Degradative Rearrangements of *N*-(*t*-Butyloxycarbonyl)-*O*-methanesulfonylhydroxamic Acids: A Novel, Reagent-Based Alternative to the Lossen Rearrangement[1]

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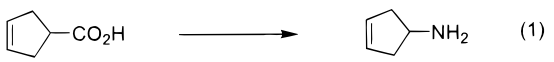
During the course of our research efforts, we required a multigram conversion of cyclopentenyl carboxylic acid **1** to the corresponding amine **2** (eq 1). Application of the Curtius rearrangement[2] on laboratory microscale satisfactorily delivered the desired product. However, due to the scale on which we needed to operate the Curtius reaction and the safety hazard[3] associated with the involvement of low molecular-weight acyl azides, we considered an alternative means for this transformation. The oxidative and relatively harsh conditions required for the Hofmann rearrangement[2] represent a liability to its application as well.

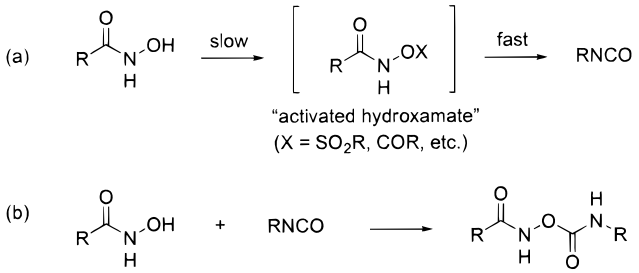


(1)

1 **2**

The Lossen rearrangement (Scheme 1), in which hydroxamic acids are O-activated to create a suitable leaving group for subsequent rearrangement, also belongs to the category of named, classical carboxyl degradation reactions that provide useful isocyanate intermediates from carboxylic acid derivatives.[2] We became interested in the use of the Lossen rearrangement due to its apparent simplicity and relatively mild conditions. In our hands, however, attempts to effect the Lossen rearrangement on the hydroxamic acid of **1** failed to provide us with the desired amine, but rather afforded complex mixtures. A survey of the chemical literature reveals that the Lossen rearrangement receives little attention as a general and practical synthetic method. The reasons for its limited use appear to be two-fold: the relative unavailability of hydroxamic acids and the competing formation of self-condensation byproducts as a result of unfavorable reaction kinetics.[4] Specifically, the rate-limiting step is the activation of the hydroxamic acid (Scheme 1a); the consequence of these kinetics is accumulation of isocyanate before complete consumption of the hydroxamic acid. Trapping of the isocyanate by

Scheme 1



the hydroxamic acid results in dimerization (Scheme 1b).[5] In this paper, we describe the development and application of a modified Lossen rearrangement.

To overcome the dimerization associated with the classical Lossen rearrangement, it would be desirable to initiate the rearrangement on the "activated hydroxamate" (Scheme 1) only after the hydroxamic acid is completely consumed. Therefore, we considered that a protected form of the activated hydroxamate could harbor a latent Lossen rearrangement substrate that would undergo spontaneous rearrangement in the event of deprotection. We recently described a method that was envisaged to be applicable to the above hypothesis, namely the removal of *tert*-butyloxycarbonyl (BOC) protecting groups from amides and carbamates using mild Lewis acid catalysis.[6] By this method, BOC deprotection of a protected and suitably activated hydroxamate would, in principle, initiate the rearrangement sequence, undisturbed by the presence of any interfering hydroxamic acid, providing stepwise control of the Lossen rearrangement.[7]

Commercially available *tert*-butyl-*N*-hydroxycarbamate (**3**) was converted to the methanesulfonyloxycarbamate **4** in 77% yield (Scheme 2). Reagent **4** is routinely prepared in batches >20 g in weight and recrystallized from diisopropyl ether.[8] The coupling of **4** to an activated carboxylic acid derivative of **1** was investigated in considerable detail. The diminished basicity conferred on the nitrogen atom in **4** by the attached *tert*-butyloxycarbonyl and methanesulfonyloxy groups compromises the reactivity of **4** for many amine−acid coupling procedures. Nevertheless, coupling of **4** with acid chloride **5**[9] in DMF provided the *N*-acylated derivative **6** in 73% yield following purification by flash chromatography. We found that the relatively low reactivity of **4** is overcome by using

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(1) Part of this work was presented by SSG at the Southeast Regional Meeting of the American Chemical Society, Greenville, SC, Nov 1996.

(2) For a recent review on carboxyl degradation reactions see: Shioiri, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 6, p 795, and references therein.

(3) (a) Landgrebe, J. A. *Chem. Eng. News* **1981**, *59*, 47. (b) Middleton, W. J. *J. Org. Chem.* **1984**, *49*, 4541.

