Reaction of Allylzinc Reagents and Zinc Enolates of Ketones with α-Amidoalkylphenyl Sulfones

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α-Amidoalkylphenyl sulfones behave as *N*-acylimino equivalents in the reaction with functionalized allylzinc reagents. The addition products obtained using the zinc derivative of ethyl 2-(bromomethyl)-acrylate can be readily transformed into α-methylene-γ-lactams using different cyclization procedures. The allylzinc reagent obtained from 3-bromo-1-acetoxy-1-propene directly affords protected 1,2-amino alcohols with a preference for the anti stereoisomer, regardless of the structure of the α-amidoalkylphenyl sulfone employed. This procedure can be extended to the use of zinc enolates obtained from α-bromo ketones and leads to the synthesis of *N*-protected β-amino ketones.

Introduction

Nucleophilic addition of stabilized carbanions to unsaturated carbon−nitrogen bonds is a common practice toward the synthesis of amino derivatives.[1] In this context, allyl organometallics have deserved special attention, since they allow the preparation of homoallylamines that are valuable synthetic intermediates.[2] The ease of preparation of such reagents is mandatory for their widespread utilization and is strongly affected by the nature of the metallic counterpart. Some metals, such as magnesium,[3] tin,[4] indium,[5] and zinc,[6] have widely been involved in preparation of allyl organometallic species. Zinc is frequently the metal of choice for these purposes, since it is cheap, nontoxic, and allows the formation of the corresponding allylzinc derivative in a number of different solvents, including THF, dichloromethane, and water. Furthermore, zinc enolates can be directly prepared from α-halocarbonyl derivatives without the need of strongly basic conditions and represent another source of stabilized carbanions known as Reformatsky reagents.[7] Addition of organometallic reagents to substrates containing C═N bonds is not a trivial task, since imines are usually less electrophilic than the corresponding carbonyl derivatives.[1] Enolization is a serious side reaction when aldimines obtained from aliphatic aldehydes are made to react with strongly basic carbanionic reagents.[8] This drawback can partially be avoided using less basic nucleophilic reagents[9] and/or more powerful electrophilic systems. Sulfonylimines satisfy these requirements because of the electron-withdrawing aptitude of the sulfonyl group.[10] However, only sulfonylimines obtained from

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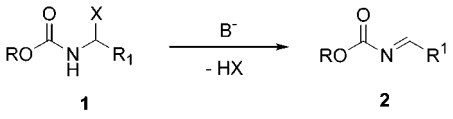
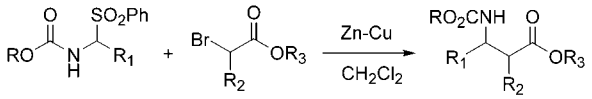
Scheme 1



Scheme 2

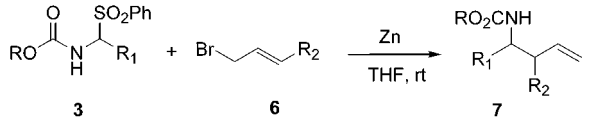


aromatic and α,β-unsaturated aldehydes are known to be stable derivatives. Aliphatic aldehydes can be transformed into *N*-sulfonylimines only at low temperature and must be used immediately in order to avoid their decomposition. A similar behavior is displayed by *N*-acylimines **2**, which can be easily generated as highly reactive intermediates starting from *N*-acyl-α-substituted amines **1** by a base-induced elimination (Scheme 1).

Carbamates **1** are thus stable precursors of *N*-acyl imines **2**, and their availability depends on the nature of the leaving group X.[11] Among various derivatives of type **1**, *N*-acyl-α-alkoxy amines (**1**, X = OR_2) are undoubtedly the most popular ones; however, they are usually generated by electrochemical oxidation of the corresponding amides or carbamates.[12] α-Amidoalkylphenyl sulfones (**1**, X = SO_2Ph) are mostly stable solids that can be prepared by reaction of an amide or a carbamate with an appropriate aldehyde and sodium benzenesulfinate in the presence of formic acid.[13]

Recently, we have reported that α-amidoalkylphenyl sulfones **3** react with Reformatsky reagents **4** to afford the corresponding β-amino esters in good yields (Scheme 2).[14] Thus sulfones **3** behave as *N*-acylimino equivalents in the reaction with nucleophiles,[15] and in this paper we will expand the synthetic significance of this procedure to other organozinc derivatives.

Scheme 3



3a: R = Bn; R_1= $PhCH_2CH_2$
3b: R = Bn; R_1= *n*-C_7H_{15}
3c: R = Bn; R_1= $Cl(CH_2)_5$
3d: R = Me; R_1= CH_2=$CH(CH_2)_7$
3e: R = Bn; R_1= Et
3f: R = *t*-Bu; R_1= *i*-Pr
3g: R = Bn; R_1= *c*-C_6H_{11}
3h: R = *t*-Bu; R_1= *c*-C_6H_{11}
3i: R = *t*-Bu; R_1= $PhCH_2CH_2$
3j: R = Bn; R_1= Me_2CHCH_2
3k: R = *t*-Bu; R_1= Ph
3l: R = *t*-Bu; R_1= CH_2=$CH(CH_2)_7$

