangles, O.; Guibé, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984.

group,[17] an excellent alternative came at hand. The Alloc-protected products could now be transprotected in very high yields to the corresponding BOC-derivatives. As examples, **38** and **39** were prepared in 89% and 92%, respectively (eqs 7 and 8). These products could now be



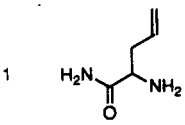
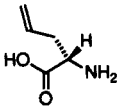
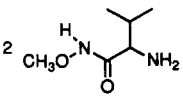
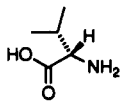
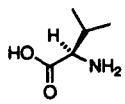
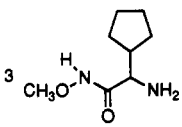
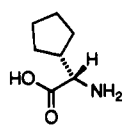
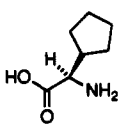
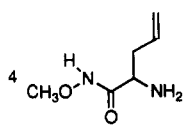
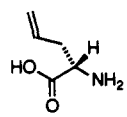
(7)

(8)

easily cleaved using formic acid at room temperature to give compounds **40** and **41** as the formate salts, after simple removal of the volatiles. Besides the free amines, these formate salts can also be used as substrates for the enzyme reaction.[18] For clarity it should be noted here that the use of the BOC protective group directly from the beginning is not feasible because the synthetic sequence contains acid-mediated steps, which would lead to premature deprotection.

Enzymatic Resolution. The so obtained α-amino amides served as the substrates for the enzymatic resolution using an L-specific aminopeptidase from *Pseudomonas putida*. It was already known that primary amides can be resolved with high yield and specificities.[3] As an example, compound **37** was subjected to the resolution. L-Allylglycine was isolated nearly in the maximum yield and optical purity (Table III, entry 1).[19] The enantiomeric excess, which was determined in all cases by using HPLC-techniques,[20] was established to be 98 (±1)%. We then investigated the reactivity of the *N*-methoxyamide derivative in this process. As a test substrate, valine *N*-methoxyamide (**42**) was synthesized from racemic valine. It can be seen from Table III that the aminopeptidase indeed showed activity toward this new type of substrate (entry 2). The enzyme demonstrated the same selectivity (the enantiomeric excess of the isolated L-acid is 98%), although the rate of the reaction was somewhat lower than in the case of the primary amides. After 1 day at 37 °C, a conversion of 32% was effected, as could be calculated from the ee's of both isolated products. The results of the other resolution reactions, with compounds **36** and **40** (entries 3, 4), were comparable to that of valine *N*-methoxyamide, again showing that α-amino *N*-methoxycarboxamides are suitable substrates for this process.[21] Finally, it should be noted that cyclopentylglycine exhibits interesting biological activities.[22]

Table III. Enzymatic Resolution of α-Amino Carboxamides Using Aminopeptidase from *P. putida*

entry	substrate	convn after 1 day[1]	isolated products[2] yields (based on conversion), $[\alpha]_D$, or ee[3]
1	 **37**	50%	 L-allylglycine 95% e.e. > 95%
2	 **42**	32%	 L-valine 99% e.e. 98% +  D-valine 82% e.e. 46%
3	 **36**	43%	 L-cyclopentylglycine 98% e.e. 98% +  D-cyclopentylgly 65% e.e. 74%
4	 **40**	ca. 21%	 L-allylglycine 100%[4] $[\alpha]^{26}_D$ -4.3 (*c* 0.5, 1 N HCl) lit.[19a] $[\alpha]^{25}_D$ -4.4 (*c* 0.5, 1 N HCl)

[1] In entry 1, the conversion was established using an ammonia electrode; in entries 2 and 3, the conversion was calculated from the ee data of the products. [2] The D-methoxycarboxamides were immediately hydrolyzed to the amino acids and analyzed as such. [3] All ee values were obtained by HPLC measurements. [4] Based on a 21% conversion.

Conclusions. A short and efficient route toward optically active, saturated and γ,δ-unsaturated α-amino acids has been developed. The synthesis of α-methoxyglycinamide precursors is straightforward. These compounds react in good yields with a range of allylsilanes, mediated by boron trifluoride etherate. Various deprotection methods furnish the substrates for an enzymatic resolution, which occurs with high selectivity. In addition to primary amides, *N*-methoxyamides can now also be used for this enzymatic process. Throughout the synthesis, the *N*-methoxyamide functionality proves to be the most convenient, while the allyloxycarbonyl (Alloc) group is the preferred protective group.

Experimental Section

General Information. Experimental techniques and analytical measurements were applied as previously described.[4] NMR data are given in ppm. IR data are given in cm^{-1}. 2-((Benzyloxycarbonyl)amino)-2-methoxy-*N*-methoxyacetamide (**13**) and 2-methoxy-2-((methoxycarbonyl)amino)-*N*,*N*-dimethylacetamide (**15**) were prepared as previously described.[9] Enantiomeric excesses of amino acids were determined by HPLC analysis,[20a] using precolumn derivatization with *o*-phthalaldehyde *N*-acetyl-L-cysteine, and are within 0.2% accuracy.

Methyl 2-Methoxy-2-((allyloxycarbonyl)amino)acetate (10). This compound was synthesized in a similar way as **8** and

(17) (a) Rutjes, F. P. J. T.; Paz, M. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 6629. (b) Roos, E. C.; Bernabé, P.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J. *Tetrahedron Lett.* **1991**, *32*, 6633.

(18) Because the enzymatic hydrolyses, using *Pseudomonas putida*, are performed at pH ≈9, the free amino acid amides are present. Small amounts of salt in the reaction mixture do not influence the result of the enzymatic hydrolysis (DSM Research, unpublished results).

(19) For some recent syntheses of enantiopure allylglycine, see, e.g.: (a) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547. (b) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353.

(20) (a) Duchateau, A.; Crombach, M.; Kamphuis, J.; Boesten, W. H. J.; Schoemaker, H. E.; Meijer, E. M. *J. Chromatogr.* **1989**, *471*, 263. (b) Miyazawa, T.; Iwanaga, H.; Yamada, T.; Kuwata, S. *Chem. Express* **1991**, *6*, 887.

(21) Also, amino acid hydrazides appear to act as substrates for the aminopeptidase from *Pseudomonas putida* (DSM Research, unpublished results).

(22) Bourgeois-Cury, A.; Doan, D.; Gorè, J. *Tetrahedron Lett.* **1992**, *33*, 1277.

9.[7] Allyl chloroformate (10.0 g, 8.8 mL, 83.0 mmol) was dissolved in benzene (100 mL). NH_3(g) was bubbled through this solution for 0.5 h. The NH_4Cl, which was formed during this reaction, was removed by filtration and the filtrate was concentrated in vacuo. The residue (allylcarbamate) was dissolved in dry ether (50.0 mL), and glyoxylic acid monohydrate (8.24 g, 89.5 mmol) was added. The mixture was stirred for 24 h at rt and then concentrated in vacuo. The residue was diluted with toluene and again concentrated in vacuo. The remaining solid was dissolved in methanol, and concentrated sulfuric acid (2.3 mL) was added. This mixture was stirred for 20 h at rt and poured into ice-cold aqueous saturated $NaHCO_3$. After extraction with EtOAc (3×), the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 15.5 g (76.4 mmol, 92%) of **10** as a light yellow oil. ^{1}H-NMR (200 MHz): 6.04 (d, 1 H, J = 8.5 Hz, N*H*), 5.95–5.75 (m, 1 H, C*H*=CH_2), 5.29–5.14 (m, 2 H, CH=CH_2), 4.55 (d, 2 H, J = 5.5 Hz, OCH_2CH=), 3.74 (s, 3 H, CH_3OC(O)), 3.38 (s, 3 H, CH_3OC). ^{13}C-NMR (50 MHz): 167.8 (*C*(O)OCH$_3$), 155.4 (*OC*(O)N), 132.0 (*C*H=CH$_2$), 117.9 (CH=*C*H$_2$), 80.5 (*C*H$_3$OC), 65.9 (*OC*H$_2$CH=), 55.8 (*C*HN), 52.6 (*C*H$_3$OC(O)). The compound was used without further purification in the following reactions.

Alcalase-Catalyzed Enzymatic Resolution of Methyl 2-Methoxy-2-((allyloxycarbonyl)amino)acetate (10). A solution of (±)-**10** (6.0 g, 29.6 mmol) in water (100 mL) was warmed to 35 °C and adjusted to pH = 7.5 using 2 N NaOH (ca. 2.3 mL) from a pH stat apparatus. To this mixture was added 200 μL of an Alcalase solution (NOVO batch PMN 4211, activity 2.5 AU/g). The pH was kept at a constant value of 7.5 by titration with 2 N NaOH using a pH stat apparatus. The titration curve reached a constant value after 10 min. At this point 7.15 mL of 2 N NaOH were added (14.3 mmol). The optically active ester was then isolated by extracting the mixture with CH_2Cl_2 (5 × 60 mL). The combined organic layers were washed with water (100 mL), dried (Na_2SO_4), and concentrated in vacuo to give 1.75 g (8.62 mmol, 29%) of (+)-**10** as a light yellow oil. ^{1}H-NMR (200 MHz): identical to starting material. $[\alpha]^{25}_D$: +30.3 (*c* 2.5, MeOH). Ee: 82 ± 5%, determined by using Eu(hfc)$_3$ as a chiral shift reagent (^{1}H-NMR) from integration of the separated ester CH_3 signals. The optical rotation of a mixture of (+)-**10** and Eu(hfc)$_3$ was constant for at least 3 h at rt, indicating that this compound is optically stable under these conditions. When mixed with boron trifluoride etherate (1 equiv) in CH_2Cl_2, the specific rotation dropped to +1.0 (*c* 2.5, MeOH) after 24 h at rt.

