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A New Method of Synthesis of 6-Substituted Piperidine-2,4-diones from Homoallylamines

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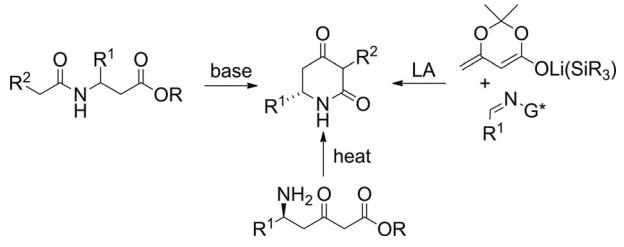
Mono- and dihomoallylamines serve as convenient precursors for the preparation of 6-substituted piperidine-2,4-diones. This transformation is based, on the one hand, on a simple and well-known halocyclocarbamation reaction proceeding by the addition of a source of cationic halogen to the *N*-Boc-protected homoallylamines and, on the other, on a new enolate-isocyanate rearrangement that proceeds by the action of strong bases on bromocyclocarbamates. A set of racemic dihomoallylamines were prepared by the allylboration of nitriles or primary amides with triallylborane and enantiomerically enriched *N*-Boc-1-phenyl-3-butenylamine was synthesized by the addition of (–)-AllB(Ipc)$_2$ to the corresponding silylimine. Chiral precursors containing a carboxylic ester group were synthesized from (*S*)-allylglycine and -alanine. The reactions of *N*-Boc derivatives with NBS smoothly produced the corresponding bromocyclocarbamates either in the form of a single diastereomer or as an isomeric mixture. All these bromourethanes were cleanly transformed into 6-substituted piperidine-2,4-diones in good yields via the formation of intermediate cyclic enolates, which was confirmed by the direct synthesis of enolate **12** and its transformation into dione **8** in a series of kinetic experiments. Based on the experimental results, a mechanism for the new enolate-isocyanate rearrangement is proposed.

Introduction

Among the various heterocycles present in natural products, piperidine occupies a privileged place.[1] As a subset, piperidin-2-one is a structural motif found in many alkaloids,[1] biologically active small synthetic molecules,[2] and peptidomimetics.[3] A special type of piperidin-2-one molecule is the piperidine-2,4-dione. These compounds are key intermediates in the syntheses of various pharmaceutically interesting compounds.[2f,4,6a] In addition, this skeleton also shows biological activity, for example, as an inhibitor of bacterial dihydroorotase[5a] with a 6-carboxylic acid group in the cycle and as inhibitors of undecaprenyl pyrophosphate synthase with 3,6-diaryl(arylmethyl) groups.[5b]

Unlike the synthesis of the parent piperidines, straightforward methods for the construction of 6-substituted piperidine-2,4-diones are limited. There are several approaches leading to piperidine-2,4-diones[6a] (racemic and enantiomerically pure form) that are based either on the enolate cyclization of β-amino esters (Dieckman condensation),[4a,4e,6b,6c,6j] δ-amino β-keto ester cyclization,[4d,4e,6d–6g] Blaise cyclization,[4c] enolate-imine addition,[6h] or enolate-cyanide cycloaddition[6i] (Scheme 1).



Scheme 1. General routes to piperidine-2,4-diones.

Piperidine-2,4-diones have been stereoselectively synthesized by using chiral sulfinyl auxiliaries[6d–6f,6h] or enantiomerically pure β-amino acids.[4a,6g] All the methods are convenient and reliable and they share a common feature: the two carbonyl groups in the piperidine-2,4-dione are transferred directly from the source material. This limits to a certain extent the planning and realization of the synthesis because of the reactivity of the carbonyl groups. In this work we describe a new method for the synthesis of 6-substituted piperidine-2,4-diones.[7] Our long-standing interest in allylboranes and allylated organic compounds[8] has led to the elaboration of a route for the conversion of the allyl group into an acetonyl group in a series of 2,6-disubstituted tetrahydropyridines (Scheme 2).[9]

The novelty of this methodology is related to the unusually effective dehydrohalogenation step upon formation of the cyclic enolate-urethane, which proceeds for a few seconds. The study of this simple transformation in a series of homodiallylamines, in which one hydrogen atom (R′-NH-

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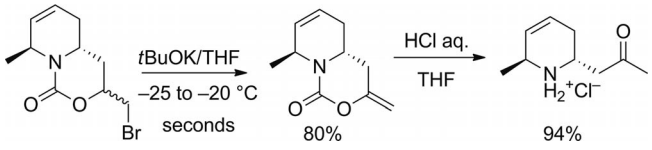


Scheme 2. Conversion of the allyl group into the acetonyl group by a rapid dehydrobromination step.

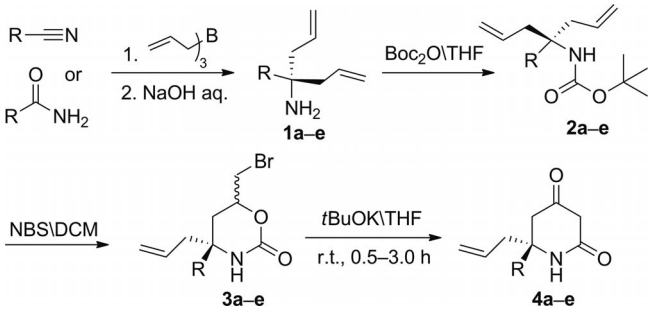
Boc) is left at the Boc-protected nitrogen atom, led to the discovery of a new base-mediated rearrangement resulting in the formation of the piperidine-2,4-dione skeleton in which the homoallylamine moiety is totally incorporated into the piperidine-2,4-dione. The advantages of this new approach are the following: (a) the easy introduction of an allyl group into a substrate, (b) the possibility of keeping the relatively inert protected homoallylic system inside a complex molecule until the preparation of the target dione, and (c) due to the wide variety of highly effective asymmetric methods of synthesis of homoallylamines, the most appropriate one can be selected depending on the chemical environment of the molecule.

The high reactivity of triallylborane (TAB) towards compounds with multiple carbon–heteroatom bonds provides an easy access to a broad spectrum of different mono- and diallylated compounds.[8,10] TAB readily reacts with aromatic azaheterocycles and derivatives of carboxylic acids such as nitriles and lactams. Two allyl groups can be introduced into these substrates in one step to form 2,6-diallyl-1,2,3,4-tetrahydropiperidines, -isoquinolines, and -pyrrolidine or 2,2-diallylated amines.[10] If the amino function is protected with an acyl or preferably a Boc group, then such products are excellent substrates for RCM with Grubbs catalysts and a number of azabicyclics have been prepared by diallylboration/metathesis.[11] The other type of reaction known for *N*-Boc-protected allylic amines is halocyclization and, in particular, the cyclobromocarbamation reaction. The effect of cationic halogens (iodine, bromine, NBS, NIS) on such substrates is well known and leads to the formation of halourethanes.[12] Surprisingly, the dehydrohalogenation of the resulting urethanes is not well studied.

Results and Discussion

The reductive allylboration of nitriles or primary amides with TAB leads to the formation of *gem*-homodiallylamines in preparative quantities. The most atom-effective process is the addition of TAB to nitriles because only one allyl group remains unreactive on the boron atom. TAB was added to benzonitrile and 3-methoxypropionitrile in accordance with the previously described procedure[10f] to give the corresponding primary amines **1a**,**b** in high yields (Table 1). Despite its high reactivity, TAB can selectively allylborate the cyano group in the presence of an ester group. To demonstrate such a possibility, the allylboration of *tert*-butyl cyanoacetate with TAB was carried out. It is known that the addition of organometallic reagents to the nitrile group of ethyl cyanoacetate proceeds with the formation of a keto acetate in moderate yield[13] because of intermediate enolate formation. In the case of TAB, the acidity of the protons at the carbon atom is not important because Lewis acid–Lewis base coordination of boron to the nitrogen of the nitrile group occurs, thus directing the allylboration towards the nitrile.

Table 1. Synthesis of *gem*-homodiallylamines and their conversion into 6-substituted piperidine-2,4-diones.



R	**1**, % Yield	**3**, % Yield; *cis**trans*	**4**, % Yield
Ph	**1a**, 94	**3a**, 94; 1:25	**4a**, 91
$CH_3O(CH_2)_2$	**1b**, 89	**3b**, 95; 16:1	**4b**, 93
*t*BuOOCCH$_2$	**1c**, 92	**3c**, 78; 1:1	**4c**, 92
FCH_2	**1d**, 54	**3d**, 84; 1:1	**4d**, 84
$(CH_3)_2CHCH_2$	**1e**, 48	**3e**, 96; 1:1	**4e**, 90

The diallylated amino ester **1c** was isolated in 92% yield after alkaline deboronation. When nitriles are less available, amides can be used instead. The allylboration of cyclic amides (lactams) with an NH group proceeds cleanly in yields of up to 95%,[14] but in the case of acyclic primary amides the isolated yields of diallylated amines do not exceed 60% because of the concurrent formation of the diallylated alcohol,[15] which is separated by consecutive acid/base extractions. Treatment of amines **1a**–**e** with Boc anhydride quantitatively gives *N*-Boc-amides **2a**–**e** (Table 1).

The amides **2** react smoothly with NBS giving rise to bromourethanes **3a**–**e** in different isomeric ratios. In the cases of **3a** and **3b**, high diastereoselectivity was observed. The major isomer of **3a** was isolated by chromatography and its structure was determined by X-ray diffraction to be the *trans* isomer (Figure 1). The structure of the major isomer of **3b** was determined to be the *cis* isomer from a NOESY experiment (Figure 2).

Bromides **3a**–**e** were treated with 2.2 equiv. of *t*BuOK. In the temperature range of –10 to +5 °C, no changes (TLC monitoring) were observed, but when the temperature reached 15–20 °C, the reaction mixture rapidly became turbid and the starting material completely disappeared over 0.5–3.0 h. A set of bases (LDA, NaH, DBU) were tested and *t*BuOK was the reagent of choice.