(4) (a) Hoare, D. G.; Olson, A.; Koshland, D. E., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 1638. (b) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376.

(5) (a) Stolberg, M. A.; Tweit, R. C.; Steinberg, G. M.; Wagner-Jauregg, T. *J. Am. Chem. Soc.* **1955**, *77*, 765. (b) Hurd, C. D.; Bauer, L. *J. Am. Chem. Soc.* **1954**, *76*, 2791. (c) Pihuleac, J.; Bauer, L. *Synthesis* **1989**, 61.

(6) Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. *Tetrahedron Lett.* **1993**, *34*, 7873.

(7) Alternative strategies to provide stepwise control of the Lossen rearrangement have been reported: (a) Miller, M. J.; Loudon, G. M. *J. Am. Chem. Soc.* **1975**, *97*, 5295. (b) King, F. D.; Pike, S.; Walton, D. R. M. *J. Chem. Soc., Chem. Commun.* **1978**, 351.

(8) While reagent **4** can be readily manipulated on the benchtop in open air, it is recommended that **4** be stored under nitrogen at 4 °C. When stored in this manner, **4** is stable and can be used for several months. (CAUTION: Formation of hazardous peroxides of diisopropyl ether has been reported. For a review on controlling the hazards associated with peroxidized ethers see: Jackson, H. L. *et al. J. Chem. Educ.* **1970**, *47*, A175.)

(9) Activation and coupling of **1** via formation of a mixed anhydride also provides good yields of **6**. This method was applied for the synthesis of **9** and **11** (*vide infra*). Attempts at carbodiimide-based coupling procedures (e.g., EDC) were unsuccessful.

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Scheme 2

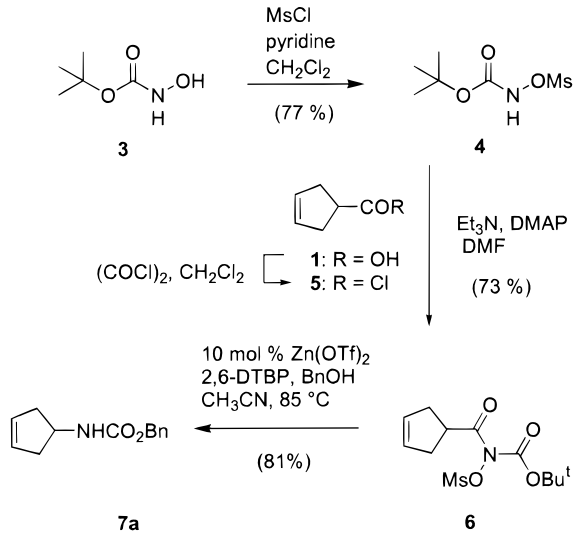


Table 1. Modified Lossen Rearrangment of Hydroxamate Derivative 6[a]

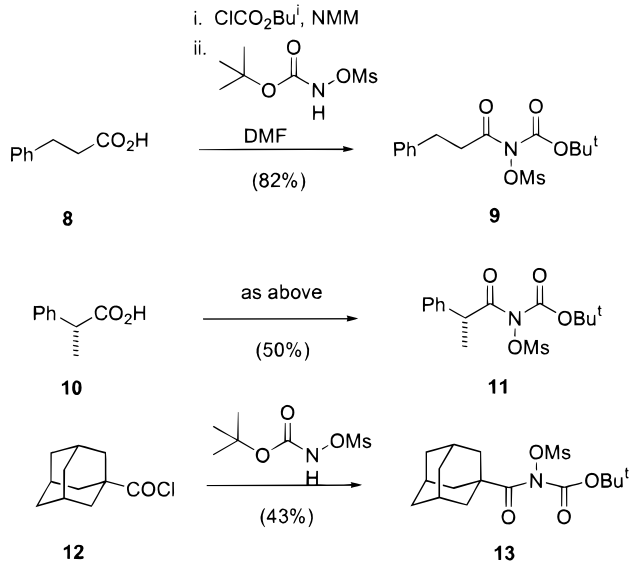
entry	Lewis acid	base	alcohol	solvent	temp (°C)	yield[b] (%)
1	$Zn(OTf)_2$	2,6-DTBP	$PhCH_2OH$	CH_3CN	85	82
2	$Zn(OTf)_2$	2,6-DTBP	$PhCH_2OH$	CH_3CN	50	–
3	$Zn(OTf)_2$	Et_3N	$PhCH_2OH$	CH_3CN	85	54
4	$Zn(OTf)_2$	pyridine	$PhCH_2OH$	CH_3CN	85	55
5	$Zn(OTf)_2$	–	$PhCH_2OH$	CH_3CN	85	35
6	$Zn(OTf)_2$	2,6-DTBP	$CH_2{=}CHCH_2OH$	CH_3CN	85	76[c]
7	$Zn(OTf)_2$	2,6-DTBP	$(CH_3)_3COH$	CH_3CN	85	19
8	$Zn(OTf)_2$	2,6-DTBP	$TMSCH_2CH_2OH$	CH_3CN	85	46[d]
9	$Zn(OTf)_2$	2,6-DTBP	$PhCH_2OH$	DME	85	47
10	$Zn(OTf)_2$	2,6-DTBP	$PhCH_2OH$	toluene	85	–
11	–	2,6-DTBP	$PhCH_2OH$	CH_3CN	85	78

