NMR Kinetic Studies on the Decomposition of β-Amidozinc Reagents: Optimization of Palladium-Catalyzed Cross-Coupling with Acid Chlorides

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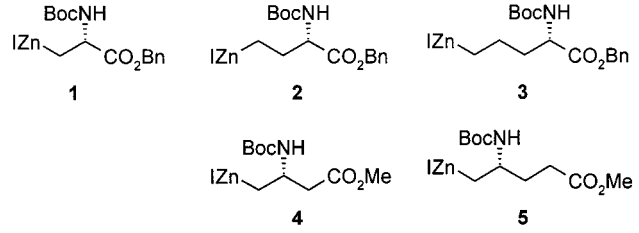
The decomposition of β-amidozinc reagent **4** by β-elimination has been shown to be a unimolecular process in both THF and DMF as solvent, with relative rates of 4:1 at room temperature, and activation parameters have been determined. These results indicate the β-elimination is a *syn*-process. NMR experiments reveal that as little as 2 equiv of DMF can have a significant stabilizing influence on reagent **4**. Use of a mixture of DMA and toluene as the bulk solvent, in place of DMF, has allowed successful palladium-catalyzed cross-coupling reactions of both **4** and the homologous reagent **5** with acid chlorides to yield unsymmetrical ketones (nine examples).

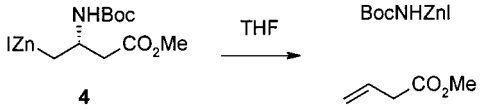
Introduction

The development of methodology for the synthesis of amino acids continues to stimulate interest within organic chemistry. In particular, β- and γ-amino acids have attracted much recent attention owing to their presence in biologically active compounds[1] and their use as building blocks in modified peptides.[2−9] We have recently extended our existing methodology for preparing α-amino acids using zinc reagents **1**, **2**, and **3**[10,11] to the synthesis of β- and γ-amino acid derivatives using the zinc reagents **4** and **5**, respectively.[12]



We observed that β-amidozinc reagents **4** and **5**, when prepared in THF, underwent β-elimination more rapidly than the closely related β-amidozinc reagent **1**.[13,14] ^{13}C NMR studies of reagents **4** and **5**, in which downfield shifts of the carbamate carbon are observed upon formation of zinc reagent from the iodide precursor, suggested that intramolecular coordination of the carbamate carbonyl group to the zinc was occurring in THF. The effect of this coordination was promotion of β-elimination, presumably due to the zinc acting as an internal Lewis acid (Scheme 1). However, when the reagents **4** and **5** were prepared in a dipolar aprotic solvent such as DMF, suppression of the internal coordination was observed by ^{13}C NMR, and β-elimination was significantly reduced. Subsequent palladium(0)-catalyzed reactions allowed cross-coupling with aryl iodides to yield phenylalanine homologues, and copper-mediated reactions with allylic halides and Michael acceptors all proceeded in good yield.[12]

Scheme 1



It was evident that the requirement for a dipolar aprotic solvent to stabilize the zinc reagents **4** and **5** would preclude reaction with some electrophiles, specifically acid chlorides, which react with DMF. We have therefore examined the decomposition of zinc reagent **4** in some detail to determine the nature of the β-elimina-

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Table 1. Activation Parameters for the Decomposition of 4 in THF and DMF[a]

	rate constant at 25 °C,[b] k/s^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}
THF-d_8	1.02×10^{-4}	+70	−85
DMF-d_7	0.26×10^{-4}	+90	−32

[a] The estimated uncertainty in $\Delta H^{\ddagger}$ is ± 5 kJ mol^{-1}, and in $\Delta S^{\ddagger}$ ± 10 J K^{-1} mol^{-1}. [b] The rate constants were measured over the range 25 °C to 55 °C in THF-d_8, and 25 °C to 70 °C in DMF-d_7.

tion as a function of solvent. We have also examined whether the addition of small amounts of dipolar aprotic solvents (e.g., DMA), which are less reactive than DMF toward acid chlorides, can stabilize reagent **4** generated in other solvents, and thus allow coupling with acid chlorides.

Results and Discussions

When the aspartic acid derived zinc reagent **4** was allowed to decompose fully in either THF-d_8 or DMF-d_7, it appeared that the sole degradation product was that occurring via β-elimination (Scheme 1). The reaction proceeded cleanly, and appeared amenable to kinetic analysis.