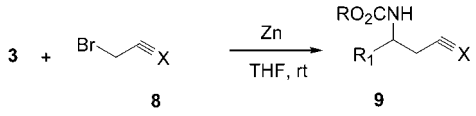
6a: R_2 = H
6b: R_2 = Me

Table 1. Synthesis of Allyl Carbamates 7, 9

entry	sulfone **3**	**bromides 6, 8**	**carbamates 7, 9**	% yield[a]
1	**3a**	**6a**	**7a**	99
2	**3b**	**6a**	**7b**	80
3	**3c**	**6a**	**7c**	90
4	**3d**	**6a**	**7d**	75
5	**3e**	**6a**	**7e**	85
6	**3a**	**6b**	**7f**	71[b]
7	**3a**	**8a**	**9a**	99
8	**3b**	**8a**	**9b**	80
9	**3a**	**8b**	**9c**	55

[a] Yields of pure, isolated products. [b] Reflux for 1 h. Diastereomeric ratio (75:25) was evaluated by ^{1}H NMR analysis.

Scheme 4



8a: X = CH
8b: X = N

Results and Discussion

Allylation of α-Amidoalkylphenyl Sulfones 3. Allylzinc bromides (1.5 equiv) obtained by reaction of bromides **6** in THF at room temperature have been made to react with sulfones **3** at the same temperature, giving the corresponding homoallylcarbamates **7** in good yields (Scheme 3, Table 1).

Organozinc derivative obtained from crotyl bromide **6b** reacts with **3a** only at reflux, leading to a diastereomeric mixture (75:25) of carbamate **7f** in moderate yield (Table 1, entry 6). In a similar fashion, propargylzinc bromide obtained from **8a** reacts with sulfones **3**, affording homopropargylcarbamates **9** (Scheme 4, Table 1) in good yields, while a less efficient process is observed using bromoacetonitrile **8b** for the same reaction (Table 1, entry 9). In this context, it is worthwhile to note that addition of lithiated nitriles to sulfones **3** represents a more efficient system to the synthesis of functionalized β-amino nitriles.[15b]

Allylindium bromide has also been tested as allylating agent, but it is completely ineffective in the reaction with sulfones **3**. Probably the allylindium reagent is unable to promote the preliminary elimination of benzenesulfinic acid, which leads to the reactive *N*-acylimine intermediate.

According to the general mechanism for the reaction of sulfones **3** with nucleophiles,[13−15] 2 equiv of carbanionic reagent are usually employed; indeed, the first equivalent acts as a base, producing the *N*-acylamine **2**, while the

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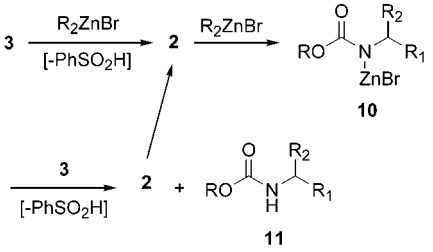
Scheme 5



Scheme 6

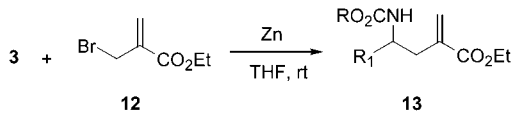


Table 2. Synthesis of Allyl Carbamates 13, 18

entry	sulfone **3**	bromo esters **12**, **17**	carbamates **13**, **18**	anti:syn	% yield[a]
1	**3a**	**12**	**13a**	-	78
2	**3g**	**12**	**13b**	-	72
3	**3h**	**12**	**13c**	-	80
4	**3i**	**12**	**13d**	-	71
5	**3f**	**12**	**13e**	-	75
6	**3b**	**17**	**18a**	80:20	51
7	**3f**	**17**	**18b**	90:10	76
8	**3i**	**17**	**18c**	85:15[b]	82
9	**3k**	**17**	**18d**	95:5	88
10	**3l**	**17**	**18e**	80:20[b]	77

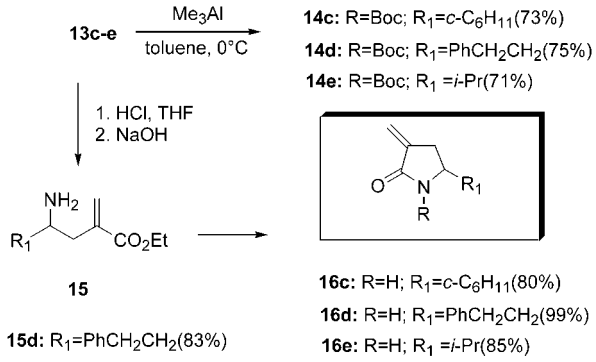
[a] Yields of pure, isolated products. [b] Diastereomeric ratio was evaluated by ^{1}H NMR.

second one adds to **2**, giving the final product. The reduced amount (1.5 equiv) of the organozinc reagent needed to convert sulfones **3** into the corresponding addition products can be explained by taking into account that adduct **10** formed through the usual addition−elimination process from sulfone **3** could be able to act as a base, thus converting to some extent **3** into *N*-acylimine **2** (Scheme 5). The efficiency of this side process would strongly depend on the experimental conditions adopted, since reaction of sulfones **3** with organomagnesium, organolithium,[13a,15b] and Reformatsky reagents[14] gives better results using 2 equiv of nucleophile.

