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Synthesis of 3-oxooxa- and 3-oxoazacycloalk-4-enes by ring-closing metathesis. Application to the synthesis of an inhibitor of cathepsin K

Catherine Taillier, Thomas Hameury, Véronique Bellosta* and Janine Cossy*

Laboratoire de Chimie Organique ESPCI, CNRS, 10 rue Vauquelin, 75231 Paris Cedex 05, France

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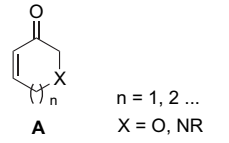
Abstract—3-Oxooxa- and 3-oxoazacycloalk-4-enes were obtained with good yield from 1-(ω-alkenyloxy)- and 1-(ω-alkenylamino)-but-3-en-2-ones by using a ring-closing metathesis. This methodology has been used to synthesize an inhibitor of cathepsin K.

1. Introduction

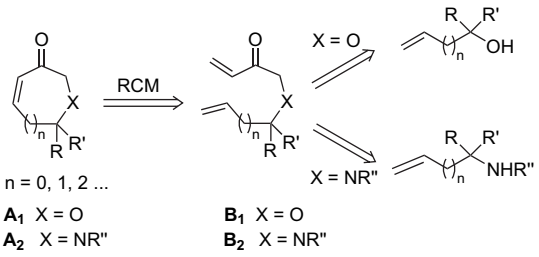
Cyclic ethers and amines[1] are present in a great variety of natural and non-natural products, which possess interesting biological properties. The interest for these heterocyclic compounds has stimulated the development of an array of methods for their synthesis.[2,3] The number of approaches available for the construction of cyclic ethers and amines has steadily increased and, among them, the ring-closing metathesis (RCM) has proved to be efficient.[4–6] We planned to use this key reaction in order to develop a general and versatile access to functionalized 3-oxooxacycloalk-4-enes and 3-oxoazacycloalk-4-enes of type **A** (Fig. 1).

When we began to investigate the synthesis of compounds of type **A**, only few examples of RCM reactions involving ω-unsaturated conjugated ketones as partners had been reported.[5d,7] Nevertheless, we decided to examine the reactivity of 1-(ω-alkenyloxy)- and 1-(ω-alkenylamino)-but-3-en-2-ones in the metathesis process with the aim of preparing six-, seven- and eight-membered 3-oxooxa- and 3-oxoazacycloalk-4-enes. Thus, a general route was required to synthesize a broad range of acyclic α-alkoxy- and α-amino enones of type $\mathbf{B_1}$ and $\mathbf{B_2}$ from ω-unsaturated alcohols and ω-unsaturated amines (Scheme 1).



A

Figure 1.



Scheme 1.

Recently, we disclosed our preliminary results related to the synthesis of 3-oxooxa- and 3-oxoazacycloalk-4-enes of type $\mathbf{A_1}$ and $\mathbf{A_2}$ by using an RCM reaction.[8,9] Herein, we would like to report a full account of our results and an application to the synthesis of an inhibitor of cathepsin K.

2. Preparation of compounds of type $\mathbf{B_1}$ and $\mathbf{B_2}$

2.1. Synthesis of compounds of type $\mathbf{B_1}$

Two different methods have been developed to synthesize compounds of type $\mathbf{B_1}$ (X=O), depending on the nature of the precursors, e.g. the ω-unsaturated alcohols. The transformation of primary ω-unsaturated alcohols of type **C** to compounds of type $\mathbf{B_1}$ was achieved via ω-unsaturated acyl chloride of type **E**, conversion of secondary or tertiary ω-unsaturated alcohols **D** was performed via stabilized phosphoranes of type **F** (Scheme 2).

Keywords: Ring-closing metathesis; Cathepsin K inhibitor; Enone; Cyclic amines; Cyclic ethers.
* Corresponding authors. Tel.: +33 0 140794429; fax: +33 0 140794660 (J.C.); tel.: +33 0 140794415; fax: +33 0 140794660 (V.B.); e-mail addresses: veronique.bellosta@espci.fr; janine.cossy@espci.fr

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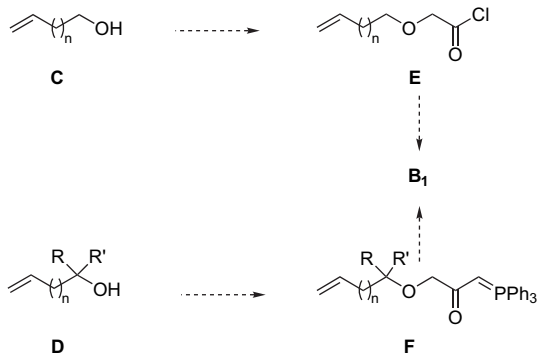
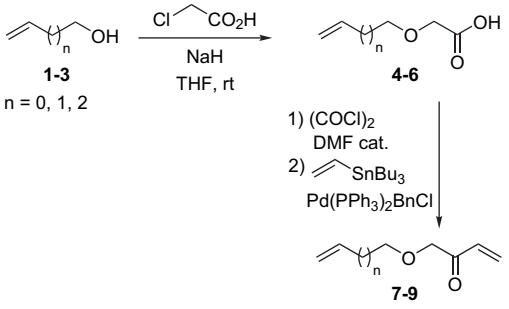


Scheme 2.

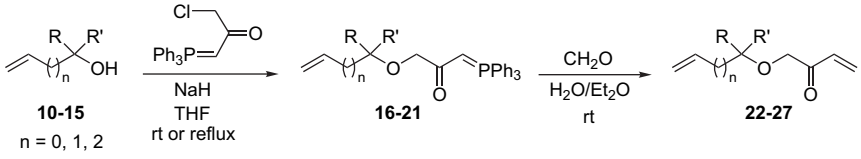
The synthesis of compounds **7–9** was achieved from the primary ω-unsaturated alcohols **1–3**, respectively. After condensation with chloroacetic acid, under basic conditions[10] (NaH, 2.2 equiv) in THF at rt, the alcohols **1–3** were transformed, respectively, to the corresponding α-alkoxy acetic acids **4–6** in yields superior to 50%. The obtained α-alkoxy acetic acids **4–6** were then treated with oxalyl chloride in the presence of a catalytic amount of DMF, in benzene for 1 h at rt, and the resulting acyl chlorides were then involved in a Pd-catalyzed reaction [$Pd(PPh_3)_2BnCl$ 0.4 mol %, HMPA, 65 °C, 45 min][11] with tri-*n*-butylvinyltin to produce the desired α-alkoxy enones **7–9** in yields greater than 37%. The results are summarized in Table 1. It is worth noting that

Table 1



Entry	Alcohols	α-Alkoxy acetic acids (yield %)	α-Alkoxy enones (yield %)
1	**1**	**4** (70%)	**7** (37%)
2	**2**	**5** (56%)	**8** (58%)
3	**3**	**6** (51%)	**9** (51%)

Table 2



Entry	Alcohols **10–15**	Phosphoranes **16–21** (yield %)	α-Alkoxy enones **22–27** (yield %)
1	**10**	**16** (94%)	**22** (67%)
2	**11**	**17** (71%)	**23** (70%)
3	**12**	**18** (48%)	**24** (49%)
4	**13**	**19** (70%)	**25** (73%)
5	**14**	**20** (82%)	**26** (49%)
6	**15**	**21** (76%)	**27** (54%)

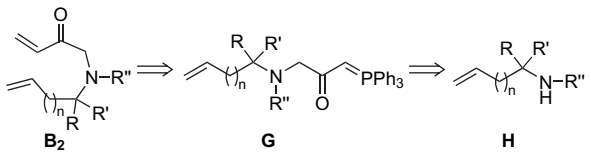
in the coupling reaction involving tri-*n*-butylvinyltin and acyl chlorides of type **E**, generated from secondary and tertiary ω-unsaturated alcohols, non-identified products were obtained.