Kinetic Studies of Decomposition of Aspartic Acid Derived Reagent Zinc 4. The zinc reagent was prepared in THF-d_8 by the procedure used in our previous studies.[12] A plot of the percentage of starting zinc reagent, %A, against time showed exponential decay of the zinc reagent at 25 °C, while a plot of ln(%A) against time generated a straight line ($R^2 = 0.9985$). This indicated that the reaction was first order with a unimolecular rate-limiting step, solely involving zinc reagent **4**. In the same manner, the rates of decomposition of **4** were monitored at 35, 45, and 55 °C. All runs were monitored for a *minimum* of two half-lives (and indeed in the majority of the kinetic runs, to more than 90% decomposition of the reagent) and the quality of fit to the first-order rate law (as measured by the value of R^2) did *not* depend on the extent of reaction monitored. The zinc reagent was also prepared in DMF-d_7 by the same procedure. A plot of ln(%A) against time generated a straight line ($R^2 = 0.9989$), again indicating that in DMF the reaction was unimolecular, involving solely zinc reagent **4**. This implies that the formation of zinc salts during the reaction plays no part in the elimination process. The rate constant for the reaction at 25 °C in DMF ($k = 0.26 \times 10^{-4}$ s^{-1}) is approximately four times smaller than the corresponding rate constant in THF ($k = 1.02 \times 10^{-4}$ s^{-1}). Although β-elimination of **4** is not totally suppressed in DMF, it is significantly slowed, thereby allowing subsequent cross-coupling reactions to have greater opportunity to proceed. The decomposition of **4** in DMF was monitored in the same manner at 40, 55, and 70 °C.

Discussion of the Activation Parameters. The activation parameters for the elimination reaction were determined in the usual way from the Arrhenius equation,[15] in both solvents (Table 1). The fact that $\Delta S^{\ddagger}$ is negative for a first-order reaction in both solvents suggests that the elimination is a *syn*-process (Figure 1); if it were *anti* we might expect an increase, rather than a decrease in entropy because there are three developing

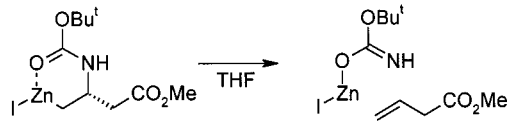

Figure 1. Syn elimination of zinc reagent 4.

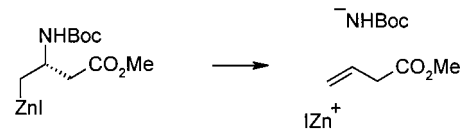

Figure 2. Anti elimination of zinc reagent **4**.

species in the transition state rather than two (Figure 2). The smaller enthalpy of activation observed in THF is most easily explained by intramolecular coordination of the carbamate group to the zinc, apparently required for elimination, already being present in the ground state. In DMF such coordination in the ground state is apparently less significant (as already observed by $\Delta\delta$ in the ^{13}C spectra),[12] presumably due to intermolecular coordination of the zinc by solvent DMF. The need to lose this solvation (at least partially) before elimination can occur results in a higher enthalpy of activation in DMF. The most reasonable explanation for the observation that $\Delta S^{\ddagger}$ is more negative in THF is that while in the ground state there is strong intramolecular coordination between the carbamate and zinc, increased solvation of the zinc is required as the transition state is reached. In DMF, the zinc is already solvated in the ground state, and the decrease in entropy resulting from coordination of the carbamate to zinc can be partially offset by the increase of entropy due to concurrent loss of coordinated DMF as the transition state forms.