To broaden the scope of this transformation, monohomoallylamine derivatives were tested because numerous methods exist for the preparation of homoallylamines both in racemic and, especially important, in enantiomerically pure[16] forms. Because our group deals with organoboron compounds, we used the simple reaction of 1-phenyl-*N*-tri-

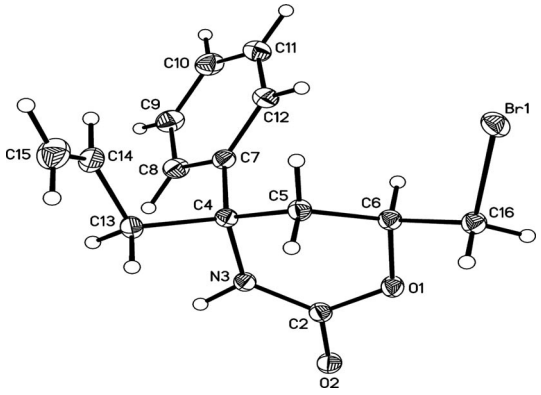


Figure 1. Molecular structure of the *trans* isomer **3a** (ellipsoids drawn at the 50% probability level).

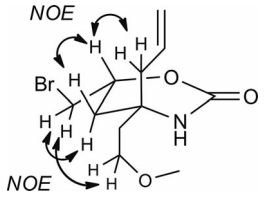
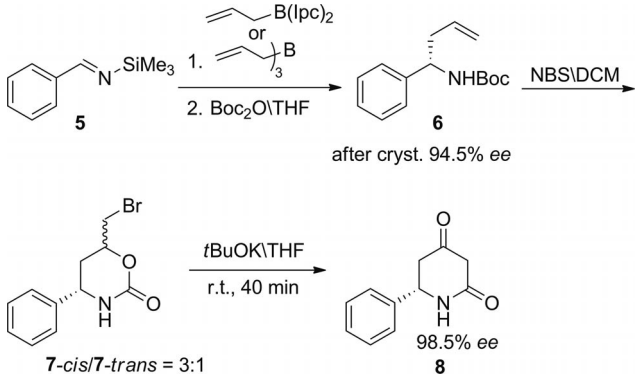


Figure 2. Structure determination of **3b** by NOE.

methylsilylmethanimine with TAB for the preparation of *rac*-phenylhomoallylamine (*rac*-**6**) or (–)-*B*-allyl(diisopinocampheyl)borane for the preparation of the *S* enantiomer (*S*)-**6** (Scheme 3).[16m]



Scheme 3.

TAB reacts with imine **5** with the evolution of heat and subsequent alkaline treatment of the reaction mixture produces the crude homoallylamine, which was treated with Boc_2O and heated at reflux in THF for 1 h to finally give *rac*-**6** in 80% yield. Following the method[16m] of Ramachandran and Burghardt, $(Ipc)_2BAll$ was added to **5** and after transformation of the crude amine to the *N*-Boc derivative, (*S*)-**6** was obtained in 53% yield and 94.5%*ee* [after crystallization from *n*-C_6H_{14}, prior to crystallization (*S*)-**6** had 91.5%*ee*]. Bromourethane **7** is formed as a mixture of *cis*-**7**/*trans*-**7** isomers (3:1 ratio) by the reaction of homoallylamide *rac*-**6** with NBS. The major isomer crystallized from the reaction mixture and was found by X-ray analysis to be *cis*-**7** (Figure 3).

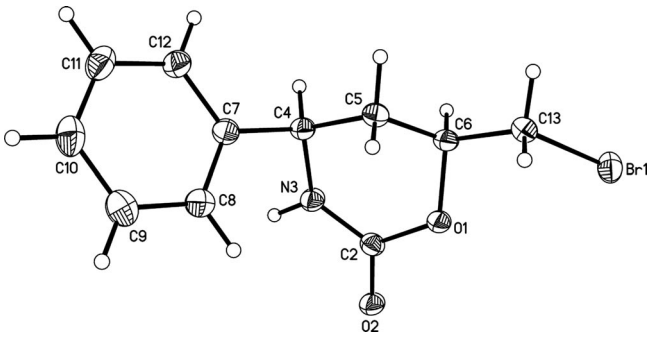
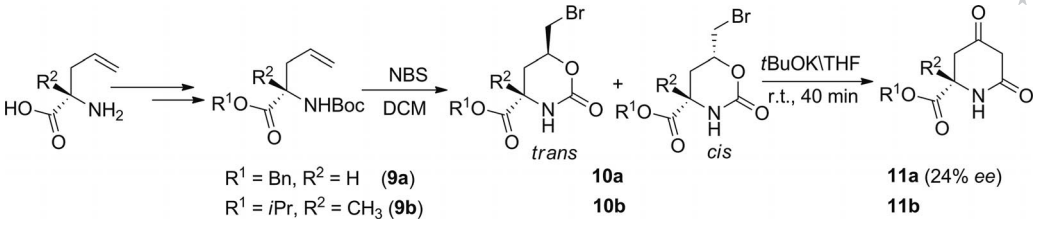


Figure 3. Structure of the major isomer *cis*-**7**.

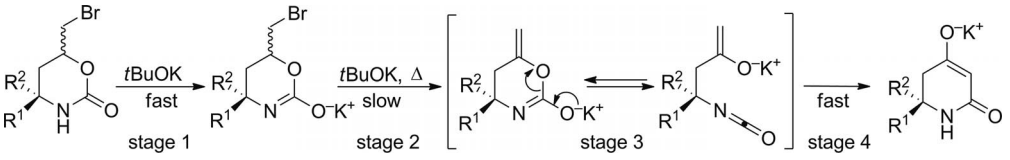
The mixture of isomers **7** reacts with *t*BuOK cleanly to give 6-phenylpiperidine-2,4-dione (**8**). From the mixture of chiral isomers (*S*)-**7**, dione (*S*)-**8** was obtained in 95% yield and 98.5%*ee*, which corresponds to the *ee* of the bromourethanes (*S*)-**7**, which was accidentally enriched by crystallization during isolation (confirmed by chiral HPLC analysis of the major *cis* isomer).

Other interesting chiral substrates with a homoallylamine fragment are allylglycines, which have previously been prepared in enantiomerically pure form by the allylation of glycine and alanine.[17] Starting from (*S*)-allylglycine and -alanine, *N*-Boc derivatives of benzyl and isopropyl esters (**9a**,**b**) were synthesized (Scheme 4). The reactions of **9a**,**b** with NBS produces mixtures of isomeric bromourethanes **10a** (*cis*/*trans* = 1:2) and **10b** (*cis*/*trans* = 1:11), the configurations of which were assigned by analogy to the formation of iodourethanes in a similar reaction.[12f] These bromides were also transformed into piperidine-2,4-diones **11a**,**b** in high yields. As we anticipated, compound **10a**, due to the presence of an acidic proton at the stereocenter, forms product **11a** in nearly racemic form (24%*ee*, Scheme 4) in the strong basic media.

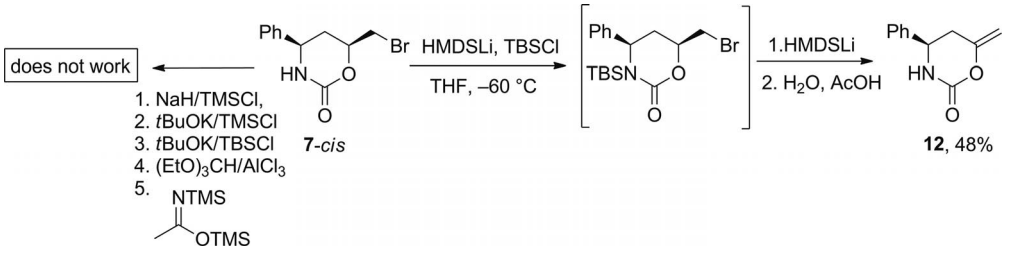
We propose the following plausible mechanism for this transformation (Scheme 5). In the first stage, *t*BuOK abstracts the acidic N–H proton to form the potassium salt. In the next slow stage, abstraction of HBr occurred in the anionic substrate to give the unstable anionic enolate, which undergoes enolate-isocyanate rearrangement in the third stage. The resulting enolato-isocyanate is irreversibly cyclized to piperidine-2,4-dione. To the best of our knowledge, such an enolate-isocyanate rearrangement is unprecedented in urethane chemistry. Although the intermolecular addition of enolates to isocyanates is a common reaction,[18] its intramolecular analogue is rare. A similar cyclization of 2-vinylphenyl isocyanates, generated in situ by radical scission, leads to the formation of quinolinones.[19a,19b] Similar rearrangements involving the formation of an enolate anion and leading to the cyclohexane- and cyclopentane-1,3-dione skeleton have been known for a long time.[19c–19g] However,



Scheme 4.



Scheme 5. Plausible mechanism for the formation of 6-substituted piperidine-2,4-diones.

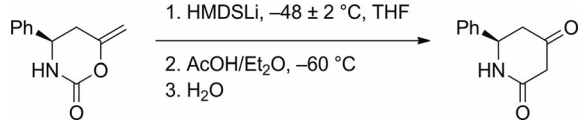


Scheme 6. Synthesis of 6-methylene-4-phenyl-1,3-oxazinan-2-one (**12**).

the mechanism postulated for these transformations is completely different to what we have proposed for the formation of piperidine-2,4-diones.

Stage 2 of the reaction is slow and proceeds only at room temperature. Evidently, the formation of a dianion is an unlikely process and hence HBr elimination would be a more concerted process. Indeed, we never detected the formation of an enolate in the dehydrobromination step. When 1 equiv. of *t*BuOK was used, a mixture was obtained that included the starting bromourethane, piperidine-2,4-dione, and the dimeric product, which arises by nucleophilic substitution of the bromide atom by the enolate form of the dione. To support the mechanism in Scheme 5, we tried to synthesize 6-methylene-4-phenyl-1,3-oxazinan-2-one (**12**), which in fact was a difficult task (Scheme 6). Our first idea was to protect the nitrogen atom with TMSCl or TBSCl and 1 equiv. of base, however, only the starting material or some dione **8** was isolated. An attempt to protect the nitrogen by the reaction of **7** with a powerful silylating agent such as *N*,*O*-bis(trimethylsilyl)acetamide left **7** almost unchanged. Thus, we used a procedure reported for the protection of oxazolidine-type[20] compounds with orthoformate in the presence of catalytic amounts of $AlCl_3$. In our case many byproducts were formed and (irreproducible) only tiny amounts of the protected bromide.