As the second step of the above strategy failed when secondary or tertiary ω-unsaturated alcohols were employed as starting materials, the synthesis of the corresponding α-alkoxy enones of type $\mathbf{B_1}$ was envisioned from stabilized phosphoranes.[12] The β-ketophosphoranes **16**–**21** were obtained by alkylation of the secondary and tertiary alcohols **10**–**15**. After treatment of **10**–**15** with NaH (4 equiv) in THF, followed by the addition of triphenylchloroacetonylphosphorane,[13] the corresponding phosphoranes **16**–**21** were isolated in yields greater than 48% and were converted to the α-alkoxy enones **22**–**27** by condensation with formaldehyde in yields up to 73%. The results are reported in Table 2.

2.2. Synthesis of compounds of type $\mathbf{B_2}$

The synthesis of compounds of type $\mathbf{B_2}$ (X=NR″) was achieved from ω-unsaturated amines **H** via stabilized phosphoranes of type **G** according to Scheme 3.

The first attempt was achieved from allyltosylamine **28**. When allyltosylamine **28** was deprotonated by NaH

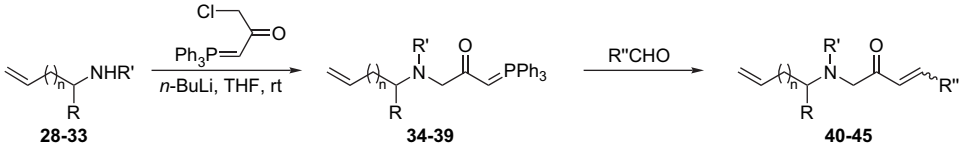


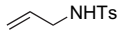
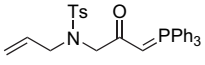
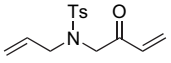
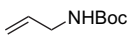
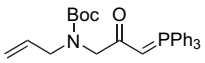
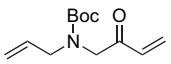
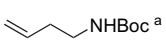
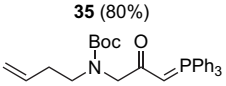
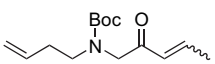
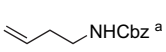
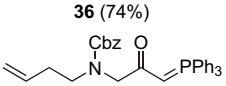
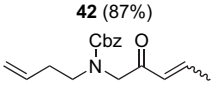
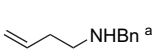
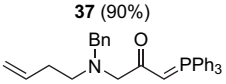
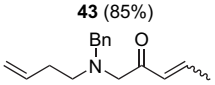
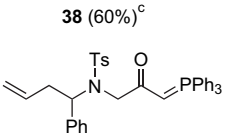
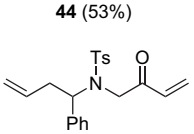
Scheme 3.

(4 equiv) followed by the addition of triphenylchloroacetonylphosphorane, the desired β-ketophosphorane **34** was not obtained. However, when **28** was treated with *n*-BuLi in THF, after addition of the triphenylchloroacetonylphosphorane, the β-ketophosphorane **34** was isolated in 85% yield. The reaction turned out to be general as under these latter conditions the ω-unsaturated amines **29**–**31** and **33** were transformed, respectively, to the corresponding β-ketophosphoranes **34**–**37** and **39** (57–90% yield). It is worth noting that the alkylation of the *N*-benzylbut-3-enylamine **32** was achieved under milder conditions e.g. with Et_3N (2 equiv) in the presence of *n*-Bu_4NI, in acetonitrile from rt to 50 °C, as the use of *n*-BuLi produced polymers.

The obtained β-ketophosphoranes **34**, **35**, and **39** were then treated with an excess of aqueous formaldehyde under Wittig conditions (Et_2O, 3 h, rt) to produce the corresponding α-amino enones **40**, **41**, and **45** in 42–74% yields (Table 3,

Table 3



Entry	Amines	β-Ketophosphoranes	α-Amino enones (yield %)
1	 **28**	 **34** (85%)	 **40** (42%)
2	 **29**	 **35** (80%)	 **41** (74%)
3	 **30**	 **36** (74%)	 **42** (87%)
4	 **31**	 **37** (90%)	 **43** (85%)
5	 **32**	 **38** (60%)[c]	 **44** (53%)
6	**33**	 **39** (57%)	 **45** (62%)

[a] The protected homoallylamines **30**–**32** were prepared from the hydrochloride salt of but-3-enamine.[14]
[b] Prepared by allylation of the *N*-tosyl imine derived from benzaldehyde.
[c] Prepared by N-alkylation of **32** in the presence of Et_3N (2 equiv), *n*-Bu_4NI (0.5 equiv) in CH_3CN from rt to 50 °C.

entries 1, 2, and 6). We have to point out that the treatment of β-ketophosphoranes **36–38** with formaldehyde led to the formation of polymers, whereas replacement of formaldehyde by acetaldehyde produced the desired α-amino enones **42–44** in good yields (53–87%) (Table 3, entries 3–5). The results are reported in Table 3.

3. Ring-closing metathesis (RCM)

The obtained ω-unsaturated α-alkoxy enones **7–9**, **22–27**, and the α-amino enones **40–45** were involved in RCM. All the reactions were carried out with 2.5–15.0 mol % of the Grubbs second generation catalyst **[Ru]-II** [(4,5-dihydro-IMes)(PCy_3)Cl_2Ru=CHPh][15] at concentrations of 5×10^{-3} to 1×10^{-2} M in refluxing CH_2Cl_2.

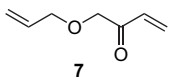
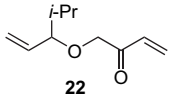
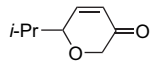
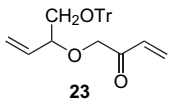
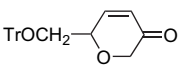
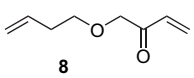
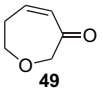
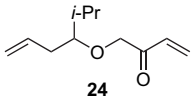
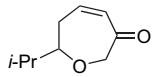
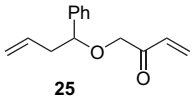
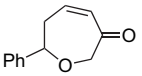
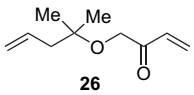
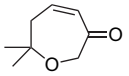
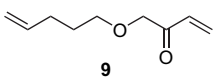
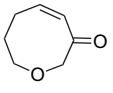
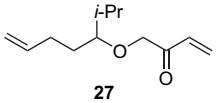
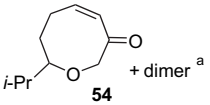
3.1. RCM applied to α-alkoxy enones