[a] All rearrangements were conducted according to the general procedure described in the Experimental Section. [b] Yields refer to isolated, pure products having proper spectral and/or analytical data. [c] Compound **7b** in Experimental Section. [d] Compound **7c** in Experimental Section.

DMF as the reaction solvent for the coupling of **4**, and by this practice we routinely obtained **6** in good yield.[10] The *N*-acyl-hydroxamate products such as **6** described herein are air stable, conveniently handled compounds possessing excellent shelf stability at room temperature.

Treatment of **6** with zinc triflate, benzyl alcohol, and 2,6-di-*tert*-butylpyridine (2,6-DTBP) in acetonitrile at 85 °C effected the desired rearrangement to the CBz-protected amine **7a** in 82% isolated yield. The rearrangement of **6** to **7a** represents a novel method for the overall conversion of a carboxylic acid to a protected amine. By comparison to the classical Lossen rearrangement, use of reagent **4** circumvents preparation of the requisite hydroxamic acid and allows direct use of a more readily available carboxylic acid. The conditions for the rearrangement of **6** were examined, and several points are noteworthy (Table 1). A lowering of the reaction temperature fails to effect the rearrangement, and starting material is recovered (entry 2). 2,6-DTBP was chosen as the base to scavenge methanesulfonic acid because we believed that its steric hindrance would also serve to inhibit coordination to the Lewis acid. The use of triethylamine or pyridine resulted in lower yields of **7a** (entries 3 and 4). Complete removal of base from the reaction mixture also resulted in lower yields (entry 5). The options of using allyl alcohol or 2-trimethylsilylethanol (entries 6 and 8) introduce additional flexibility to carbamate-deprotection strategies.[11] A dramatic solvent effect was noted. Thus, in less polar solvents (i.e., DME and toluene) little or no formation of **7a** was observed (entries 9 and 10).

Scheme 3



Interestingly, the rearrangement can be effected in equally good yield by thermolysis[12] when the Lewis acid is omitted (entry 11). This observation is in contrast to our earlier work in which simple thermolysis at 85 °C showed no effect on BOC deprotection from amides and carbamates.[6] After this finding, the Lewis acid was omitted from the reaction vessel. The omission of the Lewis acid prompted a reinvestigation into whether 2,6-DTBP is the preferred base for this transformation. Pyridine and 2,6-lutidine were both examined, but the yields were consistently lower with these bases. Further investigation to define the optimized conditions for rearrangement of **9** in the absence of zinc triflate paralleled the findings observed for hydroxamate **6** in the presence of zinc triflate. Finally, the observation that the rearrangement proceeds at 85 °C without zinc triflate led us to consider stronger Lewis acids that may indeed catalyze the process at lower temperatures (e.g., 0 °C). The use of TMSOTf and $TiCl_4$ failed to initiate the rearrangement at or below room temperature, and these efforts were discontinued.

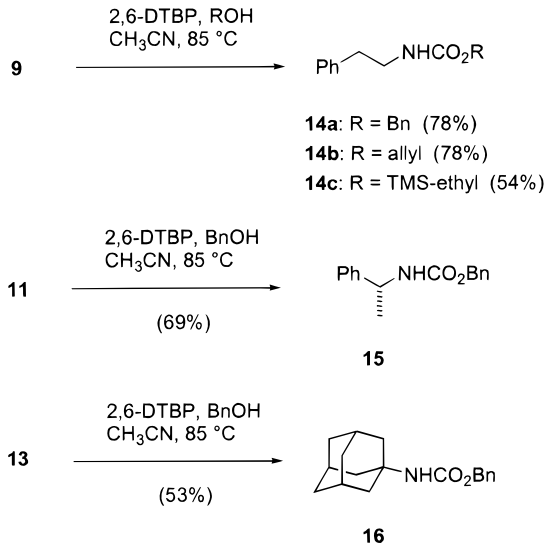
To assess the scope and generality of the present method, we investigated its application to the degradative rearrangement of other carboxylic acids (Scheme 3). Reagent **4** can be coupled to a variety of activated carboxylic acids. Coupling between **4** and the mixed anhydride derived from hydrocinnamic acid (**8**) provided compound **9** in 82% yield. Similarly, **4** couples to the mixed anhydride of (R)-(−)-2-phenylpropionic acid (**10**)

(10) The use of methylene chloride or THF for the coupling of **4** to activated carboxylic acid derivatives resulted in significantly diminished yields of coupled product.