The increasing importance of organozinc reagents is mostly due to their ability of tolerate different functional groups in their structure.[16] Allylzinc reagent obtained from ethyl 2-bromomethylacrylate **12** is able to attack aldimines, giving α-methylene-γ-lactams through a tandem addition−ring closure process.[17] The unsaturated lactams obtained present a *N*-alkyl linkage that is very difficult to cleave, and this hampers a widespread utilization of this synthetic strategy. The organozinc reagent obtained from **12** adds to sulfones **3**, but the addition products **13** fail to spontaneously cyclize to the corresponding lactam (Scheme 6 and Table 2, entries 1−5).

Nitrogen in carbamates is usually endowed of a scanty nucleophilicity with respect to the same atom in amines, and this could be the reason for the observed lack in the following cyclization step. Several attempts to induce a

Scheme 7



ring closure in compounds **13** under basic conditions led only to frustrating results. Instead, *N*-Boc-protected lactams **14** can be obtained in good yields by dissolving carbamate **13** in toluene in the presence of 2 equiv of Me_3-Al (Scheme 7).[18] Alternatively, removal of the *N*-Boc protection produces the aminoester **15** that on one occasion can be isolated (**15d**)[19] but usually cyclizes to lactam **16**. Preliminary attempts to cyclize benzyl carbamates **13a,b** using the previous method gave low yields of lactam derivative. Since removal of the carbobenzoxy group is quite difficult when unsaturations are also present in the same structure, we did not undertake any effort to improve the process.

Common synthetic approaches to the preparation of 1,2-amino alcohols usually involve reaction of nucleophiles with α-amino aldehydes[20] and α-alkoxy nitrones[21] and reduction of 1,2-nitro alcohols.[22] Reaction of heterosubstituted allylic anions with carbonyl derivatives represents a viable procedure for the synthesis of 1,2-diols,[23] but to the best of our knowledge, this strategy has never been applied to the synthesis of 1,2-amino alcohols.[24] Recently, Lombardo et al. have reported that allylzinc reagent obtained from 3-bromo-1-acetoxy-1-propene **17** is able to react with aldehydes, affording monoprotected 1,2-diols.[25] We were delighted to observe that sulfones **3** react with **17** in the presence of zinc to afford protected 1,2-amino alcohols **18** in satisfactory yields (Scheme 8 and Table 2, entries 6−10).

Amino alcohols **18** are preferentially obtained as anti stereoisomers, regardless of the nature of the sulfone **3**

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(19) Amino ester **15d** cyclizes upon standing after 48 h at room temperature in almost quantitative yield.

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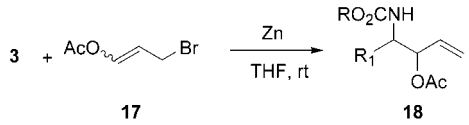
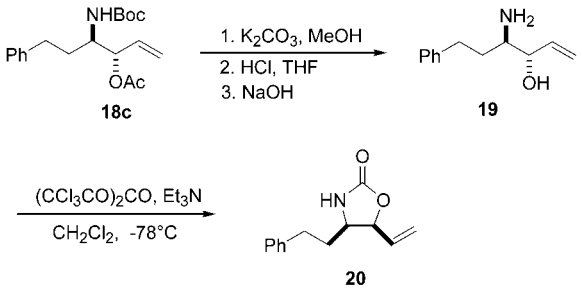
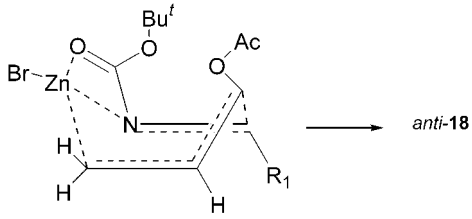
Scheme 8



Scheme 9



Scheme 10



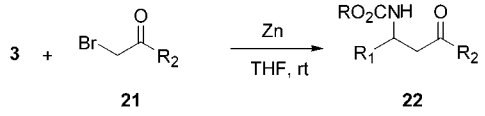
employed. Stereochemical assignments of some amino alcohols **18** were made by comparison with the literature data of their deacetylated derivatives.[26] Furthermore, the chemical shift of the CH−N proton for the syn isomer is invariably 0.3−0.5 ppm upfield with respect to the same proton in the anti one. Finally, compound **18c** has been converted into the amino alcohol **17** by a sequential cleavage of the acetyl and *N*-Boc protections and then transformed into the corresponding oxazolidin-2-one **20** using $(CCl_3CO)_2CO/Et_3N$ in CH_2Cl_2 at −78 °C (Scheme 9).

A simple experiment measuring the NOE effect between H-4 and H-5 in **20** allowed us to confirm the stereochemical assignment of compounds **18**.[27] The stereochemical outcome of this process could be rationalized by accounting for a transition state as depicted in Scheme 10.

Assuming that the *N*-acylimine intermediate is preferentially formed in the *E* configuration, the proposed transition state would take advantage, among other effects, of a favorable Zn−O interaction involving the carbamate group that arranges the acetoxy and the R_1 groups in an anti position. This coordination effect would also account for the lack of any influence exerted by the nature of the R_1 group in sulfones **3** on the stereochemistry of adducts **18**.[28]

Synthesis of *β*-Amino Ketones. Conjugate addition of amines to α,*β*-enones[29] as well as the classical Mannich reaction[30] represents the most popular approaches to the synthesis of *β*-amino ketones. Efficient additions of alkaline metal ketone enolates are experienced only with imines or *N*-acylimines derived from nonenolizable aldehydes.[31] Furthermore, reaction of lithium ketone enolates with imines or imino derivatives is usually carried out at very low temperature (−78 °C), even though no stereochemical features are involved in the process.[15e] Similarly to what is observed with zinc ester enolates,[5a] sulfones **3** are able to react at room temperature with zinc ketone enolates obtained from α-bromo ketones **21**, giving the corresponding *β*-amino ketones **22** (Scheme 11 and Table 3).