The RCM was applied to α-alkoxy enones **7–9**, **22–27** and the corresponding cyclized products were obtained in moderate to good yields. Compounds **7**, **22**, and **23** led to six-membered alkoxy enones in 69%, 87%, and 68% yields, respectively. Seven-membered cyclic alkoxy enones **49** (58% yield), **50** (90% yield), **51** (93% yield), and **52** (67% yield) were obtained, respectively, from the corresponding enones **8**, **24**, **25**, **26** and yields were found to be good to excellent when 7-alkyl- or 7-aryl-3-oxooxacyclohept-4-enes are formed. Eight-membered rings are difficult to obtain by RCM and, we were particularly gratified that α-alkoxy enones **9** and **27** were equally effective substrates in the RCM as eight-membered ring compounds **53** and **54** were respectively formed even when the reaction was performed at a concentration of 10^{-2} M. The results are reported in Table 4. However, we have to point out that for compound **27**, a cyclic dimer **55** was isolated in 14% yield in which the configuration of the two double bonds was (*E*). In the case of α-alkoxy enone **56**, the nine-membered-ring enone was never observed even at low concentration (*c* 1×10^{-3} M). The treatment of the α-alkoxy enone **56** with **[Ru]-II** led only to the cyclic dimer **57** in 75% yield. The formation of the cyclic dimers **55** and **57** can be explained by two successive metathesis reactions: a CM producing linear dimers **58** and **59** followed by an RCM reaction (Scheme 4).

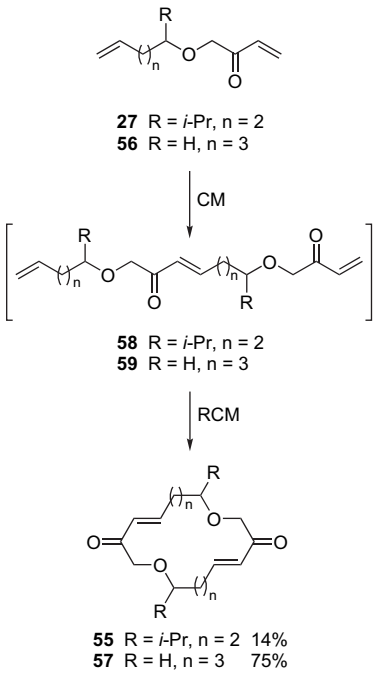
3.2. RCM applied to α-amino enones

When ω-unsaturated α-amino enones **40** and **41** were involved in an RCM in the presence of **[Ru]-II**, the

Table 4

Entry	α-Alkoxy enones	Concentration (mol L^{-1})	**[Ru]-II** (mol %)	3-Oxooxacycloalkenes	Yield %
1	 **7**	2×10^{-2}	2.5	 **46**	69
2	 **22**	4×10^{-3}	5	 **47**	87
3	 **23**	1×10^{-3}	5	 **48**	68
4	 **8**	2×10^{-2}	15	 **49**	58
5	 **24**	1.3×10^{-2}	5	 **50**	90
6	 **25**	2×10^{-2}	2.5	 **51**	93
7	 **26**	5×10^{-3}	4	 **52**	67
8	 **9**	1.3×10^{-2}	10	 **53**	66
9	 **27**	1×10^{-2}	2.5	 **54** + dimer [a]	35

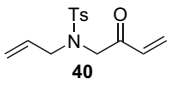
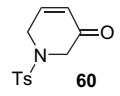
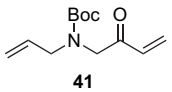
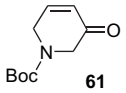
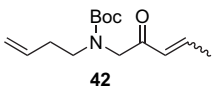
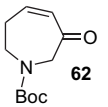
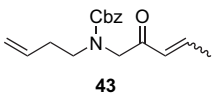
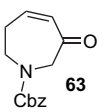
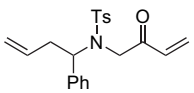
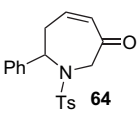
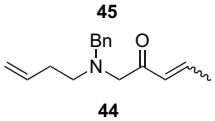
[a] The dimer **55** was isolated in 14% yield.



Scheme 4.

corresponding 3-oxoazacyclohex-4-enes **60** and **61** were obtained in good yields (65–80%). Excellent yields in tetrahydroazepinones **62**, **63**, **64**, greater than 90%, were obtained after the RCM was applied to α-amino enones **42**, **43**, and **45**. However, no cyclized products but only polymers were formed when *N*-benzyl protected enone **44** was subjected to the RCM conditions, probably due to a coordination of the **[Ru]-II** catalyst by the nitrogen atom. These results are reported in Table 5. The RCM allowed the transformation of ω-unsaturated α-amino enones to the corresponding cyclized products if the nitrogen is substituted by an electron-withdrawing group such as in carbamates or sulfonamides.

Table 5

Entry[a]	α-Amino enones	**[Ru]-II** (mol %)	3-Oxoaza-cycloalkenes	Yield %
1	 **40**	5	 **60**	65
2	 **41**	5	 **61**	80
3	 **42**	5	 **62**	90
4	 **43**	2.5	 **63**	97
5	 **45**	5	 **64**	99
6	 **44**	5	—	—

[a] All the RCM reactions were performed at 5×10^{-3} M, in refluxing CH_2Cl_2, for 12 h.

3.3. Total synthesis of 65, an inhibitor of cathepsin K

As this methodology was efficient in obtaining 3-oxoazacyclohept-4-enes from homoallylic amines, its application to the total synthesis of a potent azepanone-based inhibitor of the osteoclast-specific cysteine protease cathepsin K,[16,17] compound **65**, was achieved (Fig. 2).

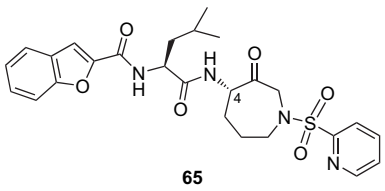
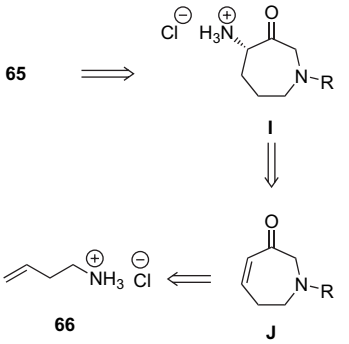