(11) The alloc- and teoc-protected amines derived from these experiments, compounds **7b** and **7c**, respectively, are described in the Experimental Section.

(12) (a) Wasserman, H. H.; Berger, G. D. *Tetrahedron* **1983**, *39*, 2459. (b) Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643. (c) Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141.

Scheme 4

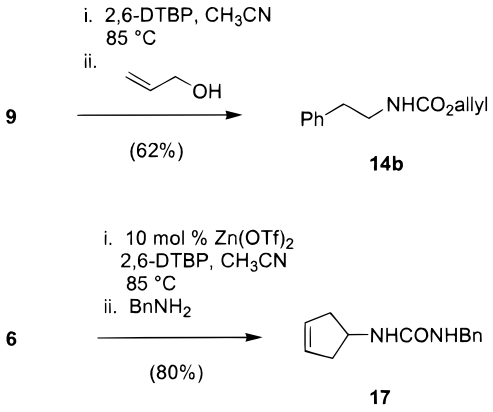


and the sterically demanding 1-adamantanecarbonyl chloride (**12**) to provide protected hydroxamates **11** and **13**, respectively.

The rearrangements of **9**, **11**, and **13** are illustrated in Scheme 4. Thermolysis of **9** in acetonitrile in the presence of 2,6-DTBP and an alcohol provided the desired carbamates **14a**−**c** in good yields.[13] Rearrangement of the enantiopure hydroxamate **11** provided the CBz-protected (*R*)-(+)-α-methylbenzylamine **15** in 69% yield. The enantiopurity of **15** was determined to be 99% (98% ee), establishing that this rearrangement, like other degradations (e.g., the Curtius rearrangement), proceeds with retention of the configuration of the migrating group.[14] The adamantyl hydroxamate **13** underwent rearrangement under identical conditions, providing benzyl carbamate **16** in 53% yield.

The mechanism of the Lossen rearrangement is thought to be similar to the related and more commonly used Curtius, Schmidt, and Hofmann rearrangements, although the exact nature of the transient intermediates in all of these processes remains unclear.[15] To probe whether an isocyanate is the initial product of the current method, the following experiments were performed (Scheme 5). When rearrangement of **9** *in the absence of a trapping nucleophile* was judged complete by TLC analysis, allyl alcohol was added to the reaction mixture; after workup and flash chromatography we obtained a 62% yield of carbamate **14b**. Likewise, expanding the scope of this process to include products other than carbamates, the isocyanate arising from the rearrangement of **6** was intercepted by benzylamine to afford an 80% yield of urea **17**. Additionally, adamantyl hydroxamate **13** was heated in acetonitrile at 85 °C for 17 h, filtered, and evaporated to a solid. IR analysis of this solid showed a strong and sharp absorbance at 2256 cm^{-1}, a stretching frequency that is highly characteristic of an isocyanate.

Scheme 5



In summary, we have described the novel rearrangement of an activated, *N*-acyl-hydroxamate to a protected amine in good yield. During the course of defining the conditions for this rearrangement we found that Lewis acids are not required to mediate this process. In this regard, the present method differs from our earlier work,[6] wherein the Lewis acid played a key role in facilitating mild BOC deprotection. The underlying basis for this difference remains unclear.

A noteworthy feature of the present rearrangement is found in the stable rearrangement precursor. The novel *N*-acyl-hydroxamates are conveniently prepared, stored, and handled. The two-step, reagent-based sequence (i.e., coupling between reagent **4** and a carboxylic acid, followed by rearrangement) is easily adapted to large-scale preparations, making this "modified Lossen" reaction an attractive alternative to the Curtius rearrangment and similar rearrangements.

Experimental Section[16]

***N-tert*-Butyloxycarbonyl-*O*-methanesulfonylhydroxylamine (4).** To a stirring solution of *tert*-butyl-*N*-hydroxycarbamate (**3**) (26.6 g, 0.2 mol) in CH_2Cl_2 (500 mL) at 0 °C was added pyridine (17.4 g, 0.22 mol). After 10 min, methanesulfonyl chloride (25.1 g, 0.22 mol) was added dropwise via an addition funnel. The reaction was allowed to stand for 3 days at 4 °C (refrigerator) and was then poured into water (200 mL). The layers were separated, and the organic layer was washed with water (100 mL), 1 M H_3PO_4 (100 mL), and brine (100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to a solid. Recrystallization from diisopropyl ether/hexanes afforded **4** as a colorless solid (32.6 g, 77%, two crops). Mp: 83−85 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.35 (s, 1), 3.19 (s, 3), 1.41 (s, 9). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.8, 84.6, 36.1, 27.9.