Influence of Solvent on Structure of Zinc Reagent 1. We appreciated that the DMF which is required to stabilize the β-amidozinc reagents **4** and **5** would be incompatible with the use of reactive electrophilic coupling partners, such as acyl chlorides. Indeed, Knochel has reported that when cross-coupling of a mixed organozinc/copper reagent was attempted with benzoyl chloride in DMF, addition of the organometallic reagent to the iminium species (formed from DMF and benzoyl chloride) was observed.[16]

Our search for a suitable solvent in which to carry out cross-coupling of **4** with acid chlorides began with further NMR studies. We required a solvent system that would both stabilize the organozinc reagents toward β-elimination, while also being tolerant of reactive electrophiles. Our previous work had shown that the structurally related serine-derived zinc reagent **1** (also a β-amidozinc reagent) was significantly less prone to β-elimination in THF than reagents **4** and **5**.[11,12] This gave us the opportunity to prepare the reagent **1** in THF-d_8 and study the change in chemical shift of the coordinating carbonyl groups upon addition of DMF to the solution (Table 2). We hoped to establish from this study how many equivalents of DMF would be required to disrupt intramolecular coordination in **1** and therefore deduce how many equivalents of DMF would be expected to stabilize the related reagent **4** (and **5**) in THF.

We interpret a downfield shift of the carbonyl group resonance, as shown by a positive value of $\Delta\delta$, as

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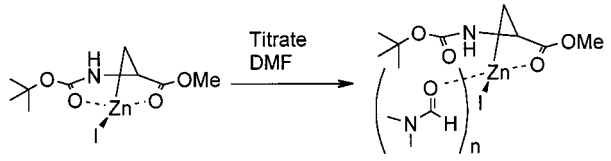
Table 2. Variation of Δδ of the ^{13}C Shifts of the Carbonyl Groups with Number of Equivalents of DMF Added to a THF-d_8 Solution of 1

DMF (equiv)	$\Delta\delta_{carbamate}$[a]	$\Delta\delta_{ester}$[a]	$\Delta\delta_{DMF\ amide}$[b]
0	+2.711	+5.347	–
0.5	+2.180	+5.586	+4.55
1	+1.785	+5.786	+4.35
2	+1.045	+6.112	+3.70
4	+0.526	+6.383	+2.50

[a] Δδ was calculated as the difference in chemical shift relative to the $\delta_{carbonyl}$ of the precursor iodide in THF-d_8 (i.e., $\Delta\delta = [\delta_{(R-ZnI)} - \delta_{(R-I)}]$). [b] These shifts are relative to $\delta_{carbonyl}$ of a reference sample of 2.0 equiv of DMF in THF-d_8.



1
in THF-d_8

Figure 3. Addition of DMF to zinc reagent **1** in THF.

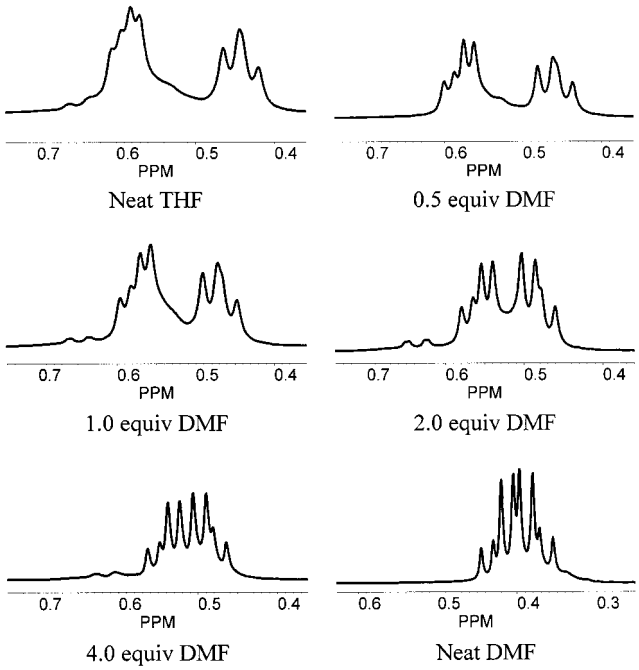
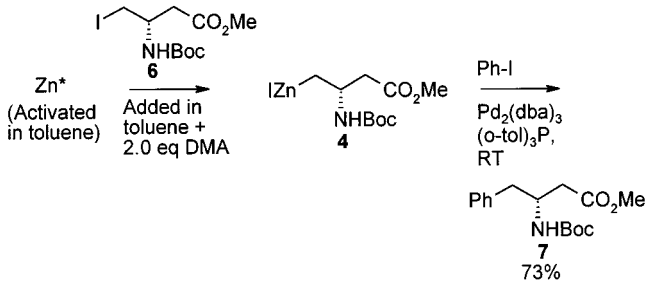