2-((Methoxycarbonyl)amino)-2-methoxyacetamide (11). A solution of methyl α-methoxy-*N*-(methoxycarbonyl)glycinate (**8**) (25.1 g, 148 mmol) in 25% aqueous ammonia (250 mL) was stirred at rt for 5 h. After removal of the solvent in vacuo, the oily residue was recrystallized from EtOH to give 16.7 g (103 mmol, 70%) of a crystalline compound, mp 89–91 °C. IR (KBr): 3460, 3330, 1720, 1695, 1530. ^{1}H-NMR (200 MHz, CD_3OD): 5.11 (s, 1 H, C*H*N), 4.86 (br s, 3 H, *H*$_2$NC(O), N*H*), 3.68 (s, 3 H, CH_3OC(O)N), 3.38 (s, 3 H, CH_3OC). ^{13}C-NMR (50 MHz, CD_3OD): 172.6 (H$_2$N*C*(O)), 159.1 (CH$_3$O*C*(O)N), 82.6 (*C*HN), 55.6 (*C*H$_3$OC), 52.7 (*C*H$_3$OC(O)N). MS: (M − CH$_3$O)$^+$ = 131.

2-((Methoxycarbonyl)amino)-2-methoxy-*N*-methoxyacetamide (12). Methyl α-methoxy-*N*-(methoxycarbonyl)glycinate (**8**) (18.4 g, 104 mmol) was dissolved in 30% aqueous *O*-methylhydroxylamine (180 mL). The solution was stirred at 55 °C for 4 h. After removal of the volatiles in vacuo the residue was dissolved in brine and extracted with dichloromethane (3×). The combined organic laters were washed with brine (1×), dried ($MgSO_4$), and concentrated in vacuo to give 17.2 g (90 mmol, 87%) of a light yellow oil, which solidified upon standing. An analytical sample was obtained by recrystallization from EtOAc/hexane, mp 77–79 °C. IR ($CHCl_3$): 3400, 3320–3220, 1750–1650, 1505. ^{1}H-NMR (200 MHz): 9.87 (s, 1 H, N*H*OCH$_3$), 6.26 (br s, 1 H, N*H*), 5.21 (d, 1 H, J = 9.2 Hz, C*H*N), 3.73 (s, 3 H, CH_3ONH), 3.67 (s, 3 H, CH_3OC(O)N), 3.35 (s, 3 H, CH_3OC). ^{13}C-NMR (50 MHz): 165.0 (*C*(O)NHOCH$_3$), 156.9 (*C*(O)N), 80.6 (*C*HN), 64.4 (*C*H$_3$ON), 55.5 (*C*H$_3$OC), 52.7 (*C*H$_3$OC(O)N). MS: (M − C(O)NHOCH$_3$)$^+$ = 144. Anal. Calcd for $C_6H_{12}N_2O_5$ (192.17): C, 37.50; H, 6.29; N, 14.58. Found: C, 37.38; H, 6.20; N, 14.42.

2-((Allyloxycarbonyl)amino)-2-methoxy-*N*-methoxyacetamide (14). Methyl α-methoxy-*N*-(allyloxycarbonyl)glycinate (**10**) (4.5 g, 22 mmol) was dissolved in 30% aqueous *O*-methylhydroxylamine (45 mL). The solution was stirred at rt for 3 h. After removal of the volatiles in vacuo the residue was dissolved in brine and extracted with dichloromethane (3×). The combined organic laters were washed with brine (1×), dried ($MgSO_4$), and concentrated in vacuo to give 4.4 g (20 mmol, 91%) of a light yellow oil, which solidified upon standing at 4 °C, mp 61–64 °C. IR ($CHCl_3$): 3400, 3380, 1750–1660, 1500. ^{1}H-NMR (200 MHz): 9.60 (s, 1 H, N*H*OCH$_3$), 6.14 (d, 1 H, J = 8.5 Hz, N*H*), 5.99–5.80 (m, 1 H, C*H*=CH$_2$), 5.35–5.18 (m, 3 H, –CH=CH_2 and C*H*N), 4.58 (d, 2 H, J = 5.5 Hz, OCH_2CH=), 3.77 (s, 3 H, CH_3ONH), 3.39 (s, 3 H, CH_3OC). ^{13}C-NMR (50 MHz): 164.6 (*C*(O)NHOCH$_3$), 156.1 (*C*(O)N), 132.2 (–*C*H=CH$_2$), 118.0 (CH=*C*H$_2$), 80.3 (*C*HN), 66.0 (*OC*H$_2$), 64.0 (*C*H$_3$ON), 55.2 (*C*H$_3$O). Anal. Calcd for $C_8H_{14}N_2O_5$ (218.21): C, 44.03; H, 6.47; N, 12.84. Found: C, 44.12; H, 6.51; N, 12.83.

2-((Methoxycarbonyl)amino)-4-pentenamide (20). To a solution of **11** (54 mg, 0.33 mmol) in formic acid (0.7 mL) was added at rt allyltrimethylsilane **16** (153 mg, 1.34 mmol). After being stirred at 35 °C for 5 h, the reaction mixture was concentrated in vacuo to give 52 mg (0.30 mmol, 91%) of **20** as a crystalline compound, mp 99–101 °C (after recrystallization from EtOH). IR ($CHCl_3$): 3520, 3480, 3410, 1750–1650, 1500. ^{1}H-NMR (200 MHz, signals broadened due to hindered rotation): 6.72 (br s, 1 H, *H*$_2$NC(O)), 6.54 (br s, 1 H, *H*$_2$NC(O)), 5.83–5.62 (m, 2 H, –C*H*=CH$_2$, N*H*), 5.27–5.07 (m, 2 H, –CH=CH_2), 4.35–4.10 (m, 1 H, C*H*N), 3.64 (s, 3 H, CH_3OC(O)N), 2.56–2.38 (m, 2 H, CH_2CH=CH$_2$).

2-((Methoxycarbonyl)amino)-3-ethenylnonamide (21). A solution of **11** (8.10 g, 49.96 mmol) and 2-nonenyltrimethylsilane (**17**)[23,24] (10.15 g, 51.2 mmol) in acetonitrile (150.0 mL) was cooled to 0 °C. Boron trifluoride etherate (BF$_3$·OEt$_2$) (26.40 g, 22.88 mL, 186.0 mmol) was added to the mixture. After being stirred for 15 min at 0 °C, the reaction mixture was allowed to warm to rt. Stirring was continued for 48 h, whereafter the reaction mixture was poured out onto ice-cold saturated aqueous $NaHCO_3$. The water layer was extracted with dichloromethane (3×). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give 8.37 g (32.7 mmol, 64%) of **21** as a crystalline compound, as a mixture of diastereomers (28:72), mp 112–114 °C. R_f: 0.35 (EtOAc). IR ($CHCl_3$): 3520, 3410, 1750–1650, 1500. ^{1}H-NMR (200 MHz, signals broadened due to hindered rotation): 6.51–6.19 (m, 2 H, *H*$_2$NC(O)), 5.94–5.46 (m, 2 H, –C*H*=CH$_2$, N*H*), 5.30–5.03 (m, 2 H, –CH=CH_2), 4.25–4.05 (m, 1 H, C*H*N), 3.65 (s, 3 H, CH_3OC(O)N), 2.65–2.47 (m, 1 H, =CHC*H*, minor isomer), 2.47–2.25 (m, 1 H, =CHC*H*, major isomer), 1.65–1.10 (m, 10 H, –(CH$_2$)$_5$–), 1.00–0.78 (m, 3 H, CH_3CH$_2$–). ^{13}C-NMR (50 MHz): 173.8, 173.3 (H$_2$N*C*(O)), 156.9, 156.8 (CH$_3$O*C*(O)N), 137.5 (–*C*H=CH$_2$), 118.2, 118.0 (–CH=*C*H$_2$), 57.8 (*C*HN), 52.4 (=*C*HCH), 46.9 (*C*H$_3$OC(O)N), 31.6, 30.1, 29.0, 27.0, 22.5 (CH$_3$(*C*H$_2$)$_5$–), 14.0 (*C*H$_3$CH$_2$). MS: M$^+$ = 256, (M − (C(O)NH$_2$)$^+$ = 212.