(13) For comparison purposes the rearrangement of **9** in the presence of zinc triflate and benzyl alcohol provided **14a** in 69% yield.

(14) Analyzed by comparison with a racemic sample using supercritical fluid chromatography in a Chiralcel OJ column (mobile phase: 5% methanol and 95% CO_2; flow rate: 2.0 mL/min; monitored at 255 nM).

(15) March, J. *Advanced Organic Chemistry*, John Wiley & Sons: New York, 1985; Chapter 18, pp 982−987.

(16) All starting materials were obtained from commercial suppliers and used without further purification. All reactions involving oxygen- or moisture-sensitive compounds were performed under a dry N_2 atmosphere. All reactions and chromatography fractions were analyzed by thin-layer chromatography on 2.5 × 7.5 cm silica gel plates (250-μm SiO_2 thickness) and visualized with UV light and/or $KMnO_4$ dip (Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 3882). Flash column chromatography was carried out using Merck silica gel 60 (230−400 mesh). Evaporation of solvents was accomplished with a rotary evaporator. ^{1}H NMR and ^{13}C NMR spectra were measured using either a Varian Unity Plus 300 or a Varian Unity Plus 400 spectrometer. Chemical shifts are expressed in ppm downfield from the internal standard, tetramethylsilane. Apparent multiplicities are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; or b, broad. *J* values are reported in Hertz. IR spectra were recorded on a Nicolet 510 FT-IR spectrometer. Mass spectra were taken in positive-ion mode by atmospheric pressure chemical ionization (APCI). Melting points were determined on a Laboratory Devices Mel-Temp III and are uncorrected. Elemental analyses were performed by Atlantic Microlab (Norcross, GA).

Anal. Calcd for $C_6H_{13}NO_5S$: C, 34.12; H, 6.20; N, 6.63. Found: C, 34.16; H, 6.25; N, 6.62.

***N*-(*t*-Butyloxycarbonyl)-*N*-(methanesulfonyloxy)cyclopent-3-enylcarboxamide (6).** To a cooled (0 °C), stirring solution of 3-cyclopentene carboxylic acid (**1**)[17] (1.12 g, 10.0 mmol) in CH_2Cl_2 (20 mL) was added, dropwise, oxalyl chloride (1.33 g, 10.5 mmol), followed by one drop of DMF. The resulting solution was stirred at ambient temperature until gas evolution ceased (ca. 3 h). The volume of CH_2Cl_2 was reduced by concentration in vacuo to provide a concentrated solution of acid chloride **5**, which was used immediately.

To a cooled (0 °C), stirring solution of **4** (1.89 g, 9.0 mmol) in DMF (30 mL) were added triethylamine (1.21 g, 12 mmol) and 4-(dimethylamino)pyridine (DMAP) (0.09 g, 0.74 mmol). This solution was then treated with the solution of **5** described above. The resulting mixture was stirred at ambient temperature for 1 h and then diluted with water (60 mL). The solution was extracted with ether (4 × 40 mL), and the combined ether extracts were washed with water (2 × 30 mL), 1 M H_3PO_4 (40 mL), and brine (50 mL). The resulting organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give an orange oil. Flash chromatography (4:1 hexanes/ethyl acetate) afforded **6** as a colorless solid (2.00 g, 73%). Mp: 62−65 °C (hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.66 (s, 2), 4.05 (quint, 1, J = 7.7), 3.33 (s, 3), 2.73 (bd, 4), 1.58 (s, 9). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 149.5, 128.6, 86.7, 42.6, 40.3, 36.6, 27.7. Anal. Calcd for $C_{12}H_{19}NO_6S$: C, 47.20; H, 6.27; N, 4.59. Found: C, 47.23; H, 6.21; N, 4.58.