Scheme 11



21a: R_2=Ph
21b: R_2=2-Furyl
21c: R_2=Me

Table 3. Synthesis of *β*-Amino Ketones 22

entry	sulfone **3**	bromo ketone **21**	carbamate **20**	% yield[a]
1	**3b**	**21b**	**22a**	65
2	**3i**	**21a**	**22b**	85
3	**3i**	**21b**	**22c**	60
4	**3j**	**21a**	**22d**	64
5	**3i**	**21c**	**22e**	72
6	**3e**	**21a**	**22f**	78

[a] Yields of pure, isolated products.

Although in this instance reaction times are quite longer (24 h) than with the use of simple allylzinc bromide (1 h), satisfactory yields of *β*-amino ketones are obtained. To shorten the reacton time of the process, we also tested the utilization of a Zn−Cu couple as metallic promoter in dichloromethane. This method allows a very fast reaction of zinc ester enolates with sulfones **3**[5a] (Scheme 2) but gives unsatisfactory results with zinc ketone enolates.

Conclusion

Simple and functionalized allylzinc reagents can be efficiently added to α-amidoalkylphenyl sulfones **3** that act as *N*-acylimino equivalents in the reaction with nucleophiles. The organozinc reagent obtained from ethyl 2-bromomethylacrylate **12** gives the corresponding adducts **13** that can be directly cyclized to the corresponding *N*-protected lactams **14** or after removal of the *N*-Boc protection to lactams **16**. The utilization of 3-bromo-1-acetoxy-1-propene **17** as organozinc precursor allows the synthesis of protected amino alcohols **18** with preferential formation of the anti stereoisomer. This stereopreference can be explained in terms of complexation between the zinc atom and the carbamate group on the *N*-acylimine intermediate. Finally, zinc enolates obtained from α-bro-

(26) (a) Toda, A.; Aoyama, H.; Mimura, N.; Ohno, H.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1998**, *63*, 7053−7061. (b) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370−4382. (c) Kanazawa, A. M.; Correa, A.; Denis, J.-N.; Luche, M.-J.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 255−257.

(27) Roush, W. R.; González, F. W.; McKerrow, J. H.; Hansell, E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2809−2812.

(28) Reaction of allylzinc reagent derived from **15** with aldehydes gives the opposite stereochemical results, depending on the nature of the aldehyde used; see ref 25.

(29) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis;* Pergamon Press: Oxford, 1992. (b) Sibi, M.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061.

(30) Arendt, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044−1070.

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mo ketone **21** add to sulfones **3**, affording the corresponding *N*-protected *β*-amino ketones **22**, which are valuable intermediates in organic synthesis.

Experimental Section

^{1}H NMR spectra were performed at 300 MHz in $CDCl_3$ as solvent.^{13}C NMR spectra were performed at 75 MHz in $CDCl_3$ as solvent. Tetrahydrofuran was dried by refluxing it over sodium wire and then distilled. All chemicals used are commercial grade. Sulfones **3**,[13a] 3-bromo-1-acetoxy-1-propene **17**,[25] and α-bromoacetyl furan **21b**[32] have been prepared as described. Compounds **22b,e,f** have been identified by comparison with the literature data.[33]

General Procedure for the Preparation of Allyl Derivatives 7, 9, 13, and 18. To a suspension of zinc dust (5 mmol) in dry THF (10 mL) was added the corresponding allyl bromide (3 mmol) at room temperature. After stirring for 30 min, the appropriate sulfone **3** (2 mmol) dissolved in dry THF (8 mL) was added dropwise. Stirring was continued for 1 h (24 h for compounds **18**) and then the mixture was quenched by addition of saturated NH_4Cl (8 mL). The mixture was extracted with CH_2Cl_2 (4 × 15 mL) and dried over $MgSO_4$. The crude product obtained after removal of the solvent was purified by column chromatography (7:3 hexanes−ethyl acetate).

Benzyl 1-Phenethylbut-3-enylcarbamate (7a). Yield: 99%. Mp: 55 °C. IR (cm^{-1}, KBr): 3310, 1685. ^{1}H NMR *δ*: 1.61−1.98 (m, 2H), 2.18−2.41 (m, 2H), 2.61−2.86 (m, 2H), 3.71−3.95 (m, 1H), 4.75 (d, 1H, *J* = 8.8 Hz), 5.05−5.19 (m, 2H), 5.15 (s, 2H), 5.70−5.92 (m, 1H), 7.19−7.41 (m, 10H). ^{13}C NMR *δ*: 32.4, 36.6, 39.6, 50.5, 66.6, 118.2, 125.9, 128.1, 128.2, 128.3, 128.4, 128.5, 133.9 136,6, 141.7, 156.0. Anal. Calcd for $C_{20}H_{23}NO_2$ (309.4): C, 77.64; H, 7.49; N, 4.53. Found: C, 77.70; H, 7.44; N, 4.57.