Finally, we found that **7** is readily protected with HMDSLi/TBSCl (1 equiv.) at low temperature. Upon addition of a second equivalent of HMDSLi, fast dehydrobromination occurred, the intermediate silyl ether was cleaved in water/acetic acid (or even on a silica gel TLC plate), and the target enol **12** was isolated in 48% yield as a crystalline solid. Having in hand enough **12**, tests were carried out at low temperature. Interestingly, the rearrangement step is a very fast process (Scheme 5); although a temperature of –78 °C is too low for the reaction to take place, at –50 °C the rearrangement reaction was completed in 30–35 min (Scheme 7, Figure 4). The rate constant for the enolate-isocyanate rearrangement was calculated on the basis of the ratios of enol **12**/dione **8** determined by ^{1}H NMR spectroscopy from a series of low-temperature experiments.



Scheme 7.

The kinetic analysis of this process reveals a first-order reaction with rate constant $k = 2.85 \times 10^{-2}$ s^{-1} at –48 °C. A relatively big deviation from linearity at 15 and 20 min (several experiments were performed) could be related to the heterogeneous character of the reaction mixture at a late stage in the transformation because of the low solubility of the lithium salt of dione **8**. Nevertheless, this analysis provides a good approximation of the value of the rate constant.

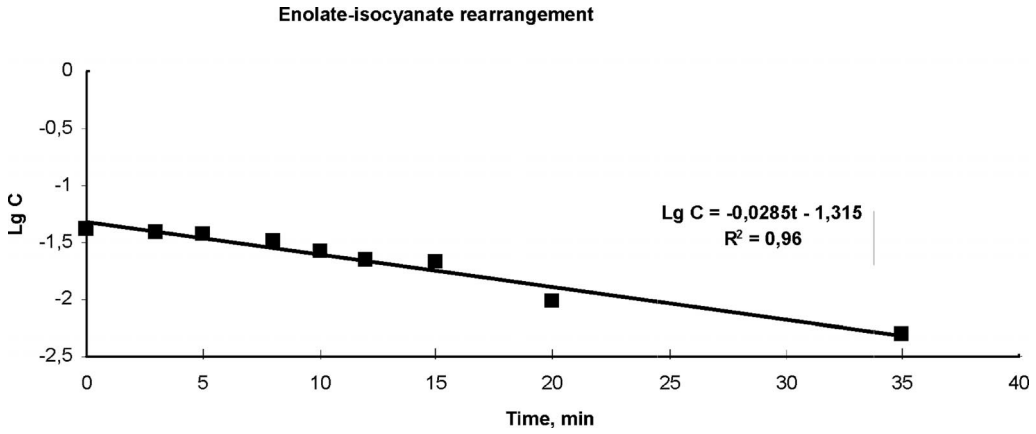


Figure 4. Kinetic study of the enolate–isocyanate rearrangement.

Conclusions

A new base-mediated enolate-isocyanate rearrangement has been discovered and a convenient synthesis of 6-substituted piperidine-2,4-diones has been elaborated. The advantages of this new approach are the following: (a) the easy introduction of the allyl group into a substrate, (b) the possibility of keeping the relatively inert protected homoallylic system inside a complex molecule until the preparation of the dione, and (c) due to a wide variety of highly effective asymmetric methods for the synthesis of homoallylamines, the most appropriate can be selected depending on the chemical environment of the molecule. Further extensions of this method for preparing further relevant compounds are underway.

Experimental Section

General: The manipulations with triallylborane were carried out under an inert atmosphere of dry Ar. Triallylborane was prepared according to a previously described procedure.[21] NMR spectra were recorded with Bruker Avance 300, 400, and 600 MHz instruments. Mass spectra were recorded with a Finnigan Polaris Q Ion Trap spectrometer. Column chromatography was carried out by using silica gel 60–230 mesh (Merck). Compounds **1a**[22] and **5**[23] were synthesized as described previously.

4-(2-Methoxyethyl)-1,6-heptadien-4-amine (1b): 3-Methoxypropionitrile (10 g, 0.118 mol) was added dropwise to neat triallylborane (19 g, 24 mL, 0.142 mol) after which the mixture was heated at 110 °C for 1 h. Excess triallylborane was destroyed by the addition of MeOH (10 mL) followed by deboronation with 20% NaOH (100 g, 0.5 mol) at 110–120 °C. The completion of the deboronation was verified by the green flame test as soon as the gas evolution had ceased. After the reaction mixture had cooled, the upper organic layer was diluted with hexane (50 mL), separated from the aqueous phase, washed with water, dried with K_2CO_3, and the solvents evaporated. The residue was distilled under reduced pressure at 93–94 °C (5 Torr) to furnish 17.70 g (89%) of **1b** as a colorless liquid. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.90–5.80 (m, 2 H, CH=), 5.05–5.00 (m, 4 H, CH_2=), 3.42 (t, J = 7.2 Hz, 2 H, CH_2O), 3.19 (s, 3 H, CH_3O), 2.01 (d, J = 7.4 Hz, 4 H, $CH_{2,allyl}$), 1.48 (t, J = 7.2 Hz, 2 H, -CH_2-), 1.31 (br. s, 2 H, NH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 135.00 (2 C), 117.43 (2 C), 68.37, 57.88, 52.61, 44.79 (2 C), 38.59 ppm. MS (70 eV, EI): *m*/*z* (%) = 170 (33) $[M + H]^+$, 169(6) $[M]^+$, 149 (16), 135 (16), 129 (10), 128 (49), 123 (18), 121 (18), 111 (26), 109 (23), 97 (43), 96 (100), 95 (31), 91 (16), 83 (24), 81 (57), 79 (47), 77 (36), 71 (30), 69 (28), 57 (33), 55 (26), 41 (24). $C_{10}H_{19}NO$ (169.2): calcd. C 70.96, H 11.31, N 8.28; found C 70.81, H 11.36, N 8.31.

***tert*-Butyl 3-Allyl-3-amino-5-hexenoate (1c):** Triallylborane (4.8 g, 6.0 mL, 35.4 mmol) was added dropwise to a solution of *tert*-butyl cyanoacetate (5.0 g, 35.4 mmol) in DCM (10 mL) at –70 °C. The resulting solution was stirred for 15 min after which it was warmed to 0 °C and heated at 100 °C (when DCM was distilled off) for 1 h. This mixture was carefully treated with 20% aq. NaOH (22 mL, 0.11 mol) keeping the temperature of the mixture in a range of 100–110 °C for 30 min. The product was extracted with hexane/Et_2O (1:1), washed with water, dried with K_2CO_3, and the solvents evaporated. The residue was distilled in vacuo at 97–98 °C (0.5 Torr) to yield 7.35 g (92%) of **1c**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.94–5.80 (m, 2 H, CH=), 5.17–5.10 (m, 4 H, CH_2=), 2.30 (s, 2 H, CH_2), 2.22 (d, J = 7.5 Hz, 4 H, $CH_{2,allyl}$), 1.62 (br. s, 2 H, NH_2), 1.48 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.29, 133.70 (2 C), 118.88 (2 C), 80.57, 53.30, 45.05, 44.67 (2 C), 28.11 (3C) ppm. MS (70 eV, EI): *m*/*z* (%) = 226 (8) $[M + H]^+$, 154 (4), 129 (8), 128 (100), 110 (65), 96 (5): 93 (4), 91 (7), 83 (5), 82 (20), 81 (6), 80 (8), 69 (8), 68 (53), 67 (33), 65 (6), 55 (5), 43 (8), 42 (5), 41 (14), 39 (11). $C_{13}H_{23}NO_2$ (225.3): calcd. C 69.29, H 10.29, N 6.22; found C 69.11, H 10.41, N 6.21.

4-(Fluoromethyl)-1,6-heptadien-4-amine (1d): Triallylborane (26.8 g, 34.6 mL, 0.2 mol) was added to a solution of α-fluoroacetamide (7.7 g, 0.1 mol) in THF (20 mL) and the reaction mixture was heated at reflux for 1.5 h. MeOH (20 mL) was added and heating was continued for 30 min before deboronation workup with 20% NaOH (120 mL). After complete deboronation (green flame test) the reaction mixture was diluted with hexane, cooled, and the organic layer separated and washed with water. The organic phase was thoroughly shaken with 6 N HCl (20 mL) and separated from the aqueous phase. The aqueous layer was extracted with hexane/EtOAc (1:1) twice. Then the aqueous phase was made alkaline with solid NaOH (10 g) and extracted with hexane (20 mL × 3). The combined extracts were dried with K_2CO_3, evaporated, and distilled under reduced pressure (b.p. 62–63 °C/10 Torr) to furnish **1d** (7.78 g, 54%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.88–5.74 (m, 2 H, CH=), 5.15–5.09 (m, 4 H, CH_2=), 4.14 (d, J_{FH} = 47.6 Hz, 2 H, CH_2F), 2.17 (dd, J = 1.2, 7.5 Hz, 4 H, $CH_{2,allyl}$), 1.27 (s, 2 H, NH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.83 (2 C), 119.24 (2 C), 89.35 and 87.03 (J_{CF} = 173.9 Hz),

53.96 and 53.73 (J_{CF} = 17.1 Hz), 41.28 and 41.24 (J_{CF} = 3.1 Hz, 2 C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –226.5 ppm. MS (70 eV, EI): *m*/*z* (%) = 144 (26) $[M + H]^+$, 124 (5), 122 (6), 102 (100), 82 (40), 80 (90), 67 (50), 60 (54), 55 (25), 42 (20), 41 (20), 39 (27). $C_8H_{14}FN$ (143.2): calcd. C 67.10, H 9.85, N 9.78, F 13.27; found C 67.05, H 9.83, N 9.84, F 13.32.