General Procedure for the Coupling of 4 to a Mixed Anhydride. *N*-(*t*-Butyloxycarbonyl)-*N*-(methanesulfonyloxy)-3-phenylpropionamide (9). To a solution of 3-phenylpropionic acid (**8**) (750 mg, 5.0 mmol) in DMF (10 mL), stirring at 0 °C, was added *N*-methylmorpholine (NMM) (510 mg, 5.0 mmol). The solution was stirred for 5 min, and then isobutyl chloroformate (690 mg, 5.1 mmol) was added dropwise. The mixture was stirred for 30 min at 0 °C and then added to a solution of *N*-(*t*-butyloxycarbonyl)-*O*-methanesulfonylhydroxylamine (1.0 g, 4.8 mmol) and 4-(dimethylamino)pyridine (DMAP) (60 mg, 0.5 mmol) in DMF (3 mL) at 0 °C. The ice bath was removed, and the mixture was stirred for 16 h at room temperature. The mixture was then partitioned between ether (50 mL) and water (100 mL). The aqueous layer was extracted with ether (3 × 20 mL), and the combined organic layers were washed with water (2 × 50 mL), 1 M H_3PO_4 (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to a solid that was triturated with 8:1 hexanes/ether to give **9** as a colorless solid (1.36 g, 82%). Mp: 85−87 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32−7.21 (m, 5), 3.29 (s, 3), 3.21 (bt, 2), 3.00 (t, 2, J = 7.6), 1.56 (s, 9), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.8, 149.6, 140.1, 128.5, 128.4, 126.4, 86.8, 40.3, 38.7, 30.4, 28.0, 27.7. Anal. Calcd for $C_{15}H_{21}NO_6S$: C, 52.47; H, 6.16; N, 4.08. Found: C, 52.53; H, 6.22; N, 4.10.

(*R*)-*N*-(*t*-Butyloxycarbonyl)-*N*-(methanesulfonyloxy)-2-phenylpropionamide (11). (*R*)-(−)-2-phenylpropionic acid was coupled to compound **4** according to the general procedure for mixed anhydride coupling to give, after flash chromatography (10% ethyl acetate/hexane), the product (1.15 g, 50%) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34−7.25 (m, 5), 4.85 (bq, 1), 3.28 (bs, 3), 1.53 (d, 3, J = 7), 1.49 (s, 9). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.1, 149.3, 139.5, 128.5, 127.8, 127.3, 86.7, 45.4, 39.9, 27.5, 19.4. Anal. Calcd for $C_{15}H_{21}NO_6S$: C, 52.47; H, 6.16; N, 4.08. Found: C, 52.72; H, 6.21; N, 4.03.

General Procedure for Coupling of 4 to Acid Chlorides. *N*-(*t*-Butyloxycarbonyl)-*N*-(methanesulfonyloxy)-3-phenylpropionamide (9). To a solution of compound **4** (6.33 g, 30 mmol) stirring in DMF (120 mL) at 0 °C was added, in order, triethylamine (3.33 g, 33 mmol), 4-(dimethylamino)pyridine (366 mg, 3 mmol), and hydrocinnamoyl chloride (5.29 g, 31.5 mmol). The mixture was stirred for 5 min at 0 °C and then allowed to warm to room temperature, being stirred 1 h longer. The mixture was partitioned between ether and water (300 mL each), the layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 120 mL). The combined organic layers were washed with water (2 × 100 mL), 1 M H_3PO_4 (100 mL), and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give a white solid. This solid was triturated with hexanes/ether (6:1) to provide **9** (8.97 g, 87%), possessing the spectral identity of that described above.

***N*-(*t*-Butyloxycarbonyl)-*N*-(methanesulfonyloxy)-1-adamantanecarboxamide (13).** 1-Adamantanecarbonyl chloride (4.16 g, 21 mmol) was treated according to the general procedure for acid chloride coupling to give, after flash chromatography (10% ethyl acetate/hexane), the product (3.2 g, 43%) as a white solid. Mp: 108−110 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.22, (s, 3), 2.08 (m, 6), 2.05 (br s, 3), 1.73 (s, 6), 1.57 (s, 9). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 181.0, 151.6, 86.6, 45.7, 38.2, 38.06, 36.2, 28.0, 27.9. Anal. Calcd for $C_{17}H_{27}NO_6S$: C, 54.67; H, 7.29; N, 3.75. Found: C, 54.79; H, 7.31; N, 3.82.

General Procedure for the Modified Lossen Rearrangement with Lewis Acid. *N*-(Benzyloxycarbonyl)cyclopent-3-enylamine (7a). To a solution of **6** (610 mg, 2.0 mmol) in CH_3CN (10 mL) were added benzyl alcohol (238 mg, 2.2 mmol), 2,6-di-*t*-butylpyridine (382 mg, 2.0 mmol), and zinc triflate (72 mg, 0.2 mmol). The mixture was heated with stirring to 85 °C for 16 h and then cooled to room temperature. It was then diluted with ethyl acetate (50 mL) and washed with water (50 mL), 1 M H_3PO_4 (50 mL), and brine (50 mL). The combined aqueous layers were back-extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (4:1 hexanes/ethyl acetate) afforded **7a** as a colorless solid (352 mg, 81%). Mp: 50−52 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.42−7.25 (m, 5), 5.63 (s, 2), 4.97 (s, 2), 4.08 (m, 1), 2.53 (dd, 2, J = 8.2, 14.8), 2.13 (dd, 2, J = 5.2, 14.7). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.8, 136.5, 128.7, 128.4, 128.0, 127.9, 66.4, 50.5, 40.2. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.83; H, 6.97; N, 6.47.