Benzyl 1-Heptylbut-3-enylcarbamate (7b). Yield: 80%. Mp: 38 °C. IR (cm^{-1}, KBr): 3305, 1695. ^{1}H NMR *δ*: 0.90 (t, 3H, *J* = 6.6 Hz), 1.18−1.56 (m, 12H), 2.11−2.40 (m, 2H), 3.62−3.84 (m, 1H), 4.66 (d, 1H, *J* = 8.8 Hz), 5.05−5.19 (m, 2H), 5.11 (s, 2H), 5.68−5.93 (m, 1H), 7.29−7.43 (m, 5H). ^{13}C NMR *δ*: 14.1, 22.7, 25.7, 25.9, 28.7, 29.2, 29.5, 29.9, 31.8, 34.6, 36.8, 39.4, 50.7, 66.5, 117.8, 128.0, 128.5, 134.3, 136.7, 156.1. Anal. Calcd for $C_{19}H_{29}NO_2$ (303.4): C, 75.21; H, 9.63; N, 4.62. Found: C, 75.29; H, 9.57; N, 4.66.

Benzyl 1-Phenethylbut-3-ynylcarbamate (9a). Yield: 99%. Oil. IR (cm^{-1}, neat): 3315, 1683. ^{1}H NMR *δ*: 1.85−1.99 (m, 2H), 2.03 (t, 1H, *J* = 1.1 Hz), 2.35−2.64 (m, 2H), 2.66−2.81 (m, 2H), 3.80−4.00 (m, 1H), 4.89−5.02 (m, 1H), 5.15 (s, 2H), 7.12−7.44 (m, 10H). ^{13}C NMR *δ*: 24.7, 32.4, 35.5, 48.9, 66.8, 71.2, 80.0, 126.0, 128.2, 128.4, 128.5, 128.6, 136.5, 141.3, 155.8. Anal. Calcd for $C_{20}H_{21}NO_2$ (307.4): C, 78.15; H, 6.89; N, 4.56. Found: C, 78.16; H, 6.94; N, 4.51.

Benzyl 1-Heptylbut-3-ynylcarbamate (9b). Yield: 80%. Mp: 47 °C. IR (cm^{-1}, KBr): 3305, 1695. ^{1}H NMR *δ*: 0.90 (t, 3H, *J* = 7.0 Hz), 1.24−1.43 (m, 10H), 1.46−1.70 (m, 2H), 2.01 (t, 1H, *J* = 2.5 Hz), 2.31−2.59 (m, 1H), 3.70−3.91 (m, 1H), 4.92 (d, 1H, *J* = 8.3 Hz), 5.12 (s, 2H), 7.34−740 (m, 5H). ^{13}C NMR *δ*: 13.8, 22.4, 24.2, 25.7, 28.9, 29.1, 31.5, 33,4, 48.9, 66.4, 70.6, 80.0, 127.9, 128.0, 128.3, 136.3, 155.6. Anal. Calcd for $C_{19}H_{27}NO_2$ (301.4): C, 75.71; H, 9.03; N, 4.65. Found C, 75.77; H, 8.98; N, 4.68.

Ethyl 2-{2-[(Benzyloxycarbonyl)amino]-4-phenylbutyl}acrylate (13a). Yield: 98%. Mp: 72 °C. IR (cm^{-1}, KBr): 3370, 1713, 1685. ^{1}H NMR *δ*: 1.30 (t, 1H, *J* = 7.0 Hz), 1.72−1,96 (m, 2H), 2.38−2.61 (m, 2H) 2.63−2.84 (m, 2H), 3.83−3.98 (m, 1H), 4.21 (q, 2H, *J* = 7.0 Hz), 4.83 (d, 1H, *J* = 9.1 Hz), 5.11 (s, 2H), 5.59 (s, 1H), 6.23 (s, 1H), 7.10−7.42 (m, 10H). ^{13}C NMR *δ*: 14.2, 32.3, 37.2, 37.5, 50.9, 60.9, 66.5, 125.9, 127.5, 128.0, 128.3, 128.4, 128.5, 137.2, 141,6, 156.0, 167.1. Anal. Calcd for $C_{23}H_{27}NO_4$ (381.4): C, 72.42; H, 7.13; N, 3.67. Found: C, 72.47; H, 7.09; N, 3.70.

Ethyl 2-{2-[(*tert*-Butoxycarbonyl)amino]-3-methylbutyl}acrylate (13e). Yield: 95%. Oil. IR (cm^{-1}, neat): 3377, 1712, 1684. ^{1}H NMR *δ*: 0.89 (d, 3H, *J* = 7.0 Hz), 0.91 (t, 3H, *J* = 7.0 Hz), 1.29 (t, 3H, *J* = 7.3 Hz), 1.37 (s, 9H), 1.68−1.84 (m, 1H), 2.20 (dd, *J* = 10,6, 13.9 Hz), 2.51 (dd, 1H, 4.0, 13.2 Hz), 3.53−3.68 (m, 1H), 4.19 (q, 2H, *J* = 7.3 Hz), 4.41 (d, 1H, *J* = 8.9 Hz), 5.59 (s, 1H), 6.19 (s, 1H).^{13}C NMR *δ*: 14.1, 17.5, 19.0, 28.3, 32.4, 34.5, 55.2, 60.7, 78.7, 126.5, 138.0, 155.8, 167.2. Anal. Calcd for $C_{15}H_{27}NO_4$ (285.4): C, 63.13; H, 9.54; N, 4.91. Found: C, 63.20; H, 9.52; N, 4.94.