4-Isobutyl-1,6-heptadien-4-amine (1e): The procedure used was the same as that used for the synthesis of **1d**. The reaction between isovaleramide (5.0 g, 49.4 mmol) and TAB (11.9 g, 15.4 mL, 89.0 mmol) produced **1e** (4.0 g, 48%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.86–5.72 (m, 2 H, CH=), 5.08–5.01 (m, 4 H, CH_2=), 2.09 (d, *J* = 7.5 Hz, 4 H, $CH_{2,allyl}$), 1.82–1.70 (m, 1 H, CH), 1.25 (d, *J* = 5.5 Hz, 4 H, CH_2), 1.12 (br. s, 2 H, NH_2), 0.92 (d, *J* = 6.6 Hz, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.33 (2 C), 118.20 (2 C), 54.14, 48.72, 45.20 (2 C), 25.18 (2 C), 23.70 ppm. MS (70 eV, EI): *m*/*z* (%) = 168 (57) $[M + H]^+$, 152 (34), 151 (15), 136 (15), 126 (100), 110 (35), 109 (12), 95 (21), 84 (46), 70 (30), 67 (20), 57 (21), 42 (26), 41 (27). $C_{11}H_{21}N$ (167.3): calcd. C 78.97, H 12.65, N 8.37; found C 79.10, H 12.74, N 8.33.

***tert*-Butyl *N*-(1-Allyl-1-phenyl-3-butenyl)carbamate (2a):** Diallylated amine **1a** (3.74 g, 20 mmol) was heated at reflux with Boc_2O (4.58 g, 21 mmol) in THF (10 mL) for 1 h. When the amine **1a** had been consumed, MeOH (10 mL) was added and the solution was heated at reflux for 30 min, after which all volatiles were removed under reduced pressure. The residual oil was passed through the short column of silica gel with *n*-C_6H_{14}/EtOAc (6:1) as eluent to give **2a** (5.63 g, 98%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.29 (m, 4 H, Ph), 7.25–7.19 (m, 1 H, Ph), 5.65–5.51 (m, 2 H, CH=), 5.13–5.07 (m, 4 H, CH_2=), 4.84 (br. s, 1 H, NH), 2.85 (br. m, 2 H, $2CH_AH_B$), 2.68–2.61 (m, 2 H, $2CH_AH_B$), 1.40 (br. s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.09, 144.43, 133.34 (2 C), 128.11 (2 C), 126.54, 125.69 (2 C), 119.02 (2 C), 79.02, 59.45, 42.99 (2 C), 28.32 (3 C) ppm. MS (70 eV, EI): *m*/*z* (%) = 287 (0.3) $[M]^+$, 246 (4), 232 (4), 191 (8), 190 (67), 170 (4), 155 (2), 147 (11), 146 (100), 129 (30), 128 (15), 117 (4), 115 (5), 104 (26), 91 (5), 77 (8), 57 (4), 44 (6), 41 (10). $C_{18}H_{25}NO_2$ (287.4): calcd. C 75.22, H 8.77, N 4.87; found C 75.19, H 8.82, N 4.90.

***tert*-Butyl *N*-[1-Allyl-1-(2-methoxyethyl)-3-butenyl]carbamate (2b):** The procedure was the same as that used for the synthesis of **2a**. Yield of **2b**: 7.62 g, 96%. B.p. 116–117 °C (0.5 Torr). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78–5.67 (m, 2 H, CH=), 5.06–5.02 (m, 4 H, CH_2=), 4.89 (br. s, 1 H, NH), 3.43 (t, *J* = 6.2 Hz, 2 H, CH_2O), 3.25 (s, 3 H, CH_3O), 2.50–2.45 (m, 2 H_{AB}), 2.39–2.34 (m, 2 H_{AB}), 1.82 (t, *J* = 6.2 Hz, 2 H, CH_2), 1.37 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.21, 133.50 (2 C), 118.40 (2 C), 78.39, 68.68, 58.53, 56.19, 40.52 (2 C), 35.01, 28.27 (3 C) ppm. MS (70 eV, EI): *m*/*z* (%) = 269 (2) $[M]^+$, 216 (3), 172 (14), 154 (4), 129 (6), 128 (76), 105 (7), 97 (10), 96 (100), 94 (12), 91 (12), 81 (20), 80 (17), 79 (34), 77 (22), 41 (15). $C_{15}H_{27}NO_3$ (269.2): calcd. C 66.88, H 10.10, N 5.20; found C 66.79, H 10.02, N 5.19.

***tert*-Butyl 3-Allyl-3-[(*tert*-butoxycarbonyl)amino]-5-hexenoate (2c):** The procedure was the same as that used for the synthesis of **2a**. Yield of **2c**: 4.33 g, 95%. R_f = 0.51 (*n*-C_6H_{14}/EtOAc, 10:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.81–5.74 (m, 2 H, CH=), 5.13 (br. s, 1 H, NH), 5.11–5.09 (m, 4 H, CH_2=), 2.55 (dd, *J* = 7.4, 13.5 Hz, 2 H, 2 CH_AH_B), 2.50 (s, 2 H, CH_2), 2.47 (dd, *J* = 7.4, 13.7 Hz, 2 H, 2 CH_AH_B), 1.43 (s, 9 H, tBu_{ester}), 1.41 (s, 9 H, tBu_{Boc}) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.73, 154.35, 133.19 (2 C), 119.05 (2 C), 80.82, 78.78, 55.92, 41.34, 40.59 (2 C), 28.38 (3 C), 28.05 (3 C) ppm. MS (70 eV, EI): *m*/*z* (%) = 327/326 (7.5/52) $[M + H]^+$, 284 (1.5), 271 (3), 270 (14), 228 (4), 226 (4), 214 (10), 196 (27), 172 (35), 154 (8), 152 (5), 129 (8), 128 (100), 124 (5), 110 (52), 107 (11), 93 (10), 91 (10), 82 (10), 80 (8), 68 (23), 67 (17), 41 (15). $C_{18}H_{31}NO_4$ (325.4): calcd. C 66.43, H 9.60, N 4.30; found C 66.37, H 9.52, N 4.36.

***tert*-Butyl *N*-[1-Allyl-1-(fluoromethyl)-3-butenyl]carbamate (2d):** The procedure was the same as that used for the synthesis of **2a**. Yield of **2d**: 4.85 g, 99%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85–5.71 (m, 2 H, CH=), 5.17–5.12 (m, 4 H, CH_2=), 4.49 (d, J_{FH} = 47.2 Hz, 2 H, CH_2F), 4.49 (br. s, 1 H, NH), 2.50 (dd, *J* = 7.3, 13.9 Hz, 2 H, $2CH_AH_B$), 2.37 (dd, *J* = 7.7, 13.9 Hz, 2 H, $2CH_AH_B$), 1.42 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.35, 132.27 (2 C), 119.51 (2 C), 85.49 and 83.16 (J_{CF} = 174.5 Hz), 79.29, 56.91 and 56.68 (J_{CF} = 17.14 Hz), 37.44 (br., 2 C), 28.30 (3 C) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –229.5 ppm. MS (70 eV, EI): *m*/*z* (%) = 243 (3) $[M]^+$, 204 (3), 188 (16), 146 (53), 102 (100), 82 (38), 80 (35), 57 (24), 41 (50), 39 (39). $C_{13}H_{22}FNO_2$ (243.3): calcd. C 64.17, H 9.11, N 5.76; found C 64.16, H 9.22, N 5.70.

***tert*-Butyl *N*-(1-Allyl-1-isobutyl-3-butenyl)carbamate (2e):** The procedure was the same as that used for the synthesis of **2a**. Yield of **2e**: 5.41 g, 97%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.83–5.69 (m, 2 H, CH=), 5.12–5.06 (m, 4 H, CH_2=), 4.32 (br. s, 1 H, NH), 2.45 (dd, *J* = 7.7, 13.8 Hz, 2 H, $2CH_AH_B$), 2.33 (dd, *J* = 7.7, 13.5 Hz, 2 H, $2CH_AH_B$), 1.82–1.70 (m, 1 H, CH), 1.60 (d, *J* = 5.5 Hz, 2 H, CH_2), 1.41 (s, 9 H, *t*Bu), 0.95 (d, *J* = 6.7 Hz, 6 H, 2 CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.97, 133.50 (2 C), 118.49 (2 C), 78.39, 57.17, 43.48, 40.26 (2 C), 28.36 (3 C), 24.48 (2 C), 23.59 ppm. MS (70 eV, EI): *m*/*z* (%) = 268 (2) $[M + H]^+$, 226 (3), 212 (8), 171 (12), 170 (100), 154 (16), 126 (72), 110 (26), 109 (20), 93 (13), 91 (11), 84 (25), 79 (9), 70 (28), 67 (17), 57 (16), 41 (31). $C_{16}H_{29}NO_2$ (267.4): calcd. C 71.86, H 10.93, N 5.24; found C 71.88, H 10.90, N 5.31.

(4*R,6*R**)-4-Allyl-6-(bromomethyl)-4-phenyl-1,3-oxazinan-2-one (3a):** NBS (0.89 g, 5.0 mmol) was added to a solution of **2a** (1.10 g, 3.85 mmol) in DCM (10 mL) and the mixture was stirred for 1.5 h. The solvent was removed under reduced pressure, the residue dissolved in Et_2O (10 mL), and the mixture stirred with 10% NaOH (5 mL) for 15 min. The organic layer was separated, dried with K_2CO_3, evaporated, and passed through a short column of silica gel (*n*-C_6H_{14}/EtOAc, 1:1) to furnish **3a** (1.12 g, 94%) as a white solid. M.p. 121–122 °C. R_f = 0.23 (*n*-C_6H_{14}/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.32 (m, 2 H, Ph), 7.29–7.26 (m, 3 H, Ph), 6.52 (s, 1 H, NH), 5.47–5.37 (m, 1 H, CH=), 5.22–5.16 (m, 2 H, CH_2=), 4.07–4.02 (m, 1 H, CHO), 3.43 (dd, *J* = 4.4, 10.8 Hz, 1 H, $BrCH_AH_B$), 3.39 (dd, *J* = 6.0, 10.8 Hz, 1 H, $BrCH_AH_B$), 2.83 (dd, *J* = 5.0, 13.9 Hz, 1 H, CH_AH_B), 2.51–2.45 (m, 2 H, $CH_{2,allyl}$), 2.05 (t, *J* = 12.0 Hz, 1 H, CH_AH_B) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.47, 143.28, 130.97, 129.03 (2 C), 127.74, 125.46 (2 C), 121.40, 72.83, 58.82, 47.51, 38.16, 33.00 ppm. MS (70 eV, EI): *m*/*z* (%) = 311/309 (0.1) $[M]^+$, 270/268 (25), 226/224 (20), 206/208 (3), 149 (20), 144 (100), 117 (7), 104 (15), 77 (10), 51 (4), 41 (3). $C_{14}H_{16}BrNO_2$ (310.2): calcd. C 54.21, H 5.20, Br 25.76, N 4.52; found C 54.38, H 5.19, Br 25.49, N 4.43.