2-((Methoxycarbonyl)amino)-2-(2-cyclopentenyl)acetamide (22). According to the same procedure as described for **21**, starting from 194 mg (1.20 mmol) of **11**, 0.40 mL (334 mg, 2.39 mmol) of 3-(trimethylsilyl)cyclopentene (**18**),[25] 0.29 mL (339 mg, 2.39 mmol) of BF$_3$·OEt$_2$, and 8.0 mL of CH_3CN, and using a reaction time of 5 h, there was obtained (after normal workup) 135 mg (0.68 mmol, 57%) of **22** as a white solid, as a mixture of diastereomers (50:50), mp 136–140 °C. IR (KBr): 3480, 3420, 3200, 1720–1630, 1495. ^{1}H-NMR (200 MHz, CD_3OD): 5.91–5.82 (m, 1 H, CHC*H*=CH), 5.62–5.59 (m, 1 H, CHCH=C*H*), 4.05–4.02 (m, 1 H, C*H*N), 3.64 and 3.63 (s, 3 H, CH_3OC(O)N, 2 isomers), 3.23–3.07 (m, 1 H, C*H*CH=CH), 2.40–2.28 (m, 2 H, CH_2CH=CH), 2.05–1.95 (m, 1 H, CH*H*CHCH$_2$), 1.69–1.62 (m, 1 H, CHHC*H*CH$_2$). ^{13}C-NMR (50 MHz, CD_3OD, some carbons show two peaks because of diastereomers): 179.1 (*C*(O)NH$_2$), 173.3 (CH$_3$O*C*(O)N), 137.4 and 136.3 (*C*HCH=CH), 134.1 and 132.9 (CHCH=*C*H), 61.8 (*C*HN), 55.0 (*C*H$_3$OC(O)N), 52.1 and 51.7 (*C*HCH=CH), 35.4 and 35.0 (CH*C*H$_2$CH$_2$), 29.7 and 29.0 (CHCH$_2$*C*H$_2$). MS: (M − (C(O)NH$_2$)$^+$ = 154.

General Procedure A for the Coupling of 11 with Allyl-

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silanes via Silylation. A 0.2–0.4 M mixture of **11** in benzene was treated with triethylamine (Et_3N) (2.2 equiv) and the silylating reagent (2.0 equiv), respectively. The mixture was refluxed for 17 h, after which a thick, white slurry was obtained. This mixture was diluted with benzene, filtered under a blanket of dry nitrogen, and concentrated in vacuo. This silylated amide was then dissolved in CH_2Cl_2 (0.2 M solution), and the silicon nucleophile (1.8–1.9 equiv) was added. The mixture was cooled to −78 °C. $BF_3{\cdot}OEt_2$ (1.8–1.9 equiv) was then added slowly to the reaction mixture. After a further 15 min at −78 °C, the reaction mixture was allowed to warm to rt and was stirred for a further 3 h. The reaction mixture was then poured out into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine (1×), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed.

2-((Methoxycarbonyl)amino)-2-(2-cyclopentenyl)acetamide (22). According to general procedure A, starting from 267 mg (1.65 mmol) of **11**, using 0.50 mL (367 mg, 3.62 mmol) of Et_3N, 352 mg (1.64 mmol) of 1,2-bis(chlorodimethylsilyl)ethane, and 4.0 mL of benzene in the silylation step and 0.51 mL (422 mg, 3.01 mmol) of 3-(trimethylsilyl)cyclopentene (**18**), 0.37 mL (428 mg, 3.02 mmol) of $BF_3{\cdot}OEt_2$, and 8 mL of CH_2Cl_2 in the coupling reaction, there was obtained (after normal workup) 267 mg (1.35 mmol, 82%) of **22**, as a white solid, as a mixture of diastereomers (50:50). Spectroscopic data: vide supra.

2-((Methoxycarbonyl)amino)-2-(2-cyclohexenyl)acetamide (23). According to general procedure A, starting from 219 mg (1.35 mmol) of **11**, using 0.41 mL (301 mg, 2.97 mmol) of Et_3N, 289 mg (1.34 mmol) of 1,2-bis(chlorodimethylsilyl)ethane, and 4.4 mL of benzene in the silylation step and 399 mg (2.59 mmol) of 3-(trimethylsilyl)cyclohexene (**19**),[25] 0.31 mL (361 mg, 2.54 mmol) of $BF_3{\cdot}OEt_2$, and 5 mL of CH_2Cl_2 in the coupling reaction, there was obtained 199 mg (0.94 mmol, 70%) of **23**, as a white solid, after flash chromatography, R_f 0.52 (acetone/CH_2Cl_2 (1.9:1)), as a mixture of diastereomers (55:45). An analytical sample was obtained by recrystallization from EtOAc/hexane, mp 152–155 °C. IR ($CHCl_3$): 3520, 3410, 1720, 1680, 1505. ^{1}H-NMR (200 MHz, CD_3OD): 5.87–5.77 (m, 1 H, CHC*H*=CH), 5.58–5.49 (m, 1 H, CHCH=C*H*), 4.09 (d, 1 H, J = 6.9 Hz, C*H*N, minor isomer), 4.00 (d, 1 H, J = 6.1 Hz, C*H*N, major isomer), 3.65 and 3.64 (s, 3 H, CH_3OC(O)N, 2 isomers), 2.65–2.50 (br s, 1 H, C*H*CH=CH), 2.05–1.90 (m, 2 H, CH_2CH=CH), 1.81–1.24 (m, 4 H, CHCH_2CH_2). ^{13}C-NMR (50 MHz, CD_3OD, some carbons show two peaks because of diastereomers): 176.3 (*C*(O)NH_2), 170.3 (CH_3*O**C**(O)N), 131.4 and 130.6 (CH*C*H=CH), 128.2 and 126.7 (CHCH=*C*H), 59.7 and 59.5 (*C*HN), 52.5 (CH_3OC(O)N), 39.0 and 38.9 (*C*HCH=CH), 27.2, 25.8, 25.0, 22.4, 22.0 ((*C*H_2)$_3$). Anal. Calcd for $C_{10}H_{16}N_2O_3$ (212.25): C, 56.59; H, 7.60; N, 13.20. Found: C, 55.12; H, 7.54; N, 13.04.

General Procedure B for the Coupling of 12–15 with Allylsilanes. The silicon nucleophile (1.2–2.5 equiv) was added at rt to a 0.2 M solution of the α-methoxy α-amino amide in dry CH_2Cl_2. The reaction mixture was cooled to −78 °C. $BF_3{\cdot}OEt_2$ (1.5–2.5 equiv) was then added slowly to the reaction mixture. After a further 15 min at −78 °C, the reaction mixture was allowed to warm to rt and was stirred for a further 3–6 h. The reaction mixture was then poured out into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine (1×), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed.

2-((Benzyloxycarbonyl)amino)-*N*-methoxy-4-pentenamide (26) Using $BF_3{\cdot}OEt_2$. According to general procedure B, starting from 690 mg (2.57 mmol) of **13**, 0.82 mL (588 mg, 5.15 mmol) of allyltrimethylsilane (**16**), 0.63 mL (730 mg, 5.14 mmol) of $BF_3{\cdot}OEt_2$, and 12.5 mL of CH_2Cl_2, there was obtained 610 mg (2.19 mmol, 85%) of **26**, as a white solid, after flash chromatography, R_f 0.22 (EtOAc/hexane (1:1)), mp 117.5–120.5 °C. IR ($CHCl_3$): 3420, 3320–3200, 1740–1640, 1500. ^{1}H-NMR (200 MHz): 9.25 (br s, 1 H, N*H*OCH_3), 7.34 (s, 5 H, Ph), 5.85–5.65 (m, 1 H, −C*H*=CH_2), 5.37 (br s, 1 H, N*H*), 5.19–5.10 (m, 4 H, −CH=CH_2, OCH_2Ph), 4.18–4.07 (m, 1 H, C*H*N), 3.74 (s, 3 H, CH_3ONH), 2.54–2.48 (m, 2 H, CH_2CH=CH_2). ^{13}C-NMR (50 MHz): 168.5 (*C*(O)N$HOCH_3$), 156.2 (*N**C**(O)O), 135.9 (Ph), 132.3 (−CH=CH_2), 128.4, 128.3, 128.2, 128.0, 127.8 (Ph), 119.0 (−CH=*C*H_2), 67.0 (O*C*H_2Ph), 64.1 (*C*H_3ON), 51.8 (*C*HN), 36.7 (*C*H_2CH=CH_2). MS: M^+ = 278; (M − C(O)N$HOCH_3$)$^+$ = 204.

2-((Benzyloxycarbonyl)amino)-*N*-methoxy-4-pentenamide (26) Using $SnCl_4$. According to general procedure B, starting from 682 mg (2.55 mmol) of **13**, 0.81 mL (582 mg, 5.09 mmol) of allyltrimethylsilane (**16**), 4.24 mL (5.09 mmol; 1.2 M solution in CH_2Cl_2) of $SnCl_4$, and 8 mL of CH_2Cl_2, there was obtained 518 mg (1.86 mmol, 73%) of **26**, after flash chromatography, R_f 0.22 (EtOAc/hexane (1:1)). Spectroscopic data: vide supra.