***anti*-1-{1-[(Benzyloxycarbonyl)amino]octyl}allyl Acetate (*anti*-18a).** Yield: 54%. Oil. IR (cm^{-1}, neat): 1712. ^{1}H NMR *δ*: 0.88 (t, 3H, *J* = 6.2 Hz), 1.20−1.55 (m, 12H), 2.06, (s, 3H), 3.82−4.03 (m, 1H), 4.65 (d, 1H, *J* = 9.5 Hz), 5.12 (s, 2H), 5.23−5.38 (m, 3H), 5.68−5.90 (m, 1H), 7.32−7.43 (m, 5H).^{13}C NMR *δ*: 14.1, 22.6, 25.9, 29.1, 29.3, 30.6, 31.7, 53.3, 66.7, 76.1, 118.7, 128.0, 128.1, 128.5, 132.3, 156.2, 170.1. Anal. Calcd for $C_{21}H_{31}NO_4$ (361.5): C, 69.78; H, 8.64; N, 3.87. Found: C, 69.82; H, 8.61; N, 3.90.

***syn*-1-{1-[(Benzyloxycarbonyl)amino]octyl}allyl Acetate (*syn*-18a).** Yield: 14%. Oil. IR (cm^{-1}, neat): 1712. ^{1}H NMR *δ*: 0.89 (t, 3H, *J* = 6.6 Hz), 1.18−1.40 (m, 10H), 1.44−1.73 (m, 2H), 2.10, (s, 3H), 3.30−3.50 (m, 1H), 4.96−5.18 (m, 3H), 5.20−5.44 (m, 3H), 5.62−5.90 (m, 1H), 7.35−7.45 (m, 5H).^{13}C NMR *δ*: 14.1, 24.7, 24.9, 28.8, 28.9, 31.7, 35.9, 53.4, 66.9, 76.5, 119.2, 128.1, 128.2, 128.6, 131.6, 155.8, 169.9. Anal. Calcd for $C_{21}H_{31}NO_4$ (361.5): C, 69.78; H, 8.64; N, 3.87. Found: C, 69.75; H, 8.65; N, 3.92.

***anti*-1-{1-[(*tert*-Butoxycarbonyl)amino]-2-methylpropyl}allyl Acetate (*anti*-18b).** Yield: 63%. Oil. IR (cm^{-1}, neat): 1710. ^{1}H NMR *δ*: 0.90 (d, 3H, *J* = 6.6 Hz), 0.99 (d, 3H, *J* = 6.6 Hz), 1.44 (s, 9H), 1.64−1.80 (m, 1H), 2.06 (s, 3H), 3.62−3.77 (m, 1H), 4.40 (d, 1H, *J* = 10.6 Hz), 5.26−5.38 (m, 2H), 5.72−5.89 (m, 1H). ^{13}C NMR *δ*: 21.6, 14.6, 22.9, 23.1, 23.6, 52.0, 69.1, 73.9, 113.7, 127.3, 150.7, 164.7. Anal. Calcd for $C_{14}H_{25}NO_4$ (271.3): C, 61.97; H, 9.29; N, 5.16. Found: C, 62.02; H, 9.33; N, 5.13.

***syn*-1-{1-[(tert-Butoxycarbonyl)amino]-2-methylpropyl}allyl Acetate (*syn*-18b).** Yield: 7%. Oil. IR (cm^{-1}, neat): 1710. ^{1}H NMR *δ*: 0.91 (d, 3H, *J* = 6.8 Hz), 0.99 (d, 3H, *J* = 6.8 Hz), 1.43 (s, 9H), 1.86−2.01 (m, 1H), 2.09 (s, 3H), 3.37−3.46 (m, 1H), 3.77 (d, 1H, *J* = 9.8 Hz), 5.25−5.40 (m, 3H), 5.70−5.89 (m, 1H). ^{13}C NMR *δ*: 13.7, 15.8, 22.9, 23.1, 24.0 53.6, 68.7, 73.6, 113.9, 126.9, 150.5, 154.9.

General Procedure for the Preparation of *N*-Boc Lactams 14. To a solution of amino ester **11** (1 mmol) in dry toluene (9 mL) was added Me_3Al (2M in toluene, 2 mmol, 1 mL) at 0 °C, stirring was continued for 1 h at 0 °C, and the solution was then quenched with brine (6 mL). The mixture was extracted with CH_2Cl_2 (4 × 15 mL) and dried over Mg SO_4. The crude product obtained after evaporation of the solvent was purified by column chromatography (75:25 hexanes−ethyl acetate).

***tert*-Butyl 5-Cyclohexyl-3-methylene-2-oxopyrrolidine-1-carboxylate (14c).** Yield: 73%. Oil. IR (cm^{-1}, neat): 1780, 1723. ^{1}H NMR *δ*: 0.81−1.40 (m, 6H), 1.56 (s, 9H), 1.58−1.96 (m, 5H), 2.63−2.75 (m, 2H), 4.05−4.15 (m, 1H), 5.44 (t, 1H, *J* = 2.2 Hz), 6.14 (t, 1H, *J* = 2.5 Hz). ^{13}C NMR *δ*: 25.8, 25.9, 26.3, 26.4, 26.6, 28.1, 29.4, 41.5, 58.7, 82.8, 119.1, 139.8, 150.8, 165.6. Anal. Calcd for $C_{16}H_{25}NO_3$ (297.4): C, 68.79; H, 9.02; N, 5.01. Found: C, 68.81; H, 9.00; N, 5.04.