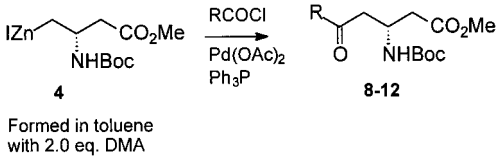
Figure 4. Convergence of the diastereotopic methylene protons on addition of DMF to a solution of **1** in THF-d_8.

implying coordination between the carbonyl group and zinc. As DMF is added, coordination between the zinc and carbamate becomes progressively weaker (Figure 3). Furthermore, with less electron density being donated from the carbamate group, the ester group is seen to coordinate more strongly. The carbonyl group of solvent DMF is also observed to shift, the magnitude decreasing as more equivalents of DMF are added. Presumably, this chemical shift reflects an average for both the coordinating and noncoordinating solvent molecules. Interestingly, as more equivalents of DMF were added, the ^1H spectra showed the diastereotopic CH_2–ZnI protons converging, becoming more like the spectrum of the same reagent in neat DMF (Figure 4). These observations show that it is possible to achieve disruption of carbamate coordination with relatively low concentrations of DMF.

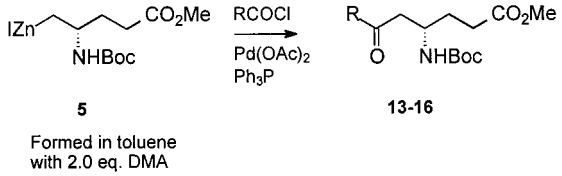
Scheme 2



Scheme 3



Scheme 4



Following these results, the aspartic acid derived zinc reagent **4** was generated in THF-d_8 containing 2 equiv of DMF, and then transferred into an NMR tube. The initial ^1H NMR spectrum indicated clean formation of the zinc reagent without significant evidence for decomposition. However, a ^1H NMR spectrum, taken after a ^{13}C NMR spectrum had been run, indicated that decomposition was starting to occur. The rate of decomposition was measured at 25 °C, which allowed us to establish that the reaction was first order, with the rate constant ($k = 0.6 \times 10^{-4}\ s^{-1}$) intermediate between the values in neat DMF and neat THF.

Palladium-Catalyzed Cross-Coupling Reactions with Acid Chlorides. Given that THF is problematic when used as a solvent for cross-coupling reactions between organozinc reagents and acid chlorides,[17,18] we identified toluene as a suitable inert bulk solvent, and dimethylacetamide (DMA) as the dipolar aprotic cosolvent. Thus, zinc reagent **4** was prepared in toluene/DMA and then cross-coupled with iodobenzene (Scheme 2) to give β-homophenylalanine derivative **7** in identical yield to that obtained in neat DMF[12] and much better than that obtained when using THF alone. We have found that activation of zinc using only chlorotrimethylsilane, and the use of three equivalents of zinc, are perfectly satisfactory for the formation of **4**.

The coupling reactions of this reagent and the homologous reagent **5** with acid chlorides (catalyzed by palladium acetate and triphenylphosphine) was then investigated. Use of a small range of acid chlorides allowed the preparation of the ketones **8**–**16** in moderate yields, with the exception of hexanoyl chloride which was a poor substrate (Schemes 3 and 4, Table 3).

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Table 3. Yields of Palladium-Catalyzed Cross-coupling Reactions between 4 and 5 with Acyl Chlorides in Toluene with 2.0 Equiv of DMA

zinc reagent	R	coupled product	% yield
4	Ph	**8**	59
4	CH_2═CH	**9**	46
4	$AcOCH_2$	**10**	49
4	$CH_3(CH_2)_4$	**11**	20
4	2-furyl	**12**	51
5	Ph	**13**	51
5	CH_2═CH	**14**	48
5	$AcOCH_2$	**15**	52
5	2-furyl	**16**	45

Experimental Section

DMF and toluene were distilled from calcium hydride and stored over 4 Å molecular sieves. DMA was obtained from Aldrich in Sure-Seal bottles and used as supplied. Organic extracts were dried over magnesium sulfate and filtered, and the solvent was then removed using a rotary evaporator.