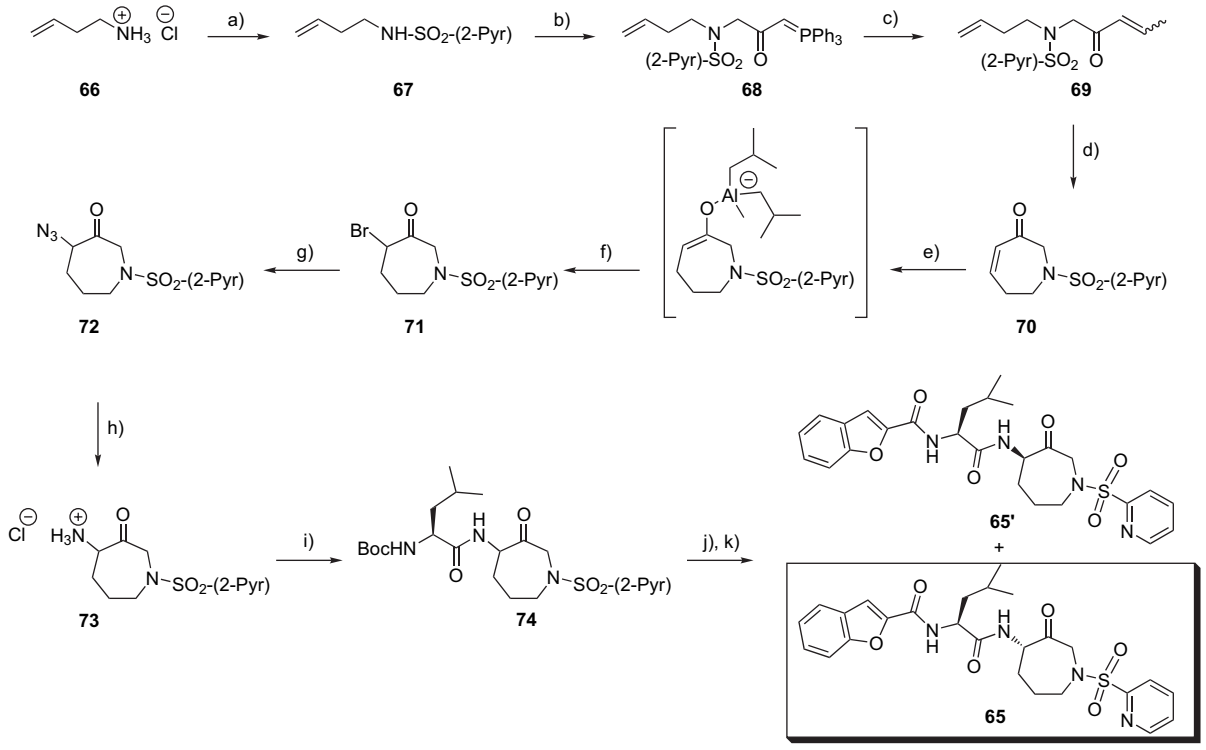
Figure 2.

Two syntheses of **65** were reported: one 12-step non-stereocontrolled synthesis,[16] which led to two HPLC separable epimers at C-4, and one enantioselective 15-step synthesis involving an Evans aldol reaction as the key-step.[18] By using an RCM applied to an ω-unsaturated α-amino enone of type $\mathbf{B_2}$, a 10-step synthesis of **65** was envisioned from the hydrochloride salt of the homoallylamine. In order to introduce the peptidic side-chain, the synthesis of **65** was planned from the α-amino ketone **I**. This latter should be obtained from 3-oxoazacyclohept-4-ene **J**, which should be synthesized from the hydrochloride salt of the homoallylamine **66** (Scheme 5).



Scheme 5.

The hydrochloride salt of the but-3-enamine **66**[14] was treated under basic conditions with 2-pyridinesulfonyl chloride[19] (Et_3N, CH_2Cl_2, rt) to produce **67** in 88% yield. The transformation of the *N*-pyridylsulfonyl but-3-enamine **67** to the desired but-3-enamino enone **69** was achieved in two steps via the stabilized phosphorane **68** (*n*-BuLi, triphenylchloroacetonylphosphorane, THF, rt) prepared in 94% yield, which was converted to the α-amino enone **69** by condensation with acetaldehyde in 94% yield. The obtained ω-unsaturated α-amino enone **69** was then involved in an RCM (**[Ru]-II**, 2.5 mol %, *c* 5×10^{-3} M, CH_2Cl_2, reflux, 12 h) and transformed to the desired seven-membered azacyclic compound



Scheme 6. *Reagents and conditions*: (a) (2-Pyr)SO_2Cl, Et_3N, CH_2Cl_2, rt, 88%; (b) $ClCH_2(CO)C{=}PPh_3$, *n*-BuLi, THF, rt, 94%; (c) CH_3CHO (10 equiv), THF, rt, 94%; (d) **[Ru]-II**, 2.5 mol %, CH_2Cl_2, reflux, 96%; (e) DIBAL-H (4 equiv), CuCN (2 equiv), *n*-BuLi (2 equiv), THF, −50 °C, 2 h; then HMPA (3 equiv), MeLi (1 equiv), −50 °C, 30 min; (f) Br_2 (10 equiv), −50 °C to −20 °C, 1 h; (g) NaN_3, DMF, (45% from **70**); (h) H_2, 10% Pd/C, MeOH/HCl; (i) *N*-Boc-L-leucine, EDCI, HOBt, Et_3N, CH_2Cl_2, rt, 51% (two steps); (j) 4 M HCl in dioxane, MeOH, rt, 2.5 h; (k) benzofuran-2-carboxylic acid, EDCI, HOBt, Et_3N, CH_2Cl_2, rt, 52% (two steps).

70 in 96% yield. This tetrahydroazepinone was transformed to the α-azido ketone **72** in two steps. The first step was the formation of the α-bromo azepanone **71** via the 1,4-addition of a 'hydrido cuprate' generated by the addition of DIBAL-H (4 equiv) in the presence of a cyanocuprate [CuCN (2 equiv), BuLi (2 equiv), THF, −50 °C, 2 h] and activation of the resulting enolate intermediate with MeLi (1 equiv) in the presence of HMPA (3 equiv, −50 °C, 30 min) to form a more reactive aluminate enolate, which was trapped with bromine (10 equiv, −50 °C to −20 °C, 1 h) to furnish the α-bromo ketone **71**.[20,21] Without purification, α-bromo ketone **71** was converted to the α-azido ketone **72** in 45% overall yield (from **70**) by treatment with NaN_3 in DMF, at rt. After hydrogenation of **72** in acidic conditions (H_2, 10% Pd/C, MeOH/HCl) the resulting hydrochloride salt **73** was condensed with the *N*-Boc-L-leucine[22] (EDCI, HOBt, Et_3N, CH_2Cl_2, rt) to furnish the desired keto amide **74** in 51% overall yield (from **72**). After cleavage of the *N*-Boc group (4 M HCl in dioxane, MeOH) and condensation with benzofuran-2-carboxylic acid in the presence of EDCI and HOBt, compound **65** and its epimer **65′** were obtained in 52% overall yield and **65** can be isolated by HPLC (Scheme 6).[16,23]

4. Conclusion

By applying an RCM to ω-unsaturated α-alkoxy enones and α-amino enones, six-, seven- and eight-membered ring 3-oxooxa- and 3-oxoazacycloalkenes were obtained in good to excellent yields. Furthermore, by using this methodology, a short synthesis of **65**, an inhibitor of cathepsin K, was achieved.