(4*S,6*R**)-4-Allyl-6-(bromomethyl)-4-(2-methoxyethyl)-1,3-oxazinan-2-one (3b):** The procedure was the same as that used for the synthesis of **3a**. Yield of **3b**: 0.57 g, 95%. Colorless crystals. M.p. 113–114 °C ($CHCl_3$). R_f = 0.20 (*n*-C_6H_{14}/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.52 (s, 1 H, NH), 5.70–5.59 (m, 1 H, CH=), 5.17–5.10 (m, 2 H, CH_2=), 4.51–4.47 (m, 1 H, CHO), 3.59 (td, *J* = 3.5, 10.1 Hz, 1 H, $BrCH_AH_B$), 3.52–3.44 (m, 2 H, CH_2O), 3.37 (dd, *J* = 7.0, 10.5 Hz, 1 H, $BrCH_AH_B$), 3.29 (s, 3 H, OCH_3), 2.44 (dd, *J* = 6.7, 14.3 Hz, 1 H, $CH_AH_{B,allyl}$), 2.33 (dd, *J* = 7.9, 14.3 Hz, 1 H, $CH_AH_{B,allyl}$), 2.15 (d, *J* = 14.0 Hz, 1 H, $CH_AH_{B,cycle}$), 1.83 (ddd, *J* = 4.7, 10.1, 15.0 Hz, 1 H, $CH_AH_{B,chain}$), 1.68 (dt, *J* =

3.8, 15.0 Hz, 1 H, $CH_AH_{B,chain}$), 1.58 (t, J = 13.4 Hz, 1 H, $CH_AH_{B,cycle}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.91, 131.81, 120.38, 72.53, 68.81, 59.05, 55.10, 42.85, 38.66, 34.65, 33.05 ppm. MS (70 eV, EI): m/z (%) = 294/292 (0.3) $[M + H]^+$, 251/249 (25), 208/206 (95), 176/174 (30), 150/148 (14), 127 (20), 108 (11), 94 (100), 82 (18), 67 (10), 45 (11). $C_{11}H_{18}BrNO_3$ (292.1): calcd. C 45.22, H 6.21, Br 27.35, N 4.79; found C 45.17, H 6.14, Br 27.08, N 4.74.

***tert*-Butyl 2-[4-Allyl-6-(bromomethyl)-2-oxo-1,3-oxazinan-4-yl]acetate (3c):** The procedure was the same as that used for the synthesis of **3a**. Yield of **3c**: 0.84 g, 78%. Colorless oil, 1:1 mixture of *cis*/*trans* isomers. R_f = 0.17 (*n*-C_6H_{14}/EtOAc, 4:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.67 and 6.25 (both br. s, 1 H total, NH), 5.80–5.62 (m, 1 H), 5.22–5.10 (m, 2 H), 4.51–4.46 (m, 1 H), 3.54–3.50 (m, 1 H), 3.43–3.38 (m, 1 H), 2.54–2.31 (m, 4 H), 2.23 (dd, J = 4.7, 14.0 Hz, 1 H), 1.70 (ddd, J = 12.0, 13.6, 21.6 Hz, 1 H), 1.42 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.50, 169.26, 152.98, 152.75, 131.42, 131.11, 121.20, 120.91, 82.04, 81.83, 72.65, 72.32, 53.99, 53.89, 44.76, 44.62, 44.40, 43.56, 34.59, 34.46, 32.78, 32.73, 28.02 (3 C) ppm. MS (70 eV, EI): m/z (%) = 349/347 (0.2) $[M]^+$, 276/274 (8), 252/250 (100), 234/232 (14), 208/206 (70), 190/188 (50), 149 (11), 127 (30), 126 (70), 108 (60), 83 (27), 80 (75), 41 (20). $C_{14}H_{22}BrNO_4$ (348.2): calcd. C 48.29, H 6.37, Br 22.95, N 4.02; found C 48.11, H 6.33, Br 22.75, N 4.11.

4-Allyl-6-(bromomethyl)-4-(fluoromethyl)-1,3-oxazinan-2-one (3d): The procedure was the same as that used for the synthesis of **3a**. Yield of **3d**: 2.64 g, 84%. Oil, 1:1 mixture of *cis*/*trans* isomers. R_f = 0.35 (*n*-C_6H_{14}/EtOAc, 7:3). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.96 (br. s, 1 H), 5.85–5.71 (m, 1 H), 5.29–5.18 (m, 2 H), 4.58–4.54 (m, 1 H), 4.41–4.15 (dm, J_{FH} = 47.0 Hz, 2 H), 3.61–3.53 (m, 1 H), 3.49–3.42 (m, 1 H), 2.50–2.28 (m, 2 H), 2.17 (t, J = 13.0 Hz, 1 H), 1.83–1.71 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.15, 154.00, 130.63, 130.10, 121.65, 121.30, 87.61, 87.27, 85.23, 84.87 (J_{CF} = 178.5 Hz), 179.6, 72.93, 72.89, 72.47, 55.62, 55.38 (J_{CF} = 18.3 Hz), 54.95, 54.70 (J_{CF} = 18.8 Hz), 41.71, 41.68 (J_{CF} = 2.6 Hz), 41.28, 41.24 (J_{CF} = 2.9 Hz), 32.85, 32.48, 31.33, 30.52, 30.47 (J_{CF} = 4.3 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –223.5, –227.8 ppm. MS (70 eV, EI): m/z (%) = 268/266 (0.7) $[M + H]^+$, 226/224 (14), 182/180 (25), 149 (4), 108 (7), 101 (10), 100 (100), 80 (46), 68 (5). $C_9H_{13}BrFNO_2$ (266.1): calcd. C 40.62, H 4.92, N 5.26; found C 40.67, H 4.81, N 5.14.

4-Allyl-6-(bromomethyl)-4-isobutyl-1,3-oxazinan-2-one (3e): The procedure was the same as that used for the synthesis of **3a**. Yield of **3e**: 3.02 g, 96%. Colorless oil, 1:1 mixture of *cis*/*trans* isomers. R_f = 0.78 (EtOAc). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.26 and 6.97 (both s, 1 H total, NH), 5.79–5.69 (m, 1 H), 5.19–5.10 (m, 2 H), 4.54–4.50 (m, 1 H), 3.56 and 3.54 (both d, J = 4.6 and 4.1 Hz, 1 H total), 3.43 and 3.40 (both dd, J = 6.9, 11.0 and 6.8, 10.5 Hz, 1 H total), 2.39–2.26 (m, 2 H), 2.05 and 2.00 (both d, J = 14.2 and 13.7 Hz, 1 H total), 1.81–1.71 (m, 1 H), 1.77 and 1.67 (both dd, J = 11.9, 13.2 and 11.9, 13.7 Hz, 1 H total), 1.52–1.40 (m, 2 H), 0.97–0.94 (m, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.23, 154.20, 132.03, 131.88, 120.35, 120.15, 72.92, 72.71, 55.63, 55.30, 48.65, 48.07, 45.99, 44.27, 35.03, 33.64, 33.11, 33.01, 25.10, 25.07, 24.70, 24.12, 23.73, 23.60 ppm. MS (70 eV, EI): m/z (%) = 291/289 (1) $[M]^+$, 250/248 (34), 234/232 (16), 206/204 (64), 190/188 (13), 170 (14), 164/162 (16), 150 (15), 149 (18), 148 (12), 126 (100), 124 (84), 108 (48), 107 (19), 106 (18), 97 (12), 95 (10), 84 (80), 82 (51), 80 (25), 77 (16), 70 (36), 68 (45), 57 (39), 42 (38), 41 (45). $C_{12}H_{20}BrNO_2$ (290.2): calcd. C 49.67, H 6.95, N 4.83; found C 49.74, H 6.90, N 4.79.

***tert*-Butyl *N*-(1-Phenyl-3-butenyl)carbamate (*rac*-6):** TAB (4.0 g, 5.2 mL, 30.0 mmol) was added dropwise to a solution of silylimine **5** (5.0 g, 28.2 mmol) in THF (15 mL) with cooling in a chilled water bath. The mixture was stirred for 2 h, after which MeOH (10 mL) and 5 N NaOH (18 mL) were added. To complete the deboronation the mixture was heated at reflux for 1 h. The solvents were removed under reduced pressure and Et_2O/*n*-C_6H_{14} was added to the residue. The organic layer was separated, washed with sat. NaCl, dried with K_2CO_3, and evaporated to furnish the crude 1-phenyl-3-butenylamine (3.79 g, 91%). Boc_2O (5.92 g, 27.2 mmol) was added to a solution of the crude amine (3.79 g, 25.7 mmol) in THF (15 mL) and the mixture was heated at reflux for 1 h. After evaporation of the reaction mixture, the residue was washed with chilled hexane to give *rac*-**6** (5.07 g, 80%) as a white solid. ^1H NMR[16g] (300 MHz, $CDCl_3$): δ = 7.41–7.31 (m, 5 H, Ph), 5.80–5.67 (m, 1 H, CH=), 5.19–5.12 (m, 2 H, CH_2=), 4.94 (br. s, 1 H, NH), 4.80 (br. s, 1 H, CH), 2.57 (br. s, 2 H, CH_2), 1.47 (s, 9 H, *t*Bu) ppm.