***tert*-Butyl 3-Methylene-2-oxo-5-phenethylpyrrolidine-1-carboxylate (14d).** Yield: 75%. Oil. IR (cm^{-1}, neat): 1784, 1722. ^{1}H NMR *δ*: 1.54 (s, 9H), 1.58−1.89 (m, 1H), 2.06−2.13 (m, 1H), 2.47−2.80 (m, 3H), 2.83−3.00 (m, 1H), 4.11−4.28 (m, 1H), 5.52 (s, 1H), 6.23 (s, 1H), 7.17−7.34 (m, 5H). ^{13}C NMR *δ*: 28.2, 29.9, 31.6, 36.6, 54.6, 83.2, 120.6, 126.3, 128.4, 128.7, 138.8, 140.9, 150.6, 166.5. Anal. Calcd for $C_{18}H_{23}NO_3$ (301.4): C, 71.73; H, 7.69; N, 4.65. Found: C, 71.77; H, 7.65; N, 4.67.

General Procedure for *N*-Boc Cleavage of of Amino Esters 13. Synthesis of Amino Ester 15d and Lactams 16. *N*-Boc amino ester **13** (1.5 mmol) was dissolved in THF (10 mL) and 37% HCl (5 mL) was then added at room

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temperature. The mixture was stirred for 30 min at room temperature, cooled by ice bath, and made alkaline by addition of NaOH pellets. After stirring for 15 min, the solution was extracted with $CHCl_3$ (4 × 15 mL) and dried over Na_2SO_4. After evaporation of the solvent, the crude lactam **16** was purified by column chromatography (6:4 hexanes−ethyl acetate). *N*-Boc amino ester **13d** gave the corresponding open chain amino ester **15d** that cyclized upon standing after 48 h at room temperature.

Ethyl 2-(2-Amino-4-phenylbutyl)acrylate (15d). Yield: 83%. Oil. IR (cm^{-1}, neat): 3300, 1710, 1680. ^1H NMR δ: 1.29 (t, 3H, J = 7.0 Hz), 1.47 (bs, 2H), 1.60−1.97 (m, 2H), 2.18 (m, 2H, J = 8.7, 13.6 Hz), 2.59−2.88 (m, 2H), 2.91−3.08 (m, 1H), 3.55−3.71 (m, 1H), 4.20 (q, 2H, J = 7.0 Hz), 5.60 (d, 1H, J = 1.5 Hz), 6.25 (d, 1H, J = 1.8 Hz), 7.15−7.35 (m, 5H).

5-Cyclohexyl-3-methylenepyrrolidin-2-one (16c). Yield: 80%. Mp: 85 °C. IR (cm^{-1}, KBr): 1723. ^1H NMR δ: 0.82−1.45 (m, 6H), 1.60−1.88 (m, 5H), 2.50−2.61 (m, 1H), 2.83−2.95 (m, 1H), 3.36−3.45 (m, 1H), 5.32 (s, 1H), 5.92−6.00 (m, 1H), 7.01 (bs, 1H). ^{13}C NMR δ: 25.7, 26.3, 28.5, 28.8, 30.9, 43.6, 56.2, 115.6, 139.5, 170.6. Anal. Calcd for $C_{11}H_{17}NO$ (179.2): C, 73.70; H, 9.56; N, 7.81. Found: C, 73.65; H, 9.54; N, 7.84.

3-Methylene-5-phenethylpyrrolidin-2-one (16d). Yield: 99% (from **15d**). Mp: 60 °C. IR (cm^{-1}, KBr): 1720. ^1H NMR δ: 1.77−2.01 (m, 2H), 2.40−2.59 (m, 1H), 2.70 (t, 2H, J = 7.7 Hz), 2.91−3.10 (m, 1H), 3.60−3.78 (m, 1H), 5.36 (s, 1H), 5.99 (s, 1H), 7.09−7.38 (m, 5H). ^{13}C NMR δ: 32.0, 33.1, 38.9, 50.8, 116.1, 126.2, 128.2, 128.3, 128.4, 128.5, 139.2, 140.9, 170.6. Anal. Calcd for $C_{13}H_{15}NO$ (201.3): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.54; H, 7.50; N, 7.00.

***anti*-4-Amino-6-phenylhex-1-en-3-ol (19).** *N*-Boc amino ester **18c** (0.33 g, 1 mmol) was dissolved in methanol (10 mL) and 2 M K_2CO_3 (2 mL) was added at room temperature. After stirring for 30 min at room temperature, methanol was partially removed at reduced pressure and the resulting solution was extracted with $CHCl_3$ (3 × 15 mL). The crude product obtained after evaporation of the solvent was dissolved in THF (6 mL), and 37% HCl (3 mL) was then added at room temperature. The mixture was stirred for 30 min at room temperature, cooled by ice bath, and made alkaline by addition of NaOH pellets. The solution was extracted with ethyl acetate (4 × 10 mL) and dried over Na_2SO_4. After evaporation of the solvent the crude amino alcohol was purified by column chromatography (9:1.8:0.2 dichloromethane−methanol−35% NH_4OH), giving 0.14 g (75%) of pure **19** as a colorless oil. IR (cm^{-1}, neat): 3300. ^1H NMR δ: 1.44−1.68 (m, 1H), 1.75−2.05 (m, 4H), 2.60−2.98 (m, 3H), 4.05−4.18 (m, 1H), 5.25−5.40 (m, 2H), 5.80−6.00 (m, 1H), 7.16−7.39 (m, 5H). Anal. Calcd for $C_{12}H_{17}NO$ (191.3): C, 75.35; H, 8.96; N, 7.32. Found: C, 75.40; H, 8.91; N, 7.35.