5. Experimental

5.1. General

All reactions were carried out under argon atmosphere. Unless otherwise specified, materials were purchased from commercial suppliers and used without purification. THF and diethyl ether were distilled from sodium/benzophenone. Methylene chloride, triethylamine, benzene, and toluene were distilled from CaH_2. Flash column chromatography was carried out on Merck Geduran Si60 silica gel (40–63 μM) and analytical thin-layer chromatography was performed on Merck precoated silica gel (60 F_{254}). Melting points (mp) are uncorrected. Elemental analysis were performed by the Centre Régional de Microanalyses (Université Pierre et Marie Curie, Paris VI). Mass spectra with electronic impact (EIMS) were recorded from a Hewlett–Packard tandem 5890 GC (12 m capillary column)–5971 MS (70 eV): only selected ions are reported. HRMS were performed at the Laboratoire de Spectrochimie de l'Ecole Normale Supérieure or by the Groupe de Spectrométrie de Masse de l'Université Pierre et Marie Curie in Paris. Infrared (IR) spectra were recorded on a Perkin–Elmer 298 or on a Bruker TENSOR™ 27 (IRFT), wave-numbers are indicated in cm^{-1}. ^1H NMR spectra were recorded on a Bruker AC 300 at 300 MHz or on a Bruker AVANCE 400 at 400 MHz in $CDCl_3$ and data are reported as follows: chemical shift in parts per million from tetramethylsilane as an internal standard, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, quint=quintuplet, m=multiplet or overlap of non-equivalent resonances, br=broad), integration. ^{13}C NMR spectra were recorded on a Bruker AC 300 at 75 MHz or on a Bruker AVANCE 400 at 100 MHz in $CDCl_3$

and data are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s=quaternary C, d=CH, t=CH_2, q=CH_3).

5.2. Prop-2-enyloxyacetic acid (4).[24] Typical procedure

To a stirred suspension of NaH (2.8 g, 60% in oil, 70 mmol, 1.0 equiv), washed with hexanes, in anhydrous THF (50 mL) at 0 °C was added dropwise prop-2-en-1-ol **1** (4.75 mL, 4.06 g, 70 mmol, 1 equiv). After 15 min at 0 °C, the reaction mixture was stirred for 15 min at rt. Besides, to another suspension of NaH (2.8 g, 70 mmol, 1.0 equiv), washed with hexanes, in anhydrous THF (25 mL) at 0 °C, was slowly added a solution of bromoacetic acid (9.722 g, 70 mmol, 1.0 equiv) in anhydrous THF (25 mL). After 5 min at 0 °C, the previously prepared sodium alkoxide solution was added (via cannula) and the reaction mixture was stirred for 2 h at rt and then heated for 3 h at 70 °C. After cooling to rt the reaction mixture was hydrolyzed with water (100 mL) and THF was removed by evaporation under reduced pressure. The aqueous layer was washed with diethyl ether (2×100 mL), and acidified until pH 3–4 with concentrated H_2SO_4. The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 90/10) afforded **4** (5.68 g, 49 mmol, 70%) as a colorless oil; R_f: 0.2 (petroleum ether/EtOAc 80/20); IR (neat) 3420, 3080, 2910, 1730, 1425, 1215, 1115, 935 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.19 (br s, 1H), 5.82 (ddt, J=17.3, 10.3, 5.9 Hz, 1H), 5.23 (dq, J=17.3, 1.4 Hz, 1H), 5.16 (dq, J=10.3, 1.4 Hz, 1H), 4.06 (s, 2H), 4.03 (dt, J=5.9, 1.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.3 (s), 133.1 (d), 118.4 (t), 72.2 (t), 66.2 (t).

5.2.1. But-3-enyloxyacetic acid (5).[25] Yield: 56% from but-3-en-1-ol **2**; colorless oil; R_f: 0.15 (petroleum ether/EtOAc 80/20); IR (neat) 3450, 3070, 2910, 1730, 1640, 1430, 1230, 1125, 915 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.65 (br s, 1H), 5.80 (ddt, J=16.9, 10.3, 6.6 Hz, 1H), 5.16–5.01 (m, 2H), 4.13 (s, 2H), 3.61 (t, J=6.6 Hz, 2H), 2.37 (apparent q, J=6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.2 (s), 134.3 (d), 116.7 (t), 71.0 (t), 67.5 (t), 36.5 (t); EIMS m/z (relative intensity) 89 ($M-C_3H_5^+$, 45), 71 (6), 61 (100), 59 (15), 55 (36), 54 (46), 53 (9).

5.2.2. Pent-4-enyloxyacetic acid (6).[26] Yield: 51% from pent-4-en-1-ol **3**; yellow oil; R_f: 0.15 (petroleum ether/EtOAc 80/20); IR (neat) 3200, 3110, 2970, 1730, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.57 (br s, 1H), 5.79 (ddt, J= 16.9, 10.3, 6.6 Hz, 1H), 5.05–4.91 (m, 2H), 4.10 (s, 2H), 3.55 (t, J=6.6 Hz, 2H), 2.12 (apparent q, J=6.6 Hz, 2H), 1.70 (apparent quint, J=6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.1 (s), 137.7 (d), 114.8 (t), 71.2 (t), 67.5 (t), 29.8 (t), 28.4 (t).

5.3. 1-(Prop-3-enyloxy)but-3-en-2-one (7). Typical procedure

To a solution of acid **4**, in anhydrous benzene (6 mL) were successively added a catalytic amount of DMF (one drop) and oxalyl chloride (0.57 mL, 0.84 g, 6.6 mmol, 1.1 equiv). The reaction mixture was stirred at rt until complete conversion of the starting material (followed by GC–MS). The excess of oxalyl chloride and solvent were evaporated under reduced pressure. The obtained crude acyl chloride was dissolved in HMPA (4 mL) and this solution was placed in a tube fitted with a screw-cap. Benzyl(chloro)-bis(triphenylphosphine)palladium(II) (18 mg, 0.024 mmol, 0.4 mol %) and tributyl(vinyl)stannane (1.9 mL, 6.6 mmol, 1.1 equiv) were added and the reaction mixture was heated up to 65 °C for 45 min. The mixture was then allowed to cool to rt, poured into an aqueous NaCl solution (15 mL, 3% in water), and extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To the crude residue were added diethyl ether (20 mL) and a half-saturated KF aqueous solution (15 mL). The biphasic mixture was stirred for 1 h at rt. After filtration, the organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O 95/5) afforded **7** (278 mg, 2.21 mmol, 37%) as a colorless oil; R_f: 0.8 (petroleum ether/EtOAc 80/20); IR (neat) 2890, 1695, 1400, 1115, 970, 930 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.51 (dd, J=17.6, 10.7 Hz, 1H), 6.30 (dd, J=17.6, 1.1 Hz, 1H), 5.96–5.76 (m, 2H), 5.32–5.15 (m, 2H), 4.23 (s, 2H), 4.03 (d, J=5.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.1 (s), 133.6 (d), 132.3 (d), 129.0 (t), 118.0 (t), 73.7 (t), 72.3 (t).

5.3.1. 1-(But-3-enyloxy)but-3-en-2-one (8). Yield: 58% from **5**; colorless oil; R_f: 0.7 (petroleum ether/EtOAc 80/20); IR (neat) 2920, 2855, 1700, 1615, 1405, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.54 (dd, J=17.6, 10.7 Hz, 1H), 6.33 (dd, J=17.6, 1.1 Hz, 1H), 5.90–5.75 (m, 2H), 5.15–5.02 (m, 2H), 4.25 (s, 2H), 3.55 (t, J=6.6 Hz, 2H), 2.43–2.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.4 (s), 134.6 (d), 132.2 (d), 129.0 (t), 116.6 (t), 74.8 (t), 70.9 (t), 33.9 (t); EIMS m/z (relative intensity) 99 ($M-C_3H_5^+$, 20), 96 (3), 86 (4), 70 (34), 69 (20), 55 (100).