***N*-(Allyloxycarbonyl)cyclopent-3-enylamine (7b).** Compound **6** (610 mg, 2 mmol) was treated according to the general procedure above using allyl alcohol (2.2 mmol) in place of benzyl alcohol to yield **7b** as a colorless oil (253 mg, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.93 (m, 1), 5.69 (overlapping dd, 2, J = 8.3), 5.30 (d, 1, J = 17.3), 5.21 (d, 1, J = 10.3), 4.88 (bs, 1), 4.56 (bd, 2, J = 4.6), 4.35 (bd, 1, J = 3.3), 2.74 (dd, 2, J = 7.5, 15.6), 2.20 (dd, 2, J = 3.8, 15.2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.8, 132.9, 128.7, 117.5, 65.3, 50.5, 40.2. Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.37; H, 7.76; N, 8.33.

***N*-(Trimethylsilylethoxycarbonyl)cyclopent-3-enylamine (7c).** Compound **6** (323 mg, 1.1 mmol) was treated according to the general procedure above using 2-trimethylsilylethanol (1 mmol) in place of benzyl alcohol to yield **7c** as a colorless solid (104 mg, 46%). Mp: 45−46 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.69 (overlapping dd, 2, J = 8.3), 4.75 (bs, 1), 4.33 (bs, 1), 4.14 (t, 2, J = 8.3), 2.73 (dd, 2, J = 7.6, 15.5), 2.19 (dd, 2, J = 3.9, 15.2), 0.97 (t, 2, J = 8.3), 0.04 (s, 9). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.3, 128.7, 62.8, 50.4, 40.3, 17.7, −1.5. Anal. Calcd for $C_{11}H_{21}NO_2Si$: C, 58.11; H, 9.31; N, 6.16. Found: C, 58.12; H, 9.38; N, 6.07.

1-(Benzyloxycarbonyl)phenethylamine (14a). Compound **9** (686 mg, 2 mmol) was treated according to the general procedure above to yield **14a** as a colorless solid (350 mg, 69%). Mp: 55−57 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34−7.17 (m, 10), 5.10 (s, 2), 4.74 (bs, 1), 3.47 (dd, 2, J = 6.6, 13.0), 2.82 (t, 2, J = 6.8). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.2, 138.6, 136.5, 128.7, 128.5, 128.4, 128.3, 128.0, 126.4, 66.6, 42.1, 36.0. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.19; H, 6.71; N, 5.49.

General Procedure for the Thermolytic Degradation of the Hydroxamates. *N*-(Benzyloxycarbonyl)cyclopent-3-enylamine (7a). To a solution of **6** (305 mg, 1.0 mmol) in CH_3CN (5 mL) were added benzyl alcohol (1.1 mmol) and 2,6-di-*tert*-butylpyridine (1.0 mmol). The mixture was heated with stirring to 85 °C for 22 h and then cooled to room temperature. It was then diluted with ethyl acetate (50 mL) and washed with water (50 mL), 1 M H_3PO_4 (50 mL), and brine (50 mL). The combined aqueous layers were back-extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (4:1 hexanes/ethyl acetate) afforded **7a** as a colorless solid (168 mg, 78%). Spectral data for this compound were identical to those described above.

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1-(Benzyloxycarbonyl)phenethylamine (14a). Compound **9** (343 mg, 1 mmol) and benzyl alcohol (1.1 mmol) were treated according to the general procedure for thermolytic rearrangement, to provide, after flash chromatography (4:1 ethyl acetate/hexane), **14a** as a colorless solid (198 mg, 78%). Spectral data for this compound were identical to those described above.

1-(Allyloxycarbonyl)phenethylamine (14b). Compound **9** (343 mg, 1 mmol) and allyl alcohol (64 mg, 1.1 mmol) were treated according to the general procedure for thermolytic rearrangement to give, after flash chromatography (10% ethyl acetate/hexane), **14b** as a white solid (160 mg, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33−7.19 (m, 5), 5.96−5.88 (m, 1), 5.29 (d, 1, J = 17.2), 5.20 (d, 1, J = 10.4), 4.72 (bs, 1), 4.56 (d, 2, J = 5.3), 3.46 (q, 2, J = 6.6, 13.1), 2.82 (t, 2, J = 7). ^{13}C NMR ($CDCl_3$, 100 MHz): δ. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.95; H, 7.33; N, 6.85.