***anti*-4-Phenethyl-5-vinyl-1,3-oxazolidin-2-one (20).** Amino alcohol **19** (0.13 g, 0.7 mmol) was dissolved in dry CH_2Cl_2 (6 mL) and Et_3N (1.0 mL, 7 mmol) was then added. The solution was cooled at −78 °C, and triphosgene (0.11 g, 0.39 mmol) dissolved in CH_2Cl_2 (2 mL) was added dropwise. After 20 min the mixture was allowed to warm to room temperature and was quenched with saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 and the organic phase was dried over $MgSO_4$. After evaporation of the solvent at reduced pressure the crude oxazolidinone was purified by column chromatography (60:40 hexanes−ethyl acetate), giving 0.091 g (60%) of pure **20** as a viscous oil. IR (cm^{-1}, neat): 1695. ^1H NMR δ: 1.71−1.85 (m, 2H), 2.54−2.63 (m, 1H), 3.90 (q, 1H, J = 7.3 Hz), 5.34 (d, 1H, J = 10.3 Hz), 5.46 (d, 1H, J = 17.2 Hz), 5.83−5.97 (m, 1H), 6.60 (bs, 1H), 7.17−7.37 (m, 5H). ^{13}C NMR δ: 32.3, 32.9, 55.3, 80.5, 120.3, 136.4, 128.4, 128.7, 130.9, 140.4, 158.7. Anal. Calcd for $C_{13}H_{15}NO_2$ (217.3) C, 71.87; H, 6.96; N, 6.45. Found: C, 71.93; H, 6.93; N, 6.49.

General Procedure for the Preparation of *N*-Boc-Protected *β*-Amino Esters 22. To a suspension of zinc dust (5 mmol) in dry THF (10 mL) was added the corresponding α-bromo ketone **21** (3 mmol) at room temperature. After stirring for 30 min, the appropriate sulfone **3** (2 mmol) dissolved in dry THF (8 mL) was added dropwise. Stirring was continued for 24 h and then the mixture was quenched by addition of saturated NH_4Cl (8 mL). The mixture was extracted with CH_2Cl_2 (4 × 15 mL) and dried over $MgSO_4$. The crude product obtained after removal of the solvent was purified by column chromatography (8:2 hexanes−ethyl acetate).

Benzyl 1-[2-(2-Furyl)-2-oxoethyl]octylcarbamate (22a). Yield: 65%. Oil. IR (cm^{-1}, neat): 1715. ^1H NMR δ: 0.88 (t, 3H, J = 7.0 Hz), 1.17−1.44 (m, 10H), 1.48−1.68 (m, 2H), 2.97 (dd, 1H, J = 5.5, 16.1 Hz), 3.18 (dd, 1H, J = 4.8, 16.1 Hz), 4.01−4.18 (m, 1H), 5.09 (s, 2H), 5.27 (d, 1H, J = 9.2 Hz), 6.52−6.55 (m, 1H), 7.22−7.40 (m, 6H), 7.57−7.59 (m, 1H). ^{13}C NMR δ: 14.1, 22.6, 26.3, 29.2, 29.3, 31.7, 34.4, 42.6, 48.7, 66.5, 112.4, 117.7, 127.9, 128.0, 128.5, 136.4, 146.6, 152.7, 155.9, 187.7. Anal. Calcd for $C_{22}H_{29}NO_4$ (371.1): C, 71.13; H, 7.87; N, 3.77. Found: C, 71.16; H, 7.84; N, 3.80.

***tert*-Butyl 3-(2-Furyl)-3-oxo-1-phenethylpropylcarbamate (22c).** Yield: 60%. Mp: 96 °C. IR (cm^{-1}, KBr): 1715. ^1H NMR δ: 1.44 (s, 9H), 1.82−2.08 (m, 2H), 2.57−2.85 (m, 2H), 2.99 (dd, 1H, J = 5.5, 15.7 Hz), 3.16 (dd, 1H, J = 5.1, 15.6 Hz), 3.98−4.16 (m, 1H), 5.11 (d, 1H, J = 8.1 Hz), 6.53 (dd, 1H, J = 1.8, 3.7 Hz), 7.12−7.36 (m, 6H), 7.58 (dd, 1H, J = 0.7, 1.8 Hz). ^{13}C NMR δ: 28.4, 32.7, 42.7, 47.9, 79.2, 112.4, 117.8, 125.9, 128.3, 128.4, 141.5, 146.6, 152.7, 155.4, 188.1. Anal. Calcd for $C_{20}H_{25}NO_4$ (343.4): C, 69.95; H, 7.34; N, 4.08. Found: C, 69.90; H, 7.38; N, 4.04.

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Supporting Information Available: Spectral and physical data for the following compounds not included in the Experimental Section: **7c**−**f**, **13b**−**d**, **14e**, **16e**, **18c**−**e**, **22d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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