5.3.2. 1-(Pent-4-enyloxy)but-3-en-2-one (9). Yield: 51% from **6**; colorless oil; R_f: 0.7 (petroleum ether/EtOAc 80/20); IR (neat) 2920, 2860, 1700, 1640, 1610, 1400, 1115, 990, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.57 (dd, J=17.3, 10.7 Hz, 1H), 6.35 (dd, J=17.3, 1.8 Hz, 1H), 5.89–5.75 (m, 2H), 5.08–4.94 (m, 2H), 4.24 (s, 2H), 3.52 (t, J=6.6 Hz, 2H), 2.20–2.11 (m, 2H), 1.79–1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.4 (s), 137.8 (d), 132.2 (d), 128.9 (t), 114.7 (t), 74.8 (t), 70.9 (t), 29.9 (t), 28.5 (t).

5.4. 2-Methylpent-4-en-3-ol (10)[27]

To a solution of vinylmagnesium chloride in anhydrous THF (32.8 mL, 1.68 M, 55.0 mmol, 1.1 equiv) at −40 °C was slowly added freshly distilled isobutyraldehyde (4.5 mL, 3.6 g, 50 mmol, 1 equiv). After 1 h at −40 °C, the reaction mixture was poured into a saturated aqueous NH_4Cl solution (50 mL) and extracted with diethyl ether (3×100 mL). The combined organic extracts were washed with water (50 mL), and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O 95/5) afforded

10 (1.99 g, 19.9 mmol, 40%) as a colorless oil; R_f: 0.85 (petroleum ether/EtOAc 80/20); IR (neat) 3360 (broad, OH), 2960, 2870, 1465, 1020, 990, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.81 (ddd, J=16.9, 10.7, 6.2 Hz, 1H), 5.21–5.07 (m, 2H), 3.80 (apparent t, J=6.2 Hz, 1H), 2.15 (br s, 1H), 1.69 (m, 1H), 0.89 (d, J=6.8 Hz, 3H), 0.85 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.4 (d), 115.4 (t), 78.1 (d), 33.5 (d), 18.0 (q), 17.8 (q).

5.5. 1-Triphenylmethyloxy-but-3-en-2-ol (11)[28]

A mixture of but-3-en-1,2-diol (1.00 mL, 1.05 g, 11.9 mmol, 1 equiv), triphenylmethyl chloride (9.94 g, 35.7 mmol, 3 equiv), and 4-*N*,*N*-dimethylaminopyridine (5.80 g, 47.5 mmol, 4 equiv) in pyridine (100 mL) was refluxed for 3 h. After cooling to rt, the reaction mixture was diluted with EtOAc (100 mL) and hydrolyzed with a saturated aqueous $CuSO_4$ solution (100 mL). After decantation, the organic layer was separated, washed successively with a saturated aqueous $CuSO_4$ solution (2×50 mL), water (50 mL), a saturated aqueous $NaHCO_3$ solution (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (hexane/CH_2Cl_2 60/40) afforded **11** (2.56 g, 7.75 mmol, 65%) as a yellow oil; R_f: 0.60 (petroleum ether/EtOAc 80/20); IR (neat) 3420 (broad, OH), 3050, 2860, 1590, 1485, 1445, 1260, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.78–7.61 (m, 5H), 7.49–7.32 (m, 10H), 5.97 (ddd, J=16.2, 11.4, 5.9 Hz, 1H), 5.45 (dt, J=17.3, 1.5 Hz, 1H), 5.28 (dt, 1H, J=10.6, 1.5 Hz, 1H), 4.43 (m, 1H), 3.43–3.29 (m, 2H), 2.86 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 143.7 (s, 3C), 137.1 (d), 128.5 (d, 6C), 127.7 (d, 3C), 127.0 (d, 6C), 116.0 (t), 86.6 (s), 71.8 (d), 67.4 (t).

5.6. 2-Methylhex-5-en-3-ol (12)[29]

To a solution of allylmagnesium chloride in anhydrous THF (12 mL, 2 M, 24.0 mmol, 1.2 equiv) at 0 °C was slowly added freshly distilled isobutyraldehyde (1.82 mL, 1.44 g, 20 mmol, 1 equiv). After 15 min at 0 °C, the reaction mixture was stirred for 1 h at rt. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (25 mL) and extracted with diethyl ether (2×50 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O 95/5) afforded **12** (1.47 g, 12.9 mmol, 64%) as a colorless oil; R_f: 0.75 (petroleum ether/EtOAc 80/20); IR (neat) 3480 (broad, OH), 2960, 1460, 1415, 990, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.84 (m, 1H), 5.19–5.10 (m, 2H), 3.40 (m, 1H), 2.31 (m, 1H), 2.12 (m, 1H), 1.69 (m, 1H), 1.62 (br s, 1H), 0.95 (d, J=6.6 Hz, 3H), 0.93 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.0 (d), 117.4 (t), 74.9 (d), 40.3 (t), 32.6 (d), 18.2 (q), 17.1 (q); EIMS *m*/*z* (relative intensity) 113 ($M-H^+$, 1), 74 (5), 73 (100), 71 ($M-C_3H_7^+$, 16), 57 (6), 55 (51).

5.7. 1-Phenylbut-3-en-1-ol (13)[30]

To a solution of allylmagnesium chloride in anhydrous THF (12 mL, 2 M, 24.0 mmol, 1.2 equiv) at 0 °C was slowly added freshly distilled benzaldehyde (2.03 mL, 2.12 g, 20 mmol, 1 equiv). After 15 min at 0 °C, the reaction mixture was stirred for 1 h at rt. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (15 mL) and extracted with diethyl ether (3×30 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O 95/5) afforded **13** (2.87 g, 19.4 mmol, 97%) as a colorless oil; R_f: 0.7 (petroleum ether/EtOAc 80/20); IR (neat) 3380 (broad, OH), 2915, 1640, 1450, 1045, 915, 760, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.21 (m, 5H), 5.78 (ddt, J=16.9, 9.9, 7.3 Hz, 1H), 5.17–5.08 (m, 2H), 4.68 (td, J=6.2, 2.9 Hz, 1H), 2.52–2.45 (m, 2H), 2.30 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.8 (s), 134.4 (d), 128.3 (d, 2C), 127.4 (d), 125.7 (d, 2C), 118.1 (t), 73.2 (d), 43.7 (t); EIMS *m*/*z* (relative intensity) 148 ($M^{+\bullet}$, 1), 108 (8), 107 (100), 105 (7), 79 (55), 78 (5), 77 (32), 51 (6).