2-((Benzyloxycarbonyl)amino)-2-(2-cyclopentenyl)-*N*-methoxyacetamide (27). According to general procedure B, starting from 11.05 g (41.2 mmol) of **13**, 10.4 mL (8.66 g, 61.8 mmol) of 3-(trimethylsilyl)cyclopentene (**18**), 10.1 mL (11.70 g, 82.5 mmol) of $BF_3{\cdot}OEt_2$, and 150 mL of CH_2Cl_2, there was obtained 13.66 g of a crude product. This material was recrystallized from EtOAc/hexane (1.5:1) to give 5.04 g of **27** as a yellow solid. A second crop was obtained by purification of the mother liquor using flash chromatography to give another 2.85 g of **27**, R_f 0.35 (EtOAc/hexane (1:1)). Total yield of **27**: 7.89 g (26.0 mmol, 63%), as a mixture of diastereomers (50:50), mp 154–158 °C. IR ($CHCl_3$): 3430, 3320–3220, 1760–1650, 1510, 1490. ^{1}H-NMR (300 MHz): 9.71 (s, 1 H, N*H*OCH_3), 7.32 (s, 5 H, Ph), 5.90–5.82 (m, 1 H, CHC*H*=CH), 5.68–5.56 (m, 2 H, N*H*, CHCH=C*H*), 5.08 (s, 2 H, OCH_2Ph), 4.12–4.04 (m, 1 H, C*H*N first isomer), 3.99–3.93 (m, 1 H, C*H*N second isomer), 3.73 (s, 3 H, CH_3ON), 3.20–3.13 (m, 1 H, C*H*CH=CH), 2.33–2.25 (m, 2 H, CH_2CH=CH), 2.02–1.93 (m, 1 H, CH*H*CHCH_2), 1.70–1.55 (m, 1 H, CHHC*H*CH_2). ^{13}C-NMR (50 MHz): 168.7 (*C*(O)N$HOCH_3$), 156.7 (N*C*(O)O), 136.0 (Ph), 134.8 and 133.8 (CH*C*H=CH), 130.0 and 129.2 (CHCH=CH), 128.4, 128.2, 128.1, 127.9 and 127.8 (Ph), 67.1 (O*C*H_2Ph), 64.1 (*C*H_3ON), 55.9 (*C*HN), 48.4 and 47.8 (*C*HCH=CH), 32.1 and 31.7 (*C*H_2CH=CH), 26.1 and 25.6 (CH*C*H_2CH_2). Anal. Calcd for $C_{16}H_{20}N_2O_4$ (304.35): C, 63.14; H, 6.62; N, 9.20. Found: C, 62.72; H, 6.68; N, 9.15.

2-((Benzyloxycarbonyl)amino)-3-cyclohexyl-*N*-methoxy-4-methyl-4-pentenamide (28). According to general procedure B, starting from 574 mg (2.14 mmol) of **13**, 0.81 mL (675 mg, 3.21 mmol) of 1-cyclohexyl-2-methyl-3-(trimethylsilyl)propene (**24**),[4] 0.53 mL (608 mg, 4.28 mmol) of $BF_3{\cdot}OEt_2$, and 10.0 mL of CH_2Cl_2, there was obtained 547 mg (1.46 mmol, 68%) of **28**, as a colorless oil, after flash chromatography, R_f 0.27 (EtOAc/hexane (1:1.5)), as a mixture of diastereomers (50:50). IR ($CHCl_3$): 3420, 3320–3220, 1740–1650, 1520–1480. ^{1}H-NMR (200 MHz): 9.15 (s, 1 H, N*H*OCH_3), 7.33 (s, 5 H, Ph), 5.41 (d, 1 H, J = 9.0 Hz, N*H*, first isomer), 5.30–5.00 (m, 3 H, N*H* second isomer, OCH_2Ph), 4.97 (s, 1 H, *H*CH=C), 4.72 (s, 1 H, HC*H*=C), 4.30–4.20 (m, 1 H, C*H*N, first isomer), 3.89 (d, 1 H, J = 4.1 Hz, C*H*N, second isomer), 3.68 (s, 3 H, CH_3ON), 2.40 (br s, 1 H, =CC*H*), 2.04–1.07 (cyclohexane, =CCH_3). ^{13}C-NMR (50 MHz): 168.8 (*C*(O)NHOCH_3), 156.2 (N*C*(O)O), 144.1 and 143.6 (H_2C=*C*), 136.0 (Ph), 128.6, 128.3 and 127.9 (Ph), 114.6 (H_2C=C), 67.2 (O*C*H_2Ph), 64.1 (*C*H_3ON), 53.0 and 52.6 (*C*HN, =*C*CH), 37.4 and 37.2 (CH_2*C*HCH_2), 31.7, 28.9, 26.7, 26.4 and 26.0 ((*C*H_2)$_5$), 24.2 (=C*C*H_3). MS: M^+ = 374.

2-((Methoxycarbonyl)amino)-*N*-methoxy-4-pentenamide (29). According to general procedure B, starting from 872 mg (4.54 mmol) of **12**, 1.45 mL (1.04 g, 9.09 mmol) of allyltrimethylsilane (**16**), 1.12 mL (1.29 g, 9.09 mmol) of $BF_3{\cdot}OEt_2$, and 20.0 mL of CH_2Cl_2, there was obtained 737 mg (3.65 mmol, 80%) of **29**, as a colorless oil, after flash chromatography, R_f 0.26 (EtOAc/hexane (4:1)). IR ($CHCl_3$): 3430, 3330–3220, 1750–1640, 1510. ^{1}H-NMR (200 MHz): 9.86 (br s, 1 H, N*H*OCH_3), 5.83–5.63 (m, 2 H, N*H*, −C*H*=CH_2), 5.18–5.09 (m, 2 H, −CH=CH_2), 4.19–4.05 (m, 1 H, C*H*N), 3.74 (s, 3 H, CH_3ON), 3.66 (s, 3 H, CH_3OC(O)-N), 2.52–2.39 (m, 2 H, CH_2CH=CH_2). ^{13}C-NMR (50 MHz, CD_3OD): 170.6 (*C*(O)N$HOCH_3$), 158.8 (N*C*(O)O), 134.2 (−*C*H=CH_2), 118.9 (CH=*C*H_2), 64.4 (*C*H_3ON), 53.9 (*C*HN), 52.7 (*C*H_3OC(O)N), 37.5 (*C*H_2CH=CH_2). MS: (M − C_3H_5)$^+$ = 161; (M − C(O)N$HOCH_3$)$^+$ = 128.

2-((Methoxycarbonyl)amino)-2-(2-cyclopentenyl)-*N*-methoxyacetamide (30). According to general procedure B, starting from 540 mg (2.81 mmol) of **12**, 0.95 mL (789 mg, 5.63 mmol) of 3-(trimethylsilyl)cyclopentene (**18**), 0.69 mL (796 mg, 5.61 mmol) of $BF_3{\cdot}OEt_2$, and 14.0 mL of CH_2Cl_2, there was obtained 495 mg (2.17 mmol, 77%) of **30**, as a light yellow solid, after flash chromatography, R_f 0.28 (EtOAc/hexane (4:1)), as a mixture of diastereomers (50:50), mp 140–142 °C (after recrystallization). IR ($CHCl_3$): 3430, 3320–3190, 1740–1640, 1530–1480. ^{1}H-NMR

(200 MHz): 9.78 (s, 1 H, NHOCH$_3$), 5.90–5.83 (m, 1 H, CHCH=CH), 5.67–5.46 (m, 2 H, CHCH=CH, NH), 4.16–3.87 (m, 1 H, CHN), 3.76 (s, 3 H, CH$_3$ON), 3.66 (s, 3 H, CH$_3$OC(O)N), 3.13 (br m, 1 H, CHCH=CH), 2.32 (br m, 2 H, CH$_2$CH=CH), 2.13–1.95 (m, 1 H, CHHCHCH$_2$), 1.74–1.57 (m, 1 H, CHHCHCH$_2$). ^{13}C-NMR (50 MHz): 168.8 (C(O)NHOCH$_3$), 157.1 (NC(O)O), 134.9 and 133.9 (CHCH=CH), 130.0 and 129.2 (CHCH=CH), 64.2 (CH$_3$ON), 56.2 (CHN), 52.5 (CH$_3$OC(O)N), 48.3 and 47.7 (CHCH=CH), 32.1 and 31.7 (CH$_2$CH=CH), 26.2 and 25.6 (CHCH$_2$CH$_2$). MS: (M – C$_5$H$_7$)$^+$ = 161; (M – C(O)NHOCH$_3$)$^+$ = 154.