1-(Trimethylsilylethoxycarbonyl)phenethylamine (14c). Compound **9** (686 mg, 2 mmol) and 2-(trimethylsilyl)ethanol (260 mg, 2.2 mmol) were treated according to the general procedure for thermolytic rearrangement to give, after flash chromatography (10% ethyl acetate/hexane), **14c** as a clear-oil compound (284 mg, 54%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33−7.18 (m, 5), 4.62 (bs, 1), 4.15 (t, 2, J = 8.6), 3.43 (q, 2, J = 6.5, 13), 2.81 (t, 2, J = 7), 0.96 (t, 2, J = 8.6), 0.03 (s, 9). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.2, 140.3, 130.3, 127.9, 64.4, 43.6, 37.7, 19.2, 1.5. Anal. Calcd for $C_{14}H_{23}NO_2Si$: C, 63.35; H, 8.73; N, 5.28. Found: C, 63.13; H, 8.66; N, 5.29.

(*R*)-(+)-1-(Benzyloxycarbonyl)-α-methylbenzylamine (15). Compound **11** (686 mg, 2 mmol) and benzyl alcohol (238 mg, 2.2 mmol) were treated according to the general procedure for thermolytic rearrangement to give, after flash chromatography (20% ethyl acetate/hexane), **15** as a white solid (353 mg, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34−7.24 (m, 10), 5.08 (ABq, 2, J = 25.3, 12.3) 5.04 (br m, 1), 4.86 (br m, 1), 1.48 (d, 3, J = 6.6). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.5, 143.4, 136.4, 128.6, 128.5, 128.1, 127.3, 125.9, 77.2, 66.7, 50.7, 22.5. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.12; H, 6.81; N, 5.48.

1-(Benzyloxycarbonyl)-1-adamantanamine (16). Compound **13** (746 mg, 2 mmol) and benzyl alcohol (238 mg, 2.2 mmol) were treated according to the general procedure for rearrangement to give, after flash chromatography (10% ethyl acetate/hexane), **16** as a white solid (302 mg, 53%). Mp: 34−36 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38−7.28 (m, 5), 5.04 (br s, 2), 4.62 (br s, 1), 2.08 (m, 3), 1.94 (d, 6, J = 2.2), 1.67 (s, 6). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.8, 128.5, 128.1, 128.0, 65.9, 50.7, 41.8, 36.5, 36.3, 29.4. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.92; H, 8.20; N, 4.91.

Stepwise Rearrangement and Trapping of *N*-Acyl-hydroxamate. 1-(Allyloxycarbonyl)-phenethylamine (14b). To solution of compound **9** (686 mg, 2 mmol) in acetonitrile (10 mL) was added 2,6-di-*tert*-butylpyridine (382 mg, 2 mmol). The mixture was heated to 85 °C. After 8 h, thin-layer chromatography indicated that starting material was still present. After 24 h, the rearrangement was judged to be complete by TLC analysis. Allyl alcohol (582 mg, 10 mmol) was added to the mixture, which was then stirred at 85 °C for an additional 2 h. The reaction was worked up as previously described and purified via flash chromatography to afford **14b** (253 mg, 62%), whose spectral characteristics were identical to those described above.

***N*-(3-Cyclopentenyl)-*N*-(phenylmethyl)urea (17).** Compound **6** (305 mg, 1.0 mmol), 2,6-di-*tert*-butylpyridine (224 μL, 1 mmol), and zinc trifluoromethanesulfonate (364 mg, 0.1 mmol) were dissolved in acetonitrile (10 mL), and the solution was heated to reflux with stirring. The reaction was monitored by TLC (4:1 hexane/ethyl acetate) for disappearance of **6**, and after 6 h, formation of the isocyanate was judged complete. Benzylamine (120 μL, 1.1 mmol) was then added in one portion, and the reaction was stirred for 20 min. The reaction was allowed to cool to room temperature and was concentrated to an oil. Flash chromatography (4:1 to 1:1 hexane/ethyl acetate) afforded **17** as a colorless solid (172 mg, 80%). Mp: 133−134 °C. Low resolution MS (CI): *m*/*e* 217.2 (MH^+), 238.9 ($M + Na^+$), 151.1. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32−7.22 (m, 5), 5.65 (m, 2), 4.33 (m, 3), 2.69 (dd, 2, J = 7.5, 15.2), 2.13 (dd, 2, J = 3.7, 15). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.8, 139.0, 128.8, 128.6, 127.5, 127.4, 50.0, 44.6, 40.6. Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.08; H, 7.44; N, 13.00.

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