5.8. 1,1-Dimethylbut-3-en-1-ol (14)[31]

To a solution of allylmagnesium chloride in anhydrous THF (15.3 mL, 2 M, 30.6 mmol, 1.50 equiv) at 0 °C was slowly added dimethylketone (1.50 mL, 1.18 g, 20.4 mmol, 1 equiv). After 15 min at 0 °C, the reaction mixture was stirred for 1 h at rt. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (20 mL) and extracted with diethyl ether (3×30 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by distillation under reduced pressure (10–15 bars, bp 50 °C) allowed to isolate **14** (1.29 g, 12.9 mmol, 63%) as a colorless oil; R_f: 0.35 (petroleum ether/EtOAc 90/10); IR (neat) 3385 (broad, OH), 3085, 2985, 2915, 1640, 1465, 1380, 1180, 1150, 945, 915 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.86 (m, 1H), 5.17–5.06 (m, 2H), 2.23 (d, J=7.7 Hz, 2H), 1.89 (br s, 1H), 1.22 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.1 (d), 118.3 (t), 70.2 (s), 48.0 (t), 28.9 (q, 2C); EIMS *m*/*z* (relative intensity) 99 ($M-H^+$, 1), 96 (9), 81 (70), 68 (76), 67 (100), 57 (25), 55 (78), 54 (88), 53 (16).

5.9. 2-Methylhept-6-en-3-ol (15)[32]

To a suspension of magnesium (1.79 g, 73.80 mmol, 3.75 equiv) in anhydrous Et_2O (10 mL) was added a solution of 4-bromobut-1-ene (2.44 mL, 3.71 g, 24.6 mmol, 1.25 equiv) in anhydrous Et_2O (25 mL) at such a rate to maintain a regular reflux. At the end of the addition, the reaction mixture was refluxed for an additional 10 min. After cooling to rt, a solution of freshly distilled isobutyraldehyde (1.8 mL, 1.4 g, 19.7 mmol, 1 equiv) in anhydrous Et_2O (15 mL) was added at such a rate to maintain a constant reflux. After cooling to rt, the reaction mixture was hydrolyzed with a saturated aqueous NH_4Cl solution (25 mL), extracted with diethyl ether (2×50 mL) and EtOAc (50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O 90/10) afforded **15** (1.77 g, 13.8 mmol, 70%) as a colorless oil; R_f: 0.65 (petroleum ether/EtOAc 80/20); IR (neat) 3350 (broad, OH), 2950, 2930, 2870, 1635, 1465, 910 cm^{-1};

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.82 (ddt, J=16.9, 10.3, 6.6 Hz, 1H), 5.02 (ddt, J=17.3, 1.8, 1.8 Hz, 1H), 4.94 (ddt, J=10.3, 1.8, 1.1 Hz, 1H), 3.34 (m, 1H), 2.30–2.01 (m, 2H), 1.82 (br d, J=3.3 Hz, 1H), 1.71–1.36 (m, 3H), 0.89 (d, J=7.0 Hz, 3H), 0.88 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6 (d), 114.6 (t), 75.9 (d), 33.4 (d), 33.1 (t), 30.3 (t), 18.6 (q), 17.0 (q); EIMS *m/z* (relative intensity) 128 ($M^{+\bullet}$, 1), 95 (35), 86 (20), 85 (59), 81 (14), 73 (61), 71 (13), 69 (12), 68 (12), 67 (100), 57 (53), 56 (25), 55 (61), 54 (12).

5.10. 1-Chloro-3-(triphenyl-λ^5-phosphanylidene)-propan-2-one[13]

To a solution of α,α′-dichloroacetone (15.0 g, 118 mmol, 1 equiv) in THF (60 mL) was added triphenylphosphine (30.95 g, 118 mmol, 1 equiv). The reaction mixture was heated for 5 h at 70 °C. After cooling to rt, the suspension was filtered. The obtained solid was washed with anhydrous THF (2×30 mL) and then dissolved at 65 °C in methanol (ca. 60 mL). EtOAc (20 mL) was added to the warm alcoholic solution. After stirring overnight at rt, the suspension was filtered and rinsed with EtOAc (20 mL). The resulting solid was dried at 50 °C for 48 h in an oven to afford triphenylchloroacetonylphosphonium chloride as a white solid (44.51 g, 114.5 mmol, 97%); mp 212 °C.

To a solution of the obtained phosphonium chloride (20.0 g, 51.4 mmol, 1.50 equiv) in methanol (30 mL) was added rapidly under stirring a solution of sodium carbonate (3.65 g, 34.4 mmol, 1.00 equiv) in water (20 mL). The resulting white suspension was diluted with water (100 mL) and stirred for 45 min at rt before it was filtered. The obtained solid was dried under reduced pressure for several hours leading to the desired triphenylchloroacetonylphosphorane (17.76 g, 50.37 mmol, 98%) as white crystals. Physical and spectral data match those previously reported.[13] Mp 182 °C; R_f: 0.5 (EtOAc/EtOH 90/10); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72–7.45 (m, 15H), 4.29 (br d, $^2J_{H-P}$=24.3 Hz, 1H), 4.03 (s, 2H).

5.11. 1-(1-Isopropylprop-2-enyloxy)-3-(triphenyl-λ^5-phosphoranylidene)propan-2-one (16). Typical procedure

To a stirred suspension of NaH (1.6 g, 60% in oil, 40 mmol, 5.0 equiv), previously washed with hexanes, in anhydrous THF (10 mL) at rt was slowly added a solution of alcohol **10** (1.0 g, 10 mmol, 1.25 equiv) in anhydrous THF (15 mL). After 30 min at rt, neat triphenylchloroacetonylphosphorane was added in one portion. The reaction mixture was stirred at rt for 2 h and then heated at 70 °C for 5 h. After cooling to rt, the reaction mixture was poured on ice and extracted with EtOAc (3×40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc) afforded **16** (3.11 g, 7.48 mmol, 94%) as a beige solid; mp 78–80 °C; R_f: 0.5 (EtOAc/EtOH 90/10); IR ($CHBr_3$) 2950, 1525, 1480, 1435, 1400, 1140, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72–7.62 (m, 5H), 7.59–7.41 (m, 10H), 5.72 (ddd, J=16.9, 10.6, 7.7 Hz, 1H), 5.26–5.16 (m, 2H), 4.26 (br d, $^2J_{H-P}$=26.1 Hz, 1H), 4.01 ($d_{syst\ AB}$, J=14.7 Hz, 1H), 3.83 ($d_{syst\ AB}$, J=14.7 Hz, 1H), 3.53 (dd, J=7.7, 6.6 Hz, 1H), 1.86 (m, 1H), 0.99 (d, J=6.6 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.6 (s), 137.1 (d), 133.0 (d, $^3J_{C-P}$=10.3 Hz, 6C), 131.9 (d, $^4J_{C-P}$=2.8 Hz, 3C), 128.7 (d, $^2J_{C-P}$=12.2 Hz, 6C), 127.0 (s, $^1J_{C-P}$=90.2 Hz, 3C), 117.9 (t), 86.9 (d), 73.1 (t, $^3J_{C-P}$=12.7 Hz), 49.2 (d, $^1J_{C-P}$=108.7 Hz), 32.3 (d), 18.8 (q), 18.2 (q); EIMS *m/z* (relative intensity) 416 ($M^{+\bullet}$, 1), 373 (2), 318 (4), 304 (23), 303 (100), 289 (7), 183 (9).

5.11.1. 1-(Triphenyl-λ^5-phosphoranylidene)-3-(1-triphenylmethyloxymethylallyloxy)propan-2-one (17).