***tert*-Butyl (*S*)-*N*-(1-Phenyl-3-butenyl)carbamate [(*S*)-6]:** (*S*)-1-Phenyl-3-butenylamine[16m] was synthesized by the addition of silylimine **5** (1.8 g, 10 mmol) to a solution of (–)-AllB(Ipc)$_2$ (4.56 g, 14 mmol) in THF (12 mL)/pentane (7 mL) at –78 °C followed by the addition of a solution of H_2O (0.2 mL) in THF (1 mL) at –100 °C. After alkaline oxidative treatment with 3 N NaOH (8 mL, 24 mmol) and 30% H_2O_2 (3 mL) with stirring overnight, the reaction mixture was concentrated under reduced pressure. A 3 N HCl (12 mL, 36 mmol) solution was added to the residue and extracted with DCM (10 mL × 3), after which the pH was adjusted to 14 with NaOH and again extracted with Et_2O (10 mL × 3). The combined extracts were dried with K_2CO_3 and the solvents evaporated. The crude amine was treated with Boc_2O (2.4 g, 11 mmol) in THF (5 mL) for 1 h at reflux. Evaporation of the volatiles gave a white solid, which was recrystallized from hexane to furnish (*S*)-**6** (1.31 g, 53%) with 94.5%*ee*. $[\alpha]_D^{25}$ = –47.3 (c = 1.5, $CHCl_3$) {ref.[24] optical rotation of the *S* isomer $[\alpha]_D^{25}$ = –48.4 (c = 1, $CHCl_3$)}.

6-(Bromomethyl)-4-phenyl-1,3-oxazinan-2-one (7): NBS (7.4 g, 41.4 mmol) was added to a solution of *rac*-**6** (8.2 g, 33.2 mmol) in DCM (60 mL) and the mixture was heated at reflux for 3 h, after which DCM was removed under reduced pressure. EtOAc/*n*-C_6H_{14} (1:2) and 10% NaOH (30 mL) were added to the residue with stirring for 10 min. The precipitate was filtered and washed with a mixture of EtOAc/*n*-C_6H_{14} and water, and drying gave *cis*-**7** (3.59 g, 40%) as a white powder. R_f = 0.21 (*n*-C_6H_{14}/EtOAc, 1:1). The organic phase of the filtrate was concentrated and the residue was dissolved in EtOAc/*n*-C_6H_{14} (1:1) and left to crystallize. Oxazinane *trans*-**7** (1.03 g, 11.4%) was obtained as colorless crystals. R_f = 0.32 (*n*-C_6H_{14}/EtOAc, 1:1). The remaining filtrate was purified by FC on silica gel in EtOAc/*n*-C_6H_{14} (1:1) to give additional amounts of *cis*-**7** (0.31 g, 3%) and *trans*-**7** (0.36 g, 4%).

***cis*-7:** M.p.[7] 180–181 °C (DCM). ^1H NMR (400 MHz, [D$_6$]-DMSO): δ = 7.79 (s, 1 H, NH), 7.44–7.41 (m, 2 H), 7.37–7.35 (m, 3 H), 4.68–4.64 (m, 2 H), 3.78 (dd, J = 3.8, 10.8 Hz, 1 H), 3.70 (dd, J = 5.4, 10.8 Hz, 1 H), 2.25 (dm, J = 13.3 Hz, 1 H), 1.68 (dt, J = 11.4, 13.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 153.08, 142.26, 129.07 (2 C), 128.22, 126.62 (2 C), 74.83, 53.90, 35.77, 35.42 ppm. ***trans*-7**: M.p.[7] 155–156 °C (EtOAc/*n*-C_6H_{14}). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 2 H), 7.35–7.28 (m, 3 H), 6.70 (s, 1 H, NH), 4.80 (narrow m, 1 H), 4.38 (m, 1 H), 3.50 (dd, J = 5.0, 11.0 Hz, 1 H), 3.46 (dd, J = 6.4, 11.0 Hz, 1 H), 2.37 (ddd, J = 5.9, 10.0, 13.7 Hz, 1 H), 2.15 (dm, J = 14.2 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.73, 141.24, 129.03 (2 C), 128.13, 125.81 (2 C), 72.22, 52.01, 32.70, 32.43 ppm. In the case of

(*S*)-**6**, the major isomer (*S*)-*cis*-**7**, which precipitates from the reaction mixture during the workup has $[a]_D^{25}$ = –59.8 (*c* = 1, MeOH).

Benzyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-4-pentenoate (9a): (*S*)-Allylglycine (0.34 g, 2.95 mmol), Boc_2O (0.90 g, 4.10 mmol), and K_2CO_3 (0.83 g, 6.0 mmol) were dissolved in THF (3 mL)/H_2O (3 mL) and the mixture was stirred for 6 h. The solution was acidified with 6 N HCl (2.3 mL, 14 mmol) to pH 3–4, extracted with DCM (10 mL × 3), washed with sat. NaCl, dried with Na_2SO_4, and evaporated to give the crude protected amino acid. A solution of (*S*)-*N*-Boc-allylglycine in DMF (7 mL) was cooled to 0-+5 °C in an ice/water bath and Cs_2CO_3 (1.01 g, 3.1 mmol) was added with stirring for 1 h. BnBr (0.58 g, 0.4 mL, 3.4 mmol) was added and the mixture was stirred overnight at 25 °C. The mixture was poured into water (20 mL), extracted with hexane (50 mL), washed with water, dried with Na_2SO_4, evaporated, and subjected to FC on silica gel (*n*-C_6H_{14}/EtOAc, 9:1) to yield **9a** (0.88 g, 98%) as a colorless oil. $[a]_D^{25}$ = –7.8 (*c* = 1, DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (narrow m, 5 H, Ph), 5.78–5.64 (m, 1 H, CH=), 5.29–5.11 (m, 5 H, CH_2=, CH_2O, NH), 4.78 (dd, *J* = 6.0, 13.5 Hz, 1 H, CHN), 2.66–2.49 (m, 2 H, CH_2CHN), 1.49 (s, 9 H, *t*Bu) ppm. The spectrum coincides with literature data.[25]

Isopropyl (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-2-methyl-4-pentenoate (9b): Et_3N (1.52 g, 2.08 mL, 15.0 mmol) was added with stirring to a solution of the hydrochloride of the isopropyl ester of (*S*)-allylalanine (2.08 g, 10.0 mmol) and Boc_2O (2.29 g, 10.5 mmol) in *i*PrOH (10 mL). After 10 min the mixture was heated at reflux for another 10 min. The solvent was removed under reduced pressure and the residue was taken up in hexane and washed with water. Purification by flash chromatography gave protected ester **9b** (2.57 g, 95%) as a colorless liquid. R_f = 0.64 (*n*-C_6H_{14}/EtOAc, 6:1). $[a]_D^{25}$ = –3.73 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.70–5.56 (m, 1 H, CH=), 5.20 (br. s, 1 H, NH), 5.09–5.04 (m, 2 H, CH_2=), 5.01 [sept., *J* = 6.3 Hz, 1 H, C*H*(CH_3)$_2$], 2.75–2.69 (br. m, 1 H, CH_2CH=), 2.51 (dd, *J* = 7.3, 13.8 Hz, 1 H, CH_2CH=), 1.48 (s, 3 H, Me), 1.39 (s, 9 H, *t*Bu), 1.21 [dd, *J* = 1.3, 6.3 Hz, 6 H, CH(CH_3)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.39, 154.23, 132.42, 119.20, 79.25, 68.91, 58.82, 41.19, 28.31 (3 C), 23.16, 21.68 (2 C) ppm. MS (70 eV, EI): *m*/*z* (%) = 272 (6) $[M + H]^+$, 271 (0.8) $[M]^+$, 184 (55), 174 (29), 132 (13), 130 (29), 128 (100), 110 (10), 88 (55), 85 (10), 84 (48), 57 (17), 42 (69), 41 (43). $C_{14}H_{25}NO_4$ (271.4): calcd. C 61.97, H 9.29, N 5.16; found C 61.94, H 9.33, N 5.17.

Benzyl (4*S*)-6-(Bromomethyl)-2-oxo-1,3-oxazinane-4-carboxylate (10a): A solution of **9a** (0.6 g, 1.96 mmol) in DCM (2 mL) was added dropwise to a solution of NBS (0.66 g, 3.7 mmol) in DCM (12 mL) at reflux. After completion of the addition the heating was continued for 1 h (TLC control, R_f = 0.51; *n*-C_6H_{14}/EtOAc, 4:1), then the solvent was evaporated under reduced pressure and the residue was dissolved in Et_2O/EtOAc (2:1, 15 mL) and treated with 5% NaOH (5 mL) for 15 min. The organic layer was separated, washed with water, dried with K_2CO_3, evaporated, and subjected to FC (*n*-C_6H_{14}/EtOAc, 3:1) to give **10a** (0.48 g, 75%) as a white powder. Mixture of isomers *cis*/*trans* = 1:2.2 was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.38 (m, 5 H), 6.60 and 6.23 (both br. s, 1 H, NH), 5.27–5.17 (m, 2 H, CH_2O), 4.50–4.43 (m, 1 H), 4.24–4.23 (m, 1 H), 3.58–3.43 (m, 2 H), 2.63 and 2.43 (both d, *J* = 12.4 and 13.4 Hz, 1 H), 2.21–2.14 and 1.93–1.84 (both m, 1 H) ppm. MS (70 eV, EI): *m*/*z* (%) = 329/327 (0.2) $[M]^+$, 302/300 (0.2), 278/276 (1), 232/230 (0.3), 194/192 (11), 150/148 (11), 105 (5), 91 (51), 79 (11), 69 (11), 68 (100), 65 (14). $C_{13}H_{14}BrNO_4$ (328.2): calcd. C 47.58, H 4.30, N 4.27; found C 47.63, H 4.39, N 4.15.