2-((Allyloxycarbonyl)amino)-*N*-methoxy-pentenamide (31). According to general procedure B, starting from 4.93 g (22.6 mmol) of **14**, 5.35 mL (3.85 g, 33.7 mmol) of allyltrimethylsilane (**16**), 5.52 mL (6.37 g, 44.9 mmol) of BF$_3$·OEt$_2$, and 12 mL of CH$_2$Cl$_2$, there was obtained 4.64 g (20.3 mmol, 90%) of **31**, as a colorless oil, after flash chromatography, R_f 0.36 (EtOAc/hexane (3:1)). IR (CHCl$_3$): 3370, 3100, 1770–1580, 1500. ^{1}H-NMR (200 MHz): 10.24 (s, 1 H, NHOCH$_3$), 5.93–5.59 (m, 3 H, 2 × –CH=CH$_2$, NH), 5.27–5.03 (m, 4 H, 2 × –CH=CH$_2$), 4.49 (d, 2 H, J = 5.1 Hz, OCH$_2$CH=), 4.20–4.07 (m, 1 H, CHN), 3.68 (s, 3 H, CH$_3$ON), 2.47–2.38 (m, 2 H, CH$_2$CH=CH$_2$). ^{13}C-NMR (50 MHz): 168.4 (C(O)NHOCH$_3$), 155.7 (NC(O)O), 132.3, 132.2 (2 × –CH=CH$_2$), 118.4, 117.3 (2 × –CH=CH$_2$), 65.5 (CH$_2$O), 63.6 (CH$_3$ON), 51.6 (CHN), 36.6 (CH$_2$CH=CH$_2$). MS: (M – C$_3$H$_5$)$^+$ = 187; (M – C(O)NHOCH$_3$)$^+$ = 154.

2-((Allyloxycarbonyl)amino)-2-(2-cyclopentenyl)-*N*-methoxyacetamide (32). According to general procedure B, starting from 1065 mg (4.89 mmol) of **14**, 1.24 mL (1026 mg, 7.33 mmol) of 3-(trimethylsilyl)cyclopentene (**18**), 1.20 mL (1387 mg, 9.77 mmol) of BF$_3$·OEt$_2$, and 25.0 mL of CH$_2$Cl$_2$, there was obtained 871 mg (3.43 mmol, 70%), of **32**, as a yellow solid, after flash chromatography, R_f 0.36 (EtOAc/hexane (2:1)), as a mixture of diastereomers (50:50). An analytical sample was obtained by recrystallization from EtOAc/hexane, mp 128–130 °C. IR (CHCl$_3$): 3430, 3320–3200, 1740–1650, 1505. ^{1}H-NMR (200 MHz): 9.87 (s, 1 H, NHOCH$_3$), 5.97–5.56 (m, 4 H, NH, –CH=CH$_2$, –CH=CH–, –CH=CH), 5.31–5.16 (m, 2 H, –CH=CH$_2$), 4.52 (d, 2 H, J = 5.1 Hz, OCH$_2$CH=), 4.07–3.88 (m, 1 H, CHN), 3.74 (s, 3 H, CH$_3$ON), 3.12 (br s, 1 H, CHCH=CH), 2.31 (m, 2 H, –CH$_2$CH=CH), 2.04–1.94 (m, 1 H, CHHCHCH$_2$), 1.70–1.60 (m, 1 H, CHHCHCH$_2$). ^{13}C-NMR (50 MHz): 168.7 (C(O)NHOCH$_3$), 156.4 (NC(O)O), 134.7 and 133.7 (–CH=CH$_2$), 132.5 and 132.4 (CHCH=CH), 130.1 and 129.0 (CHCH=CH), 117.9 and 117.8 (–CH=CH$_2$), 65.9 (CH$_2$O), 64.1 and 63.9 (CH$_3$ON), 62.0 and 62.5 (CHN), 48.4 and 47.9 (CHCH=CH), 32.1 and 31.6 (CH$_2$CH=CH), 26.1 (CHCH$_2$CH$_2$). Anal. Calcd for C$_{12}$H$_{18}$N$_2$O$_4$ (254.29): C, 56.68; H, 7.13; N, 11.02. Found: C, 56.71; H, 7.19; N, 10.94.

2-((Allyloxycarbonyl)amino)-2-(2-cyclohexenyl)-*N*-methoxyacetamide (33). According to general procedure B, starting from 277 mg (1.27 mmol) of **14**, 0.35 mL (315 mg, 2.05 mmol) of 3-(trimethylsilyl)cyclohexene (**19**), 0.34 mL (387 mg, 2.73 mmol) of BF$_3$·OEt$_2$, and 6.5 mL of CH$_2$Cl$_2$, there was obtained 250 mg (0.93 mmol, 73%) of **33**, as a white solid, after flash chromatography, R_f 0.41 (EtOAc/hexane (1.5:1)), as a mixture of diastereomers (60:40). An analytical sample was obtained by recrystallization from EtOAc/hexane, mp 139–142 °C. IR (CHCl$_3$): 3420, 3320–3200, 1740–1650, 1520–1480. ^{1}H-NMR (200 MHz): 9.48 (br s, 1 H, NHOCH$_3$), 5.97–5.80 (m, 2 H, CHCH=CH, CH=CH$_2$), 5.63–5.46 (m, 2 H, CHCH=CH, NH), 5.35–5.19 (m, 2 H, CH=CH$_2$), 5.55 (m, 2 H, OCH$_2$CH=, two isomers), 4.00–3.85 (m, 1 H, CHN), 3.77 (s, 3 H, CH$_3$ON), 2.61 (br s, 1 H, CHCH=CH), 2.10–1.85 (m, 2 H, CH$_2$CH=CH), 1.75–1.21 (m, 4 H, CHCH$_2$CH$_2$). ^{13}C-NMR (50 MHz): 168.4 (C(O)NHOCH$_3$), 156.4 (NC(O)O), 132.3 (–CHCH$_2$), 131.2 and 130.5 (CHCH=CH), 126.1 and 125.4 (CHCH=CH), 118.0 and 117.9 (–CH=CH$_2$), 66.0 (CH$_2$O), 64.2 (CH$_3$ON), 56.3 and 56.1 (CHN), 37.8 (CHCH=CH), 25.8, 25.0, 24.9, 24.3, 21.2 and 20.5 ((CH$_2$)$_3$). Anal. Calcd for C$_{13}$H$_{20}$N$_2$O$_4$ (268.31): C, 58.19; H, 7.51; N, 10.44. Found: C, 58.06; H, 7.51; N, 10.36.

2-((Allyloxycarbonyl)amino)-*N*-methoxy-4-methyl-4-pentenamide (34). According to general procedure B, starting from 199 mg (0.91 mmol) of **14**, 0.33 mL (251 mg, 1.96 mmol) of methallyltrimethylsilane (**25**),[26] 0.24 mL (278 mg, 1.96 mmol) of BF$_3$·OEt$_2$, and 5.0 mL of CH$_2$Cl$_2$, there was obtained 89 mg (0.37 mmol, 41%) of **34**, as a colorless oil, after flash chromatography, R_f 0.41 (EtOAc/hexane (1.5:1)). IR (CHCl$_3$): 3420, 3320–3180, 1750–1650, 1640, 1540–1480. ^{1}H-NMR (200 MHz): 10.27 (s, 1 H, NHOCH$_3$), 5.93–5.74 (m, 1 H, CH=CH$_2$, NH), 5.27–5.12 (m, 2 H, CH=CH$_2$), 4.80 (s, 1 H, HCH=C), 4.75 (s, 1 H, HCH=C), 4.50 (d, 2 H, J = 5.1 Hz, OCH$_2$CH=), 4.24 (m, 1 H, CHN), 3.69 (s, 3 H, CH$_3$ON), 2.48–2.35 (m, 2 H, CH$_2$C=), 1.70 (s, 3 H, CH$_3$C=). ^{13}C-NMR (50 MHz): 169.0 (C(O)NHOCH$_3$), 156.2 (NC(O)O), 140.2 (H$_2$C=C), 132.3 (–CH=CH$_2$), 117.8 (–CH=CH$_2$), 114.5 (H$_2$C=C), 65.9 (CH$_2$O), 64.1 (CH$_3$ON), 50.7 (CHN), 40.3 (=CCH$_2$), 21.9 (CH$_3$C=). MS: (M – C$_4$H$_7$)$^+$ = 187; (M – C(O)NHOCH$_3$)$^+$ = 168.

2-((Methoxycarbonyl)amino)-*N*,*N*-dimethyl-4-pentenamide (35). According to general procedure B, starting from 471 mg (2.48 mmol) of **15**, 0.59 mL (424 mg, 3.71 mmol) of allyltrimethylsilane (**16**), 0.61 mL (704 mg, 4.96 mmol) of BF$_3$·OEt$_2$, and 12.5 mL of CH$_2$Cl$_2$, there was obtained 443 mg (2.22 mmol, 90%) of **35**, as a yellow oil, after flash chromatography, R_f 0.17 (EtOAc/hexane (1.5:1)). IR (CHCl$_3$): 3430, 1710, 1635, 1500. ^{1}H-NMR (200 MHz): 6.08 (d, 1 H, J = 7.7 Hz, NH), 5.77–5.63 (m, 1 H, –CH=CH$_2$), 5.13–5.04 (m, 2 H, –CH=CH$_2$), 4.73 (m, 1 H, CHN), 3.62 (s, 3 H, CH$_3$OC(O)N), 3.08 (s, 3 H, CH$_3$N), 2.93 (s, 3 H, CH$_3$N), 2.42–2.31 (m, 2 H, CH$_2$CH=CH$_2$). ^{13}C-NMR (50 MHz): 171.6 (C(O)N(CH$_3$)$_2$), 156.6 (NC(O)O), 132.4 (CH=CH$_2$), 118.5 (CH=CH$_2$), 52.0 (CHN), 50.1 (CH$_3$OC(O)N), 37.1 and 35.7 (2 × CH$_3$N), 37.0 (CH$_2$CH=CH$_2$). MS: M$^+$ = 200; (M – C$_3$H$_5$)$^+$ = 159; (M – C(O)N(CH$_3$)$_2$)$^+$ = 128.