Formation of Amino Acid Derived Organozinc Reagents 1, 4, and 5 in DMF. General Procedure. Zinc dust (0.284 g, 4.5 mmol) was weighed into a 50 mL round-bottom flask with sidearm which was flushed with nitrogen. Dry DMF (0.5 mL) and 1,2-dibromoethane (19 μL, 0.225 mmol) were added, and the mixture was stirred vigorously. The mixture was gently heated using a heat gun, so that the evolution of ethene was observed, before being allowed to attain room temperature. Chlorotrimethylsilane (6 μL, 0.046 mmol) was added to the mixture which was stirred for a further 30 min. A solution of amino acid derived iodide (0.75 mmol) in DMF was transferred under nitrogen via syringe to the reaction mixture at room temperature. The reaction was judged to be complete by TLC analysis (petroleum ether−ethyl acetate, 2:1) after approximately 15 min (*The starting iodide is UV active while the products are not*).

NMR Experiments: Studies of the Aspartic Acid Derived Organozinc Reagent in both THF-d_8 and DMF-d_7. Organozinc reagent **4** was prepared from iodide **6** using the general procedure described above, but using DMF-d_7 and THF-d_8 in place of the nondeuterated solvents. When no starting material remained (as judged by TLC), the excess zinc dust was allowed to settle. The supernatant was transferred via syringe into a nitrogen-filled NMR tube fitted with a Young's tap. Generally, a small amount of excess zinc was unavoidably transferred into the NMR tube, although this did not appear to affect the quality of the spectra. References used for the deuterated solvents; DMF-d_7 (δ_H 2.90, δ_C 161.70) and THF-d_8 (δ_H 1.80, δ_C 26.70).

Measurement of the Rates of Decomposition. The NMR tube containing zinc reagent **4** was placed in the spectrometer and allowed to equilibrate at the temperature of the experiment. The proportions of zinc reagent to elimination product were measured by comparison of the CH_2ZnI protons at approximately 0.3 ppm and the CH_2CO_2Me protons at approximately 3 ppm, since these signals did not overlap with any others. Spectra were recorded at intervals of approximately 15 min for temperatures below 50 °C, and every 5 min for temperatures above 50 °C, until a minimum of two half-lives had elapsed, and in most cases for a substantially longer period.

Preparation of 5 Oxo-β-amino Acid Derivatives and 6-Oxo-γ-amino Acid Derivatives. General Procedure. Zinc dust (0.142 g, 2.25 mmol) was weighed into a 50 mL round-bottom flask with sidearm which was flushed with nitrogen. Dry toluene (0.5 mL) and chlorotrimethylsilane (6μL, 0.046 mmol) were added to the zinc dust and stirred for 30 min at room temperature. Iodide **4** or **5** (0.75 mmol) was dissolved in dry toluene (0.5 mL) and DMA (0.2 mL) under nitrogen. The iodide solution was transferred via syringe to the zinc mixture, and stirring was continued at room temperature. TLC (petroleum ether−ethyl acetate 2:1) showed complete consumption of the starting material within 15 min. The electrophile (1.0 mmol), palladium acetate (0.0112 g, 0.050 mmol), and triphenylphosphine (0.0264 g, 0.010 mmol) were added successively to the reaction mixture, which was stirred at room temperature for 3 h. The mixture was partitioned between saturated aqueous ammonium chloride (30 mL) and ethyl acetate (50 mL), and then the mixture was filtered. The organic layer was separated, washed with brine (20 mL), dried, filtered, and evaporated to dryness. Flash chromatography over silica gel eluting with an appropriate petroleum ether−ethyl acetate gradient furnished the protected 5-oxo-β-amino acids **8**−**12** and the 6-oxo-γ-amino acids **13**−**16**.