Isopropyl (4*S*)-6-(Bromomethyl)-4-methyl-2-oxo-1,3-oxazinane-4-carboxylate (10b): A mixture of **9b** (0.65 g, 2.39 mmol) and NBS (0.64 g, 3.58 mmol) in $CHCl_3$ (8 mL) was stirred for 2 h at reflux. The solvent was removed under reduced pressure and Et_2O (6 mL) and 5% aq. NaOH (8 mL) were added to the residue with vigorous stirring for 5 min. The organic layer was separated, washed with sat. NaCl, dried with K_2CO_3, evaporated, and subjected to FC in *n*-C_6H_{14}/EtOAc (2:1) to give **10b** (0.57 g, 81%) as a solid. R_f = 0.78 (EtOAc). A (1:11) *cis*/*trans* mixture was obtained. Major *trans* isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93 (s, 1 H, NH), 5.03 [sept., *J* = 6.3 Hz, 1 H, C*H*(CH_3)$_2$], 4.38–4.30 (m, 1 H, CHO), 3.53 (dd, *J* = 4.3, 10.9 Hz, 1 H, CH_ACH$_B$Br), 3.45 (dd, *J* = 6.3, 10.9 Hz, 1 H, CH$_A$CH_BBr), 2.67 (d, *J* = 13.7 Hz, 1 H, CH_ACH$_{B,cycle}$), 1.73 (dd, *J* = 12.1, 13.7 Hz, 1 H, CH$_A$C$H_{B,cycle}$), 1.50 (s, 3 H, Me), 1.26 [dd, *J* = 2.1, 6.3 Hz, 6 H, CH(CH_3)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.63, 152.72, 73.73, 70.12, 57.43, 35.00, 32.69, 26.21, 21.65, 21.60 ppm. MS (70 eV, EI): *m*/*z* (%) = 296/294 (2) $[M + H]^+$, 208/206 (29), 164/162 (12), 83 (11), 82 (100), 67 (9), 42 (5), 41 (4). $C_{10}H_{16}BrNO_4$ (294.1): calcd. C 40.83, H 5.48, Br 27.17, N 4.76; found C 40.77, H 5.49, Br 27.04, N 4.80.

6-Allyl-6-phenyl-5,6-dihydro-2,4(1*H*,3*H*)-pyridinedione (4a): *t*BuOK (0.25 g, 2.22 mmol) was added to a cooled solution of bromide **3a** (0.3 g, 0.96 mmol) in THF (6 mL) at 0 °C and the solution was stirred for 2 h at room temperature (TLC control, R_f = 0.53, *n*-C_6H_{14}/EtOAc, 1:1). The turbid solution was neutralized with AcOH (0.07 g, 1.2 mmol) and passed through a pad of silica gel on a glass filter, washed with EtOAc (8 mL × 3), evaporated, and subjected to FC to yield **4a** (0.20 g, 91%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 1 H, NH), 7.44–7.32 (m, 5 H, Ph), 5.59–5.48 (m, 1 H, CH=), 5.30–5.26 (m, 2 H, CH_2=), 3.27 (d, *J* = 16.2 Hz, 1 H$_{AB}$, CH_AH$_B$CON), 3.22 (d, *J* = 20.6 Hz, 1 H$_{A'B'}$, COCH_AH$_B$), 2.99 (d, *J* = 20.3 Hz, 1 H$_{A'B'}$, COCH$_A$$H_B$), 2.88 (d, *J* = 15.9 Hz, 1 H$_{AB}$, CH$_A$$H_B$CON), 2.82 (dd, *J* = 5.4, 14.0 Hz, 1 H, CH_AH$_{B,allyl}$), 2.61 (dd, *J* = 8.9, 14.0 Hz, 1 H, CH$_A$$H_{B,allyl}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.61, 169.74, 142.18, 130.82, 129.22 (2 C), 128.04, 125.40 (2 C), 121.71, 58.45, 50.78, 47.65, 46.75 ppm. MS (70 eV, EI): *m*/*z* (%) = 229 (0.3) $[M]^+$, 189 (13), 188 (100) $[M – Allyl]^+$, 146 (10), 120 (34), 104 (31), 103 (26), 77 (13), 51 (4), 42 (3). $C_{14}H_{15}NO_2$ (229.3): calcd. C 73.34, H 6.59, N 6.11; found C 73.24, H 6.65, N 6.03.

6-Allyl-6-(2-methoxyethyl)-5,6-dihydro-2,4(1*H*,3*H*)-pyridinedione (4b): The procedure was the same as that used for the synthesis of **4a**. Yield of **4b**: 0.39 g, 93%. Oil. R_f = 0.27 (*n*-C_6H_{14}/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (s, 1 H, NH), 5.70–5.62 (m, 1 H, CH=), 5.19–5.12 (m, 2 H, CH_2=), 3.55 (ddd, *J* = 3.8, 8.9, 10.2 Hz, 1 H, CH_AH$_B$O), 3.48 (ddd, *J* = 4.8, 5.1, 10.2 Hz, 1 H, CH$_A$$H_B$O), 3.28 (s, 3 H, CH_3O), 3.16 (s, 2 H, CH_2CON), 2.60 (d, *J* = 15.6 Hz, 1 H$_{AB}$, CH_2CO), 2.54 (d, *J* = 15.3 Hz, 1 H$_{AB}$, CH_2CO), 2.31 (d, *J* = 7.3 Hz, 2 H, $CH_{2,allyl}$), 1.87 (ddd, *J* = 4.4, 8.6, 14.9 Hz, 1 H, CH_2CH_AH$_B$), 1.75 (dt, *J* = 4.4, 15.6 Hz, 1 H, CH_2CH$_A$$H_B$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.79, 169.47, 131.73, 121.92, 68.94, 59.30, 55.86, 49.08, 45.95, 45.16, 39.74 ppm. MS (70 eV, EI): *m*/*z* (%) = 211 (1) $[M]^+$, 210 (4), 208 (6), 197 (6), 184 (20), 169 (15), 157 (32), 154 (46), 149 (16), 138 (8), 128 (9), 126 (20), 112 (42), 96 (20), 85 (57), 83 (100), 45 (28), 41 (12). $C_{11}H_{17}NO_3$ (211.3): calcd. C 62.54, H 8.11, N 6.63; found C 62.17, H 8.15, N 6.59.

***tert*-Butyl 2-(2-Allyl-4,6-dioxo-2-piperidinyl)acetate (4c):** The procedure was the same as that used for the synthesis of **4a**. Yield of **4c**: 0.46 g, 92%. Oil. R_f = 0.56 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (s, 1 H, NH), 5.77–5.63 (m, 1 H, CH=), 5.22–5.12 (m, 2 H, CH_2=), 3.24 (d, *J* = 20.8 Hz, 1 H$_{AB}$, CH_AH$_B$CON), 3.17 (d, *J* = 20.8 Hz, 1 H$_{AB}$, CH$_A$$H_B$CON), 2.62 (s, 2 H, CH_2CO), 2.44 (d, *J* = 4.3 Hz, 2 H, $CH_{2,allyl}$), 2.38 (d, *J* = 7.3 Hz, 2 H, CH_2),

1.41 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.32, 169.16, 168.33, 130.75, 121.92, 82.17, 54.25, 47.95, 45.76, 44.67, 44.57, 28.00 (3 C) ppm. $C_{14}H_{21}NO_4$ (267.3): calcd. C 62.90, H 7.92, N 5.24; found C 62.84, H 7.83, N 5.26.

6-Allyl-6-(fluoromethyl)-5,6-dihydro-2,4(1*H*,3*H*)-pyridinedione (4d): The procedure was the same as that used for the synthesis of **4a**. Yield of **4d**: 0.4 g, 84%. White powder. M.p. 94–95 °C (acetone). R_f = 0.23 (*n*-C_6H_{14}/EtOAc, 7:3), ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (br. s, 1 H, NH), 5.82–5.68 (m, 1 H, CH=), 5.30–5.20 (m, 2 H, CH_2=), 4.31 (d, J_{FH} = 46.8 Hz, 2 H, CH_2F), 3.28 (d, J = 21.0 Hz, 1 H, CH_AH$_B$CON), 3.18 (dd, J = 2.0, 21.0 Hz, 1 H, CH$_A$$H_B$CON), 2.61 (s, 2 H, CH_2CO), 2.41 (dd, J = 6.4, 14.1 Hz, 1 H, CH_AH$_B$), 2.29 (dd, J = 8.2, 14.1 Hz, 1 H, CH$_A$$H_B$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.05, 170.16, 129.54, 122.24, 89.41 and 87.04 (J_{CF} = 177.9 Hz), 56.39 and 56.16 (J_{CF} = 16.8 Hz), 45.34 and 45.31 (J_{CF} = 2.6 Hz), 44.91 and 44.97 (J_{CF} = 2.0 Hz), 40.50 and 40.44 (J_{CF} = 4.6 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –145.58 ppm. MS (70 eV, EI): *m*/*z* (%) = 185 (0.7), 165 (2), 150 (2), 149 (22), 144 (100), 135 (2), 124 (5), 111 (4), 102 (7), 96 (6), 85 (5), 82 (5), 81 (5), 76 (84), 69 (14), 60 (10), 56 (27), 43 (11), 41 (10). $C_9H_{12}FNO_2$ (185.2): calcd. C 58.37, H 6.53, F 10.26, N 7.56; found C 58.40, H 6.47, F 10.24, N 7.60.

6-Allyl-6-isobutyl-5,6-dihydro-2,4(1*H*,3*H*)-pyridinedione (4e): The procedure was the same as that used for the synthesis of **4a**. Yield of **4e**: 0.78 g, 90%. White crystals. M.p. 117–118 °C (acetone). R_f = 0.49 (*n*-C_6H_{14}/EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (s, 1 H, NH), 5.84–5.70 (m, 1 H, CH=), 5.22–5.12 (m, 2 H, CH_2=), 3.20 (s, 2 H, CH_2CON), 2.57 (s, 2 H, CH_2CO), 2.41 (dd, J = 14.0, 7.0 Hz, 1 H, CH_AH$_{B,allyl}$), 2.31 (dd, J = 14.0, 7.8 Hz, 1 H, CH$_A$$H_{B,allyl}$), 1.82 (m, 1 H, CH), 1.47 (dd, J = 5.8, 14.6 Hz, 2 H, CH_2), 0.99 (d, J = 6.6 Hz, 6 H, 2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.64, 169.43, 131.29, 121.20, 56.16, 48.62, 48.46, 45.31, 45.00, 24.63, 24.49, 23.86 ppm. MS (70 eV, EI): *m*/*z* (%) = 209 (0.5) [M]$^+$, 169 (9), 168 (87), 152 (35), 126 (100), 124 (14), 112 (11), 84 (17), 57 (6), 43 (7), 42 (8), 41 (9). $C_{12}H_{19}NO_2$ (209.3): calcd. C 68.87, H 9.15, N 6.69; found C 68.92, H 9.14, N 6.54.