2-Amino-2-cyclopentyl-*N*-methoxyacetamide (36). To a solution of **27** (7.70 g, 25.3 mmol) in 1:1 EtOH/THF (ca. 40 mL) was added 10% Pd/C (600 mg). The mixture was hydrogenated at 40 psi for 17 h and then filtered through Celite to remove the catalyst, concentrated in vacuo, and washed with ether to give 3.30 g (19.2 mmol, 76%) of a light-red solid, mp 95–98 °C. IR (CHCl$_3$): 3430–3320, 1680, 1455. ^{1}H-NMR (200 MHz, CDCl$_3$/CD$_3$OD): 3.67 (s, 3 H, CH$_3$ON), 2.98 (d, 1 H, J = 8.1 Hz, CHN), 2.12–2.00 (m, 1 H, CHCHN), 1.79–1.10 (m, 8 H, (–CH$_2$–)$_4$). ^{13}C-NMR (50 MHz, CDCl$_3$/CD$_3$OD): 171.0 (C(O)NHOCH$_3$), 63.8 (CH$_3$ON), 57.0 (CHN), 43.7 (CHCHN), 29.1, 28.6, 25.1 and 25.0 ((–CH$_2$–)$_4$). MS: (M – C$_5$H$_9$)$^+$ = 103; (M – C(O)NHOCH$_3$)$^+$ = 98.

2-Amino-4-pentenamide (37). To a solution of **20** (54 mg, 0.32 mmol) in acetonitrile (3.0 mL) was added at rt TMSI (135 mg, 0.63 mmol). The reaction mixture was stirred for 2 h at 50–55 °C, whereafter it was poured into a 5% aqueous NaHSO$_4$. After extraction with CH$_2$Cl$_2$ (3×), the water layer was made basic with Na$_2$CO$_3$. The water layer was extracted with CH$_2$Cl$_2$ (3×), dried (MgSO$_4$), and concentrated in vacuo to give 13.4 mg (0.12 mmol, 37%) of **37**, as a white crystalline compound, mp 50–52 °C (after recrystallization from ethanol). IR (CHCl$_3$): 3500, 3380, 3080, 2990, 2920, 1675, 1550. ^{1}H-NMR (200 MHz): 7.15 (br s, 1 H, H$_2$NC(O)), 6.44 (br s, 1 H, H$_2$NC(O)), 5.83–5.62 (m, 1 H, –CH=CH$_2$), 5.14–5.06 (m, 2 H, –CH=CH$_2$), 3.38 (dd, 1 H, J = 4.0, 8.4 Hz, CHN), 2.61–2.49 (m, 1 H, HCHCH=CH$_2$), 2.32–2.17 (m, 1 H, HCHCH=CH$_2$), 1.55 (s, 2 H, NH$_2$). ^{13}C-NMR (50 MHz): 177.8 (C(O)NH$_2$), 134.2 (–CH=CH$_2$), 118.6 (–CH=CH$_2$), 53.9 (CHN), 39.3 (CH$_2$CH=CH$_2$).

2-((*tert*-Butyloxycarbonyl)amino)-*N*-methoxy-4-pentenamide (38) via Pd(0)-Catalyzed Transprotection. To a stirred solution of **31** (415 mg, 1.82 mmol) and di-*tert*-butyl dicarbonate (992 mg, 4.55 mmol) in dry CH$_2$Cl$_2$ (17.0 mL) was added a solution of Pd[(PPh$_3$)$_4$] (42 mg, 36 μmol) in 1 mL of CH$_2$Cl$_2$ immediately followed by the addition of *n*-Bu$_3$SnH (0.54 mL, 582 mg, 2.00 mmol).[17b] After the solution was stirred for 15 min at rt the solvent was evaporated in vacuo and the residue was chromatographed, R_f 0.38 (EtOAc/hexane (1.5:1)), to give 393 mg (1.62 mmol, 89%) of **38** as a white solid. An analytical sample was obtained by recrystallization from EtOAc/hexane, mp 108–109 °C. IR (CHCl$_3$): 3430, 3250, 1700, 1495. ^{1}H-NMR (200 MHz): 10.18 (s, 1 H, NHOCH$_3$), 5.82–5.57 (m, 1 H, –CH=CH$_2$), 5.44 (d, 7.2 Hz, NH), 5.12–5.03 (m, 2 H, –CH=CH$_2$), 4.17–4.05 (m, 1 H, CHN), 3.69 (s, 3 H, CH$_3$ON), 2.46–2.36 (m, 2 H, CH$_2$CH=CH$_2$), 1.37 (s, 9 H, (CH$_3$)$_3$C–). ^{13}C-NMR (50 MHz): 168.7 (C(O)NHOCH$_3$), 155.7 (NC(O)O–), 132.7 (–CH=CH$_2$), 118.8 (–CH=CH$_2$), 80.4 ((CH$_3$)$_3$CO–), 64.2 (CH$_3$ON), 36.7 (CH$_2$CH=CH$_2$), 28.2 ((CH$_3$)$_3$C–). Anal. Calcd for C$_{11}$H$_{20}$N$_2$O$_4$ (244.29): C, 54.08; H, 8.25; N, 11.47.

(26) Carr, S. A.; Weber, W. P. *J. Org. Chem.* **1985**, *50*, 2782.

Found: C, 53.97; H, 8.20; N, 11.38.

2-((*tert*-Butyloxycarbonyl)amino)-2-(2-cyclopentenyl)-*N*-methoxyacetamide (39). According to the same procedure as described for **38**, starting from 386 mg (1.52 mmol) of **32**, 829 mg (3.80 mmol) of di-*tert*-butyl dicarbonate, 8.0 mL of CH_2Cl_2, 35 mg (30 μmol) of $Pd[(PPh_3)_4]$, and 0.45 mL (487 mg, 1.67 mmol) of Bu_3SnH, there was obtained 377 mg (1.40 mmol, 92%) of **39**, as a white solid, after flash chromatography, R_f 0.54 (EtOAc/hexane (1.5:1)), as a mixture of diastereomers (50:50). An analytical sample was obtained after recrystallization from EtOAc/hexane, mp 140–141 °C. IR ($CHCl_3$): 3430, 3300–3200, 1730–1640, 1505, 1495. ^{1}H-NMR (200 MHz): 9.90 (N*H*OCH$_3$), 5.88–5.80 (m, 1 H, CHC*H*=CH), 5.68–5.55 (m, 1 H, CHCH=C*H*), 5.41 (d, 1 H, J = 7.6 Hz, N*H*, first isomer), 5.28 (d, 1 H, J = 8.8 Hz, N*H*, second isomer), 4.02–3.83 (m, 1 H, C*H*N), 3.74 (CH_3O-N), 3.25–3.00 (br m, 1 H, CH-CH=CH), 2.35–2.17 (m, 2 H, CH_2-CH=CH), 2.02–1.93 (m, 1 H, CH*H*CHCH$_2$), 1.67–1.51 (m, 1 H, CHHC*H*CH$_2$), 1.41 (s, 3 H, (C*H*$_3$)$_3$C). ^{13}C-NMR (50 MHz): 168.9 (*C*(O)NHOCH$_3$), 156.9 (N*C*(O)O), 134.5 and 133.6 (CH*C*H=CH), 130.2 and 129.5 (CHCH=*C*H), 80.3 ((CH$_3$)$_3$*C*O), 64.1 (*C*H$_3$ON), 55.3 (*C*HN), 48.4 and 47.9 (*C*HCH=CH), 32.1 and 31.7 (*C*H$_2$C-H=CH), 28.2 ((*C*H$_3$)$_3$C*O*), 26.2 and 25.7 (CH*C*H$_2$CH$_2$). Anal. Calcd for $C_{13}H_{22}N_2O_4$ (270.33): C, 57.76; H, 8.20; N, 10.36. Found: C, 57.81; H, 8.28; N, 10.33.