Methyl 3(*R*)-[(*N*-*tert*-Butoxycarbonyl)amino]-5-oxo-5-phenylpentanoate (8). Treatment with benzoyl chloride yielded **8** (0.142 g, 59%), isolated as a pale brown solid, mp 61−64 °C; found C, 63.41; H, 7.14; N, 4.18, $C_{17}H_{23}NO_5$ requires C, 63.54; H, 7.21; N, 4.36%; ν_{max} (KBr disk)/cm^{-1} 3373, 2983, 1740, 1679, 1529, and 1160; δ_H 1.41 (9 H, s), 2.72 (1 H, dd, *J* 6.4 and 16.2), 2.82 (1 H, dd, *J* 5.2 and 16.2), 3.29 (1 H, dd, *J* 6.6 and 17.4), 3.41 (1 H, dd, *J* 4.0 and 17.4), 3.66 (3 H, s), 4.43−4.48 (1 H, m), 5.49 (1 H, d, *J* 7), 7.44 (2 H, m), 7.53−7.59 (1 H, m), and 7.94−7.97 (2 H, m); δ_C 28.30, 37.80, 41.64, 44.34, 51.66, 79.44, 128.07, 128.63, 133.39, 136.63, 153.04, and 172.06; *m*/*z* (EI) 265 (9%, $M^+ - C_4H_8$), 220 (19), 105 (100, $PhCO^+$), 77 (28) and 57 (78); found M^+ 321.1564, $C_{17}H_{23}NO_5$ requires 321.1576; $[\alpha]^{26}_D$ −14.1 (*c* 1.085 in CH_2Cl_2).

Methyl 3(*R*)-[(*N*-*tert*-Butoxycarbonyl)amino]-5-oxohept-6-enoate (9). Treatment with acryloyl chloride yielded **9** (0.092 g, 46%), isolated as a pale brown oil. ν_{max} (cap. film)/cm^{-1} 3366, 2978, 1736, 1713, 1367, and 1168; δ_H 1.43 (9 H, s), 2.65 (1 H, dd, *J* 6.4 and 16.2), 2.74 (1 H, dd, *J* 5.1 and 16.2), 2.91 (1 H, dd, *J* 4.9 and 17.0), 3.04 (1 H, dd, *J* 6.7 and 17.0), 3.68 (3 H, s), 4.28−4.36 (1 H, m), 5.36 (1 H, d, *J* 7.6), 5.89 (1 H, dd, *J* 1.2 and 10.2), 6.26 (1 H, dd, *J* 1.2 and 17.7), and 6.33 (1 H, dd, *J* 10.2 and 17.7); δ_C 28.35, 37.83, 42.57, 44.17, 51.67, 79.55, 129.19, 136.54, 155.05, 172.00, and 198; *m*/*z* (EI) 215 (3%, $M^+ - C_4H_8$), 184 (40), 170 (10), 154 (20), 102 (30), and 57 (100); found MH^+ 272.1492, $C_{13}H_{22}NO_5$ requires 272.1498. $[\alpha]^{26}_D$ +3.2 (*c* 0.25 in CH_2Cl_2).

Methyl 3(*R*)-[(*N*-*tert*-Butoxycarbonyl)amino]-6-acetoxy-5-oxohexanoate (10). Treatment with acetoxyacetyl chloride yielded **10** (0.116 g, 49%), isolated as a pale brown oil. ν_{max} 3371, 2978, 1734, 1368, 1236, and 1169; δ_H 1.45 (9 H, s), 2.17 (3 H, s), 2.64−2.88, 2.64 (1 H, dd, *J* 6.3 and 16.2), 2.71 (1 H, dd, *J* 5.4 and 16.2), 2.77 (1 H, dd, *J* 6.6 and 17.0), 2.88 (1 H, dd, *J* 5.1 and 17.0), 3.68 (3 H, s), 4.29−4.33 (1 H, m), 4.64 (2 H, d, *J* 1.3), and 5.34 (1 H, br d, *J* 8.2); δ_C 20.42, 28.32, 31.70, 42.10, 43.74, 68.16, 79.72, 155.01, 170.20, and 202.56. *m*/*z* (EI) 201 (13%), 188 (32), 157 (24), 102 (65), and 57 (100). $[\alpha]^{26}_D$ +4.4 (*c* 0.5 in CH_2Cl_2).