6-Phenyl-5,6-dihydro-2,4(1*H*,3*H*)-pyridinedione [*rac*- and (*S*)-8]: The isomeric bromides (*S*)-**7** (0.12 g, 0.44 mmol) in THF (3 mL) was treated with *t*BuOK (87 mg, 0.78 mmol) and the mixture was stirred for 40 min at room temp. TLC control in EtOAc: R_f = 0.46. Purification by FC in EtOAc furnished **(*S*)-8** (79 mg, 95%) as a solid, 98.5% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.32 (m, 5 H, Ph), 7.20 (s, 1 H, NH), 4.87–4.84 (m, 1 H, CH), 3.35 (s, 2 H, CH_2CON), 2.92 (dd, J = 4.4, 16.1 Hz, 1 H, COCH_AH$_B$), 2.79 (dd, J = 9.5, 16.1 Hz, 1 H, COCH$_A$$H_B$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.46, 169.25, 139.29, 129.38 (2 C), 128.82, 126.04 (2 C), 52.81, 47.22, 46.94 ppm. The spectra coincide with the literature data.[7]

Benzyl 4,6-Dioxo-2-piperidinecarboxylate (11a): The procedure was the same as that used for the synthesis of **4a**. Yield of **11a**: 0.19 g, 79%, 24% *ee*. White crystals. M.p. 95–96.5 °C (ref.[6g] m.p. 102–103 °C for the pure *S* isomer). R_f = 0.56 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 6 H, Ph, NH), 4.69 (s, 2 H, CH_2O), 3.69 (m, 1 H, C*H*COOBn), 2.38 (d, J = 24.9 Hz, 1 H, CH_aH$_b$C=O), 2.26 (d, J = 25.1 Hz, 1 H, CH$_a$$H_b$C=O), 1.82 (dd, J = 6.6, 21.0 Hz, 1 H, CH_aH$_b$CH), 1.61 (dd, J = 8.2, 21.0 Hz, 1 H, CH$_a$$H_b$CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.88, 169.73, 168.69, 134.40, 128.99, 128.84 (2 C), 128.56 (2 C), 68.31, 50.74, 47.56, 40.74 ppm. The spectra coincide with the literature data.[6g] MS (70 eV, EI): *m*/*z* (%) = 247 (0.5) [M]$^+$, 221 (0.5), 149 (1.5), 112 (56), 105 (2), 95 (6), 92 (12), 91 (100), 89 (5), 84 (7), 77 (6), 70 (11), 65 (26), 44 (60). $C_{13}H_{13}NO_4$ (247.3): calcd. C 63.15, H 5.30, N 5.67; found C 63.02, H 5.34, N 5.48.

Isopropyl (2*S*)-2-Methyl-4,6-dioxohexahydro-2-pyridinecarboxylate (11b): The procedure was the same as that used for the synthesis of **4a**. Yield of **11b**: 0.26 g, 84%. White powder. R_f = 0.43 (*n*-C_6H_{14}/EtOAc, 1:1). M.p. 78–80 °C. $[a]_D^{25}$ = +53.7 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (br. s, 1 H, NH), 4.98 (sept., J = 6.3 Hz, 1 H, CHO), 3.27 (d, J = 21.0 Hz, 1 H, NCOCH_AH$_B$), 3.18 (d, J = 21.4 Hz, 1 H, NCOCH$_A$$H_B$), 2.87 (d, J = 15.7 Hz, 1 H, COCH_AH$_B$), 2.56 (d, J = 16.1 Hz, 1 H, COCH$_A$$H_B$), 1.55 (s, 3 H, CH_3), 1.21 (d, J = 6.3 Hz, 6 H, 2 CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.35, 171.52, 169.59, 70.74, 56.82, 48.26, 45.67, 25.05, 21.53, 21.45 ppm. MS (70 eV, EI): *m*/*z* (%) = 214(3) [M + H]$^+$, 213 (0.5), 149 (5), 126 (100), 97 (4), 84 (16), 83 (11), 69 (15), 58 (79), 43 (12), 42 (26), 41 (10). $C_{10}H_{15}NO_4$ (213.2): calcd. C 56.33, H 7.09, N 6.57; found C 56.22, H 7.15, N 6.60.

6-Methylene-4-phenyl-1,3-oxazinan-2-one (12): Half of the volume of a solution of HMDSLi freshly prepared from HMDS (3.54 g, 4.57 mL, 22 mmol) and *n*BuLi (2.5 M, 9.3 mL, 23 mmol) was added to a solution of bromide *cis*-**7** (2.7 g, 10 mmol) in THF (50 mL) at –60 °C and the mixture was stirred for 3 min. Then TBSCl (1.81 g, 12 mmol) was added and stirring was continued for another 15 min to ensure silylation at this temperature. Then the rest of the HMDSLi solution was injected by syringe and the reaction mixture was warmed to room temperature. The resulting solution was evaporated under reduced pressure and a mixture of THF/AcOH/H_2O (20:10:10 mL) was added to the residue, which was stirred for 30 min at 50 °C (TLC control, R_f = 0.48, *n*-C_6H_{14}/EtOAc, 1:1). The residue that was obtained after evaporation of the mixture was dissolved in DCM (15 mL) and dried with K_2CO_3, again evaporated and purified by flash chromatography to finally yield 0.90 g (48%) of **12** as colorless crystals. M.p. 139–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H, Ph), 6.70 (s, 1 H, NH), 4.72 (s, 1 H, CH_AH$_B$=), 4.59 (m, 1 H, CH), 4.25 (s, 1 H, CH$_A$$H_B$=), 2.81 (dd, J = 4.4, 13.9 Hz, 1 H, CH_AH$_B$), 2.52 (dd, J = 7.9, 13.9 Hz, 1 H, CH$_A$$H_B$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.77, 151.27, 139.86, 129.00 (2 C), 128.51, 126.01 (2 C), 94.77, 53.51, 34.33 ppm. MS (70 eV, EI): *m*/*z* = 189 (8) [M$^+$], 188 (2), 174 (4), 160 (13), 147 (8), 146 (33), 145 (11), 132 (27), 131 (6), 119 (8), 118 (8), 115 (6), 106 (5), 105 (26), 104 (100), 103 (36), 102 (5), 91 (5), 78 (41), 77 (34), 51 (10), 43 (4). $C_{11}H_{11}NO_2$ (189.2): calcd. C 69.83, H 5.86, N 7.40; found C 69.86, H 5.87, N 7.36.

Procedure for the Kinetic Experiments: A freshly prepared solution of HMDSLi (0.138 mL, 0.22 mmol) [from HMDS (1 mL/0.77 g, 4.79 mmol) and *n*BuLi (2.5 M, 2.02 mL, 5.04 mmol)] was added to a solution of **12** (40 mg, 0.2 mmol) in THF (5 mL) at –55 °C (to compensate an increase in the temperature) and the mixture was stirred for the required time (3, 5, 8, 10, 12, 15, 20, 35 min). To terminate the reaction a solution of AcOH [0.26 mL in Et_2O (2 mL)] (0.015 mL, 0.28 mmol) was added and the solution was warmed to room temp., then treated with water (0.3 mL), stirred for 30 min, filtered through "Super Cel", evaporated, and analyzed by ^{1}H NMR in $CDCl_3$. The integration was performed for the peaks at δ = 4.72 ppm (for **12**) and δ = 4.86 ppm (for **8**).

X-ray Structure Determinations

Crystal Data for 3a: $C_{14}H_{16}NO_2Br$, M = 310.19, triclinic, space group $P\bar{1}$, T = 120 K, a = 6.4169(3), b = 8.4943(4), c = 12.5947(6) Å, α = 79.601(1), β = 82.835(1), γ = 77.719(1)°, V = 657.11(5) Å^3, Z = 2, $d_{calcd.}$ = 1.568 g/cm^3, F(000) = 316, μ = 3.121 mm^{-1}. A total of 7688reflections (3786 unique reflections, R_{int} = 0.018) were measured with a three-circle Bruker SMART 1K CCD diffractometer [λ(Mo-K_α) radiation, graphite monochroma-

tor, ϕ and ω scan mode, $2\theta_{max}$ = 60°] and corrected for absorption.[26] The structure was determined by direct methods and refined by the full-matrix least-squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atom of the NH group was localized in the difference Fourier map and included in the refinement with fixed positional and isotropic displacement parameters [U_{iso}(H) = 1.2U_{eq}(N)]. The other hydrogen atoms were placed in calculated positions and refined within the riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.2U_{eq}(C)]. The final divergence factors were R_1 = 0.023 for 3540 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.059 for all independent reflections (S = 1.003). All calculations were carried out by using the SHELXTL program.[27]

Crystal Data for *cis*-7: $C_{11}H_{12}NO_2Br$, M = 270.13, monoclinic, space group $C2/c$, T = 120 K, a = 17.1029(10), b = 11.9023(7), c = 11.3889(7) Å, β = 108.510(1)°, V = 2198.4(2) Å^3, Z = 8, $d_{calcd.}$ = 1.632 g/cm^3, F(000) = 1088, μ = 3.718 mm^{-1}. A total 12484 reflections (3190 unique reflections, R_{int} = 0.032) were measured with a three-circle Bruker SMART 1K CCD diffractometer [λ(Mo-K_α) radiation, graphite monochromator, ϕ and ω scan mode, $2\theta_{max}$ = 60°] and corrected for absorption.[26] The structure was determined by direct methods and refined by the full-matrix least-squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atom of the NH group was localized in the difference Fourier map and included in the refinement with fixed positional and isotropic displacement parameters [U_{iso}(H) = 1.2U_{eq}(N)]. The other hydrogen atoms were placed in calculated positions and refined within the riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.2U_{eq}(C)]. The final divergence factors were R_1 = 0.033 for 2406 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.090 for all independent reflections (S = 1.006). All calculations were carried out by using the SHELXTL program.[27]

CCDC-832555 (for **3a**) and -832556 (for *cis*-**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Copies of the 1H and 13C NMR spectra, HPLC traces, and selected crystallographic data.

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