2-Amino-*N*-methoxy-4-pentenamide (40). A. Via Deprotection of 29. To a solution of **29** (8.10 g, 40.1 mmol) in acetonitrile (200 mL) was added at rt TMSI (11.4 mL, 16.03 g, 80.1 mmol). The reaction mixture was stirred for 1–2 h at 50 °C, whereafter it was poured out into 10% aqueous $NaHSO_4$ (200 mL). The water layer was extracted with CH_2Cl_2 (3×). The combined organic layers were extracted with 10% aqueous $NaHSO_4$. The combined water layers were made basic with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (4 × 400 mL). The organic layers were dried (K_2CO_3) and concentrated in vacuo to give 1.09 g (7.6 mmol, 19%) of a light yellow solid. An analytical sample was obtained by recrystallization from EtOAc/hexane, mp 73–75 °C. IR ($CHCl_3$): 3370, 1730–1630, 1460, 1440. ^{1}H-NMR (200 MHz): 5.82–5.61 (m, 1 H, –C*H*=CH$_2$), 5.20–5.07 (m, 2 H, –CH=C*H*$_2$), 3.72 (s, 3 H, C*H*$_3$ON), 3.41 (dd, 1 H, J = 7.8, 7.7 Hz, C*H*N), 2.61–2.49 (m, 1 H, *H*CHCH=CH$_2$), 2.37–2.21 (m, 1 H, HC*H*CH=CH$_2$). ^{13}C-NMR (50 MHz): 172.9 (*C*(O)NHOCH$_3$), 134.7 (*C*H=CH$_2$), 118.8 (CH=*C*H$_2$), 64.3 (*C*H$_3$ON), 53.5 (*C*HN), 40.6 (*C*H$_2$CH=CH$_2$). Anal. Calcd for $C_6H_{12}N_2O_2$ (144.17): C, 49.99; H, 8.39. Found: C, 49.83; H, 8.45.

B. Via Deprotection of 31. To a solution of **31** (5.61 g, 24.6 mmol) in CH_2Cl_2 (100 mL) was added $Pd[(PPh_3)]_4$ (0.57 g, 0.5 mmol). Immediately after this Bu_3SnH (7.28 mL, 7.88 g, 27.1 mmol) was added.[16c] The reaction mixture was stirred for 15 min, at which point the reaction was shown to be complete on TLC. HCl(g) was bubbled through the solution for 15 min (to cleave the tributyltincarbamate). After the solution was stirred for another 15 min the solvent was evaporated in vacuo. The residue (which contains the HCl salt of the free amine) was taken up in CH_2Cl_2, and K_2CO_3 was added. The mixture was stirred for 1 h, filtered, and concentrated in vacuo to give 8 g of a red oil. The crude product was further purified using flash chromatography (eluent MeOH) to give 1.38 g (9.6 mmol, 39%) of **39** (not completely pure). Spectroscopic data: vide supra.

C. Via Deprotection of 38. A solution of **38** (645 mg, 2.64 mmol) in formic acid (20.0 mL) was stirred at rt for 4 h. The mixture was then concentrated in vacuo. The residue was taken up in water and extracted with CH_2Cl_2 (3×). The water layer was concentrated in vacuo to give 453 mg (2.38 mmol, 90%) of the formate salt of **40**, as a thick, light yellow oil. ^{1}H-NMR (200 MHz, D_2O): 8.50 (s, 1 H, *H*C(O)O–), 5.89–5.73 (m, 1 H, C*H*=CH$_2$), 5.40–5.23 (m, 2 H, CH=C*H*$_2$), 4.03–3.97 (m, 1 H, C*H*N), 3.81 (s, 3 H, C*H*$_3$ON), 2.73–2.67 (m, 2 H, C*H*$_2$CH=). ^{13}C-NMR (50 MHz): 173.0 (H*C*(O)O–), 168.2 (*C*(O)NHOCH$_3$), 132.2 (*C*H=CH$_2$), 123.9 (CH=*C*H$_2$), 66.9 (*C*H$_3$ON), 52.3 (*C*HN), 37.5 (*C*H$_2$CH=).

2-Amino-2-(2-cyclopentenyl)-*N*-methoxyacetamide (41) via Deprotection of 39. A solution of **39** (153 mg, 0.57 mmol) in formic acid (5.0 mL) was stirred at rt for 2 h. The mixture was then concentrated in vacuo. The remaining solid was washed with CH_2Cl_2 and filtered to give 117 mg (0.54 mmol, 95%) of **41** as the formate salt, as a white solid, as a mixture of diastereomers (50:50), mp 113.5–115 °C. ^{1}H-NMR (200 MHz, D_2O): 8.40 (s, 1 H, *H*C(O)O–), 6.08–5.99 (m, 1 H, CHC*H*=CH), 5.67–5.55 (m, 1 H, CHCH=C*H*), 3.83–3.79 (m, 1 H, C*H*N), 3.73 and 3.71 (s, 3 H, C*H*$_3$ON, two isomers), 3.30–3.17 (m, 1 H, C*H*CH=CH), 2.44–2.30 (m, 2 H, C*H*$_2$CH=CH), 2.20–2.00 (m, 1 H, CH*H*CHCH$_2$), 1.82–1.58 (m, 1 H, CHHC*H*CH$_2$). ^{13}C-NMR (50 MHz, most carbons show two peaks because of diastereomers): 172.6 (H*C*-(O)O–), 167.6 and 167.4 (*C*(O)NHOCH$_3$), 138.8 and 138.6 (CH-*C*H=CH), 129.0 and 128.8 (CHCH=*C*H), 66.3 (*C*H$_3$ON), 56.1 and 55.9 (*C*HN), 48.9 (*C*HCH=CH), 33.5 and 33.4 (*C*H$_2$CH=CH), 26.5 and 26.3 (CH*C*H$_2$CH$_2$). Anal. Calcd for $C_9H_{16}N_2O_4$ (216.24): C, 49.99; H, 7.46; N, 12.95. Found: C, 48.82; H, 7.32; N, 12.42.

Synthesis of Valine *N*-Methoxyamide (42). This compound was synthesized from valine via protection of the amine using the benzyloxycarbonyl group as the protective group. D,L-Valine (35 g, 0.3 mol) was dissolved in 4 N NaOH (75 mL) and water (10 mL). The solution was cooled to 0 °C, and then equimolar amounts of 4 N NaOH (90 mL) and benzyl chloroformate (56 g, 0.33 mol) were added in six portions.[27] The mixture was allowed to warm to rt in 1 h and extracted with ether (2 × 100 mL). The water layer was acidified to pH = 2 using 4 N HCl. After extraction with CH_2Cl_2 (4 × 100 mL), the combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallized from hot toluene (150 mL) and hexane (300 mL) to give 62 g (0.25 mol, 82%) of *N*-(benzyloxycarbonyl)valine (Z-Val-OH) as a white solid, as a mixture of rotamers (*Z*/*E* (1:1.5)), mp 71–72 °C (lit.[27] mp 76–78 °C). ^{1}H-NMR (200 MHz): 8.1 (br s, 1 H, CO_2H), 7.38 (s, 5 H, Ph), 6.06 (d, J = 12.0 Hz) and 5.27 (d, J = 12.0 Hz, 1 H, N*H*, two rotamers), 5.12 (s, 2 H, C*H*$_2$O), 4.36 (dd, J = 4.5, 12.0 Hz) and 4.20 (br s, 1 H, C*H*N, two rotamers), 2.22 (m, 1 H, C*H*(CH$_3$)$_2$), 1.00 and 0.92 (2 × d, 6 H, J = 6.5 Hz, (C*H*$_3$)$_2$, two rotamers). Z-Val-OH (25.1 g, 0.10 mol) was dissolved in dioxane (250 mL). To this solution was added 30% aqueous *O*-methylhydroxylamine (25 mL, 7.5 g, 0.18 mol). Then DCC (21.0 g, 0.10 mol) was added dropwise in 10 min. After 5 h of stirring at rt the mixture had turned into a white suspension. The solid material was removed by filtration and washing with dioxane. The filtrate was concentrated in vacuo. The residue was diluted with toluene, again concentrated in vacuo, and recrystallized from toluene (250 mL) to give 19.5 g (0.071 mol, 71%) of *N*-(benzyloxycarbonyl)valine *N*-methoxyamide (Z-Val-NHOCH$_3$) as a white solid, mp 144–145 °C. ^{1}H-NMR (200 MHz): 9.55 (s, 1 H, N*H*OCH$_3$), 7.35 (s, 5 H, Ph), 5.59 (d, 1 H, J = 9.5 Hz, N*H*), 5.09 (AB system, 2 H, J = 11.0 Hz, C*H*$_2$O), 3.82 (m, 1 H, C*H*N), 3.72 (s, 3 H, C*H*$_3$ON), 2.06 (octet, 1 H, J = 6.8 Hz, C*H*(CH$_3$)$_2$), 0.95 (d, 6 H, J = 6.8 Hz, (C*H*$_3$)$_2$). ^{13}C-NMR (50 MHz): 168.8 (*C*(O)NHOCH$_3$), 156.7 (O*C*(O)N), 136.1 (Ph), 128.5, 128.2 and 127.9 (Ph), 67.1 (O*C*H$_2$Ph), 64.1 (*C*H$_3$ON), 58.2 (*C*HN), 31.1 (*C*H(CH$_3$)$_2$), 19.1 and 18.4 (2 × *C*H$_3$C). Z-Val-NHOCH$_3$ (10.0 g, 36.4 mmol) was dissolved in MeOH (250 mL). To this solution was added 5% Pd/C (1.2 g), and nitrogen was bubbled through this mixture for 15 min. After this, the mixture was hydrogenated at 1 atm for 2.5 h. After bubbling nitrogen through the resulting mixture for another 15 min, it was filtered and concentrated in vacuo to give 5.6 g (≈quantitative) of Val-NHOCH$_3$ (**42**) as a white solid, mp 103–105 °C. ^{1}H-NMR (200 MHz): 9.6 (br s, 1 H, N*H*OCH$_3$), 3.77 (s, 3 H, C*H*$_3$ON), 3.35 (d, 1 H, J = 4.5 Hz, C*H*N), 2.28 (m, 1 H, C*H*(CH$_3$)$_2$), 1.4 (br s, 2 H, NH$_2$), 1.00 (d, 3 H, J = 6.5 Hz, C*H*$_3$), 0.87 (d, 3 H, J = 6.5 Hz, C*H*$_3$). ^{13}C-NMR (50 MHz, $CDCl_3/CD_3OD$): 171.6 (*C*(O)NHOCH$_3$, 63.7 (*C*H$_3$ON), 58.5 (*C*HN), 31.7 (*C*H(CH$_3$)$_2$), 18.8 and 17.0 (2 × *C*H$_3$C). Anal. Calcd for $C_6H_{14}N_2O_2$ (146.19): C, 49.30; H, 9.65; N, 19.16. Found: C, 49.15; H, 9.53; N, 18.96.