Methyl 3(*R*)-[(*N*-*tert*-Butoxycarbonyl)amino]-5-oxodecanoate (11). Treatment with hexanoyl chloride yielded **11** (0.045 g, 20%), isolated as a pale brown oil. ν_{max} (cap. film)/cm^{-1} 3371, 2956, 1714, 1517, 1366, 1249, and 1097; δ_H 0.89 (3 H, t, *J* 7), 1.21−1.34 (4 H, m), 1.42 (9 H, s), 1.55 (2 H, quint, *J* 7), 2.32 (2 H, t, *J* 7), 2.62 (1 H, dd, *J* 6.6 and 16), 2.68−2.72 (2 H, m), and 2.83 (1 H, dd, *J* 4.7 and 17.3), 3.67 (3 H, s), 4.22−4.30 (1 H, m), and 5.34 (1 H, d, *J* 7.6); δ_C 13.84, 22.37, 22.54, 28.29, 31.23, 37.93, 43.19, 43.99, 45.53, 51. 65, 79.44, 155.00, 171.92, and 209.69; *m*/*z* (EI) 260 (42%, $MH^+ - C_4H_8$), 216 (37, $MH^+ - C_4H_8 - CO_2$), 116 (66), 102 (56), and 57 (100); found MH^+ 316.2128, $C_{16}H_{30}NO_5$ requires 316.2151. $[\alpha]^{26}_D$ +10.0 (*c* 2.15 in CH_2Cl_2).

Methyl 3(*R*)-[(*N*-*tert*-Butoxycarbonyl)amino]-5-oxo-5-(2′-furyl)pentanoate (12). Treatment with 2-furoyl chloride yielded **12** (0.118 g, 51%), isolated as a pale brown oil. ν_{max} (KBr disc/cm^{-1}) 3365, 2978, 1735, and 1712; δ_H 1.35 (9H, s), 2.63 (1H, dd, *J* 6.4 and 16.2), 2.72 (1H, dd, *J* 4.8 and 16.5), 3.05 (1H, dd, *J* 6.4 and 16.5), 3.20 (1H, dd, *J* 4.6 and 16.2), 3.61 (3H, s), 4.32−4.39 (1H, m) 5.40 (1H, brd, *J* 8.0), 6.48 (1H, dd, *J* 1.8, 3.5), 7.20 (1H, d, *J* 3.4), and 7.53−7.55 (1H, m); δ_C 28.18, 37.87, 41.59, 44.42, 51.58, 79.37, 112.27. 117.86. 146.70, 152.36, 154.92, 171.78, and 187.00; *m*/*z* (EI) 255 (61%, $M^+ - C_4H_8$), 238 (14), 211 (100) 195 (20), 116 (12), 95 (26), and 57 (57); found $M^+ - C_4H_8$ 255.0743 $C_{11}H_{13}NO_6$ requires 255.0747; $[\alpha]^{24}_D$ −10.2 (*c* 0.500 in CH_2Cl_2).

Methyl 4(*S*)-[(*N*-*tert*-Butoxycarbonyl)amino]-6-oxo-6-phenylheptanoate (13). Treatment with benzoyl chloride yielded **13** (0.128 g, 51%), isolated as a pale brown solid, mp 67−68 °C; found C, 64.4; H, 7.9; N, 4.1, $C_{18}H_{25}NO_5$ requires C, 64.5; H, 7.5; N, 4.2%; ν_{max} (KBr disc/cm^{-1}) 3361, 2982, 1733, 1694, and 1526; δ_H 1.41 (9H, s), 1.89−2.04 (2H, m), 2.43 (2H, dt, *J* 2.4 and 7.5), 3.15 (1H, dd, *J* 6.1 and 17.0), 3.34 (1H, dd, *J* 3.7 and 17.1), 3.66 (3H, s), 4.03−4.11 (1H, m), 5.16−5.19 (1H, brd, *J* 8.2), 7.45−7.49 (2H, m), 7.56−7.59 (1H, m), and 7.93−7.96 (2H, m); δ_C 28.32, 29.38, 31.13, 42.83, 47.48, 51.66, 79.29, 128.05, 128.66, 133.35, 136.83, 155.46, 173.79, and 199.73; *m*/*z* (EI) 279 (7%, $M^+ - C_4H_8$), 262 (6), 234 (34), 105 (100), 77 (22), and 57 (79); found $M^+ - C_4H_8$ 279.114, $C_{14}H_{17}NO_5$,requires 279.1107; $[\alpha]^{26}_D$ −18.0 (*c* 0.850 in CH_2Cl_2).