Yield: 71% from **11**; wax; R_f: 0.40 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70–7.08 (m, 30H), 5.80 (ddd, J=17.4, 10.3, 7.3 Hz, 1H), 5.32 (d, J=17.4 Hz, 1H), 5.18 (d, J=10.3 Hz, 1H), 4.42 (br d, $^2J_{H-P}$=25.4 Hz, 1H), 4.18–3.94 (m, 3H), 3.34 (dd, $J_{syst\ AB}$=9.6, J=6.6 Hz, 1H), 3.10 (dd, $J_{syst\ AB}$=9.6, J=6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.1 (s), 144.1 (s, 3C), 136.2 (d), 133.0 (d, $^3J_{C-P}$=10.2 Hz, 6C), 131.9 (d, $^4J_{C-P}$=2.6 Hz, 3C), 128.7 (d, $^3J_{C-P}$=12.1 Hz, 6C), 128.6 (d, 6C), 127.6 (d, 6C), 126.7 (d, 3C), 126.4 (s, $^1J_{C-P}$=90.1 Hz, 3C), 117.7 (t), 86.4 (s), 80.9 (d), 73.8 (t, $^3J_{C-P}$=12.6 Hz), 66.6 (t), 50.1 (d, $^1J_{C-P}$=109.3 Hz).

5.11.2. 1-(1-Isopropyl-but-3-enyloxy)-3-(triphenyl-λ^5-phosphoranylidene)propan-2-one (18).

Yield: 48% from **12**; beige solid; mp 86–90 °C; R_f: 0.55 (EtOAc/EtOH 90/10); IR ($CHBr_3$) 3050, 2960, 1530, 1480, 1435, 1400, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69–7.36 (m, 15H), 5.88 (ddt, J=16.9, 9.9, 7.4 Hz, 1H), 5.09–4.89 (m, 2H), 4.26 (m, 1H), 4.01 ($d_{syst\ AB}$, J=14.8 Hz, 1H), 3.91 ($d_{syst\ AB}$, J=14.8 Hz, 1H), 3.23 (apparent q, J=5.5 Hz, 1H), 2.31–2.23 (m, 2H), 1.89 (m, 1H), 0.93 (d, J=8.1 Hz, 3H), 0.89 (d, J=8.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.3 (s), 136.0 (d), 133.0 (d, $^3J_{C-P}$=10.3 Hz, 6C), 132.0 (d, $^4J_{C-P}$=2.6 Hz, 3C), 128.8 (d, $^2J_{C-P}$=12.3 Hz, 6C), 126.7 (s, $^1J_{C-P}$=90.3 Hz, 3C), 116.1 (t), 84.8 (d), 74.3 (t, $^3J_{C-P}$=12.5 Hz), 49.7 (d, $^1J_{C-P}$=109.6 Hz), 35.0 (t), 30.5 (d), 18.2 (q), 18.1 (q); EIMS *m/z* (relative intensity) 430 ($M^{+\bullet}$, 1), 389 (3), 304 (23), 303 (100), 289 (9), 262 (4), 183 (8), 165 (4).

5.11.3. 1-(1-Phenylbut-3-enyloxy)-3-(triphenyl-λ^5-phosphoranylidene)propan-2-one (19).

Yield: 70% from **13**; beige solid; mp 126–128 °C; R_f: 0.7 (EtOAc/EtOH 90/10); IR ($CHBr_3$): 3050, 3010, 2900, 1530, 1480, 1435, 1400, 1140, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70–7.21 (m, 20H), 5.84 (ddt, J=16.9, 9.9, 7.4 Hz, 1H), 5.09–4.90 (m, 2H), 4.51 (dd, J=7.7, 5.9 Hz, 1H), 4.28 (br s, 1H), 3.95 ($d_{syst\ AB}$, J=15.4 Hz, 1H), 3.78 ($d_{syst\ AB}$, J=15.4 Hz, 1H), 2.67 (m, 1H), 2.48 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.0 (s), 142.0 (s), 135.2 (d), 133.0 (d, $^3J_{C-P}$=10.1 Hz, 6C), 132.0 (d, $^4J_{C-P}$=6.1 Hz, 3C), 128.6 (d, $^2J_{C-P}$=12.2 Hz, 6C), 128.3 (d, 2C), 128.1 (d), 126.9 (s, $^1J_{C-P}$=90.4 Hz, 3C), 126.8 (d, 2C), 116.6 (t), 82.2 (d), 73.2 (t, $^3J_{C-P}$=13.1 Hz), 49.5 (d, $^1J_{C-P}$=109.2 Hz), 42.6 (t); EIMS *m/z* (relative intensity) 293 (1), 278 (39), 277 (100), 201 (14), 183 (14), 152 (8), 77 (10).

5.11.4. 1-(1,1-Dimethylbut-3-enyloxy)-3-(triphenyl-λ^5-phosphoranylidene)propan-2-one (20).

Yield: 82% from **14**; beige wax; R_f: 0.1 (EtOAc); IR ($CHBr_3$) 3050, 3020, 2970, 2920, 1530, 1515, 1435, 1400, 1140, 1105,

875 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72–7.40 (m, 15H), 5.91 (ddt, J=17.3, 10.3, 7.4 Hz, 1H), 5.10–5.00 (m, 2H), 4.28 (br d, $^2J_{H-P}$=27.0 Hz, 1H), 3.92 (s, 2H), 2.32 (d, J=7.4 Hz, 2H), 1.22 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.2 (s), 134.9 (d), 132.7 (d, $^3J_{C-P}$=10.8 Hz, 6C), 131.8 (d, $^4J_{C-P}$=2.8 Hz, 3C), 128.6 (d, $^2J_{C-P}$=12.3 Hz, 6C), 127.2 (s, $^1J_{C-P}$=90.0 Hz, 3C), 116.9 (t), 74.9 (s), 66.7 (t, $^3J_{C-P}$=12.5 Hz), 49.0 (d, $^1J_{C-P}$=108.8 Hz), 45.3 (t), 25.2 (q, 2C); EIMS *m/z* (relative intensity) 416 ($M^{+\bullet}$, 1), 304 (23), 303 (100), 289 (9), 262 (7), 183 (9).

5.11.5. 1-(1-Isopropylpent-3-enyloxy)-3-(triphenyl-λ^5-phosphoranylidene)propan-2-one (21). Yield: 76% from **15**; wax; R_f: 0.40 (EtOAc/EtOH 90/10); IR (film) 3050, 2950, 1530, 1480, 1435, 1400, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.78–7.40 (m, 15H), 5.82 (ddt, J=16.9, 10.3, 6.6 Hz, 1H), 5.03–4.87 (m, 2H), 4.30 (br d, $^2J_{H-P}$=27.0 Hz, 1H), 4.00 (s, 2H), 3.19 (apparent dt, J=7.3, 4.8 Hz, 1H), 2.34–2.06 (m, 2H), 1.93 (m, 1H), 1.67–1.49 (m, 2H), 0.93 (d, J=6.2 Hz, 3H), 0.91 (d, J=6.2 Hz, 3H); EIMS *m/z* (relative intensity) 444 ($M^{+\bullet}$, 1), 304 (22), 303 (100), 262 (11), 183 (14).

5.12. 1-(1-Isopropylprop-2-enyloxy)but-3-en-2-one (22). Typical procedure

To a