Enzymatic Resolution of 2-Amino-4-pentenamide (37). A solution of **37** (3.08 g, 27.0 mmol) in water (36.0 mL) was adjusted to pH = 8.2 with 40% aqueous KOH. To the solution was added 1.0 g of a crude enzyme paste from *P. putida*. After the solution was stirred for 16 h at 37 °C a complete conversion was achieved. After removal of the enzymes by centrifugation benzaldehyde (1.43 g, 13.5 mmol) was added (to effect the formation of the Schiff base of the remaining starting material). After 3 h the resulting crystals were removed by filtration and then washed with water (ca. 4 mL) to yield after drying in vacuo 2.25 g (11.1 mmol, 82%)

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of the Schiff base of the D-amino amide. The filtrate (containing the L-amino acid) was concentrated in vacuo and applied to a Dowex 50 W ion-exchange column, which was eluted with 2 N NH_4OH. The ninhydrine positive fractions were collected and concentrated in vacuo. The resulting solid was washed with a 2-propanol/diethyl ether mixture to give (after drying in vacuo) 1.47 g (12.83 mmol, 95%) of L-allylglycine. $[\alpha]^{24}_D$ –42.7 (*c* 4, H_2O), $[\alpha]^{24}_D$ –6.6 (*c* 2, 5 N HCl).[28] Ee: 9.8 ± 1% (according to HPLC, using a Crownpack CR(+) column[19b]).

Enzymatic Resolution of 2-Amino-2-cyclopentyl-*N*-methoxyacetamide (36). A solution of **36** (3.01 g, 17.5 mmol) in water (60 mL) was adjusted to pH = 8.3 using NH_4OH. To the solution was added 2.5 g of a crude enzyme paste from *P. putida*. The resulting mixture was left at 37 °C for 22 h, after which the conversion was 43% (according to HPLC data, vide infra). The mixture was centrifuged at 10000 rpm for 15 min to remove the enzymes. Then benzaldehyde (1.35 mL, 1.41 g, 1.3 equiv relative to remaining starting material) was added and the solution was stirred for 1 h, during which time it became a white suspension due to the (selective) formation of the Schiff base of the remaining starting material. This suspension was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with water. The combined water layers were concentrated in vacuo, and the resulting residue was washed with acetone to give L-cyclopentylglycine (1.02 g, 98% based on 43% conversion) as a yellow solid. ^{1}H-NMR (200 MHz, D_2O/DCl): 3.61 (d, 1 H, *J* = 7.0 Hz, C*H*N), 2.34–2.17 (m, 1 H, CH_2CHCHN), 1.84–1.37 (m, 8 H, $-(CH_2)_4-$). Ee: (HPLC) 98%. The D-amino acid could be obtained as follows: to the combined organic layers was added 4 N HCl (50 mL) and the mixture was stirred for 17 h at rt (to effect cleavage of the Schiff base). After the layers were separated, the aqueous layer was refluxed for 24 h (to hydrolyze the *N*-methoxyamide). The solution was concentrated in vacuo, the residue (which contained the HCl salts of the D-amino acid and *O*-methylhydroxylamine) was dissolved in water (100 mL), and then Amberlyst 15 strongly acidic ion-exchange resin (20 g) was added. After 3 h of frequent swirling the mixture was filtered and washed several times with water until the water had a neutral pH. To the residue was then added NH_4OH (100 mL). After 1 h of frequent swirling the mixture was again filtered and washed with water until neutral pH. The filtrate (which now contained the free D-amino acid and free *O*-methylhydroxylamine) was decolorized by treatment with activated charcoal and concentrated in vacuo to give D-cyclopentylglycine (0.89 g, 65% based on 43% conversion) as a white solid. ^{1}H-NMR: vide supra. Ee: (HPLC) 74%. Conversion = 100 × ee (substrate)/(ee (substrate) + ee (product))% = 74/(74 + 98) = 43%.

Enzymatic Resolution of Valine *N*-Methoxyamide (42). Starting from 4 g of **42**, the same procedure as described for **36** was applied. The reaction was stopped after 32% conversion (according to HPLC data, vide infra). The yield of L-valine was 1.02 g (99% based on 32% conversion). ^{1}H-NMR (200 MHz, D_2O/DCl): 3.59 (d, 1 H, *J* = 4.2 Hz, C*H*N), 2.31–2.18 (m, 1 H, $(CH_3)_2CH$), 1.02 (d, 3 H, *J* = 7.2 Hz, CH_3CH), 0.97 (d, 3 H, *J* = 7.0 Hz, CH_3CH). Ee: (HPLC) 98%. The yield of D-valine was 1.69 g (82% based on 32% conversion). ^{1}H-NMR: vide supra. Ee: (HPLC) 46%. Conversion = 46/(46 + 98) = 32%.

Enzymatic Resolution of 2-Amino-*N*-methoxy-4-pentenamide (40). Starting from 0.98 g of **40**, the same procedure as described for **36** was applied (both the free amine and the formate salt of **40** can be used as the starting material). The reaction was stopped after 17 h, and after workup 0.16 g (21% of maximum total yield) of L-allylglycine was obtained as a yellow solid. ^{1}H-NMR (200 MHz, D_2O/DCl): 5.86–5.69 (m, 1 H, $-CH{=}CH_2$), 5.33–5.25 (m, 2 H, $-CH{=}CH_2$), 3.82 (m, 1 H, C*H*N), 2.60 (m, 2 H, $CH_2CH{=}$). $[\alpha]^{26}_D$ –4.3 (*c* 0.5, 1 N HCl) (lit.[19a] $[\alpha]^{25}_D$ –4.4 (*c* 0.5, 1 N HCl)). The remaining *N*-methoxyamide was not isolated because of the low conversion.

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Supplementary Material Available: ^{13}C NMR spectra for compounds **10, 11, 20–23, 28–30** and **34–37** and ^{1}H NMR spectra for compounds **26** and **31** (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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A Peptide–Aluminum Complex as a Novel Chiral Lewis Acid. Asymmetric Addition of Cyanotrimethylsilane to Aldehydes

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The enantioselective addition of cyanotrimethylsilane (TMSCN) to aldehydes promoted by the addition of a stoichiometric or catalytic amount of organoaluminum complexes of dipeptide esters or α-amino acid amides whose amino terminals are modified by a variety of protective groups is described. The reaction of benzaldehyde with TMSCN in the presence of a stoichiometric or catalytic amount of the complex prepared from *N*-[(2-hydroxy-1-naphthyl)methylene]-(*S*)-valyl-(*S*)-phenylalanine methyl ester (**1a**) or *N*-[(2-hydroxy-1-naphthyl)-methylene]-(*S*)-valine cyclohexylamide (**2a**) and trimethylaluminum gives (*R*)-mandelonitrile in good yield with enantioselectivity as high as 71%. The reaction of cyclohexanecarbaldehyde in the presence of the aluminum complex of *N*-(1-methyl-2-acetyl-vinyl)-(*S*)-valine cyclohexylamide (**3b**) furnishes the corresponding (*R*)-cyanohydrin in 38% ee, and the reaction of 2,2-dimethylpropionaldehyde with the aluminum complex of *N*-(4-toluenesulfonyl)-(*S*)-valyl-(*S*)-phenylalanine methyl ester (**4a**) gives the corresponding (*S*)-cyanohydrin in 67% ee.

Introduction

The design of chiral Lewis acids as catalysts for a variety of asymmetric reactions of carbonyl and related compounds has attracted much interest in synthetic organic chemistry. Derivatives of tartaric acid, binaphthyl, and oxazoline have been successfully used as chiral auxiliaries in the form of metal ligands, furnishing optically active molecules with high enantiopurities.[1] On the other hand, we recently demonstrated the utility of synthetic peptides

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