Methyl 4(*S*)-[(*N*-*tert*-Butoxycarbonyl)amino]-6-oxooct-7-enoate (14). Treatment with acryloyl chloride yielded **14** (0.102 g, 48%), isolated as a brown oil. ν_{max} (KBr disc/cm^{-1}) 3364, 2977, 1737, 1711, and 1171; δ_H 1.44 (9H, s), 1.75−1.86 (2H, m), 2.33 (2H, dt, *J* 1.2 and 7.5), 2.71 (1H, dd, *J* 5.8 and 16.8), 2.85 (1H, dd, *J* 4.0 and 16.6), 3.61 (3H, s), 3.86−3.91 (1H, m), 4.95 (1H, brd, *J* 8.2), 5.81 (1H, dd, *J* 0.9 and 10.4), 6.17 (1H, dd, *J* 1.0 and 17.4), and 6.27 (1H, dd, *J* 10.4 and 17.7); δ_C 28.42, 29.51, 31.12, 44.00, 47.36, 51.76, 79.43, 129.04, 136.70, 155.51, 173.83, and 199.25; *m*/*z* (EI) 229 (18%, $M^+ - C_4H_8$), 212 (44), 185 (100), 168 (48) and 154 (22); found $M^+ - C_4H_8$ 229.0958, $C_{10}H_{15}NO_5$ requires 229.0950; $[\alpha]^{22}_D$ −15.8 (*c* 1.750 in CH_2Cl_2).

Methyl 4(*S*)-[(*N*-*tert*-Butoxycarbonyl)amino]-7-acetoxy-6-oxoheptanoate (15). Treatment with acetoxyacetyl chloride yielded **15** (0.130 g, 52%), isolated as a pale brown solid, mp 83−84 °C. Found: C, 54.72; H, 7.78; N, 4.13: $C_{15}H_{25}NO_7$ requires C, 54.38; H, 7.55; N, 4.23); ν_{max} (KBr disc/cm^{-1}) 3346, 2984, 1731, 1370, 1228, and 1170; δ_H 1.35 (9H, s), 1.77−1.84 (2H, m), 2.10 (3H, s), 2.32 (2H, t, *J* 7.4), 2.55−2.66 (2H, m), 3.61 (3H, s), 3.84−3.91 (1H, m), 4.57 (2H, d, *J* 1.8), and 4.90 (1H, brd, *J* 8.0); δ_C 20.55, 28.44, 29.46, 31.03, 43.65, 47.04, 51.85, 68.34, 79.69, 155.51, 170.32, 173.76, and 202.81; *m*/*z* (EI) 331 (25%, M^+), 288 (44), 230 (47) 215 (17), and 57 (100); found M^+ 331.1644, $C_{15}H_{25}NO_7$ requires 331.1631; $[\alpha]^{26}_D$ −12.9 (*c* 0.820 in CH_2Cl_2).

Methyl 4(*S*)-[(*N*-*tert*-Butoxycarbonyl)amino]-6-oxo-6-(2′-furyl)hexanoate (16). Treatment with 2-furoyl chloride yielded **16** (0.111 g, 45%), isolated as a pale brown oil. ν_{max} (KBr disc/cm^{-1}) 3362, 2977, 1735, 1711, and 1169; δ_H 1.35 (9H, s), 1.83−1.87 (2H, m), 2.36 (2H, t, *J* 7.5), 2.93 (1H, dd, *J* 5.5 and 16.0), 3.10 (1H, dd, *J* 4.0 and 16.0), 3.60 (3H, s), 3.96−4.01 (1H, m), 5.03 (1H, brd, *J* 8.2), 6.47 (1H, dd, *J* 1.5 and 3.4), 7.17 (1H, d, *J* 3.4), and 7.52−7.54 (1H, m); δ_C 28.29, 29.49, 31.02, 42.82, 47.61, 51.64, 79.29, 112.35. 117.71. 146.64, 152.62, 155.37, 173.69, and 187.47; *m*/*z* (EI) 326 (72%, MH^+), 269 (10), 252 (9) 224 (63), 116 (33), 95 (42), and 57 (100); found MH^+ 326.1603, $C_{16}H_{24}NO_6$ requires 326.1595; $[\alpha]^{25}_D$ −12.3 (*c* 0.600 in CH_2Cl_2).

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Supporting Information Available: Arrhenius plots for the decomposition of **4** in both THF and DMF, and ^{1}H and ^{13}C NMR spectra for all coupled products (**8**−**16**). This information is also available free of charge via the Internet at http://pubs.acs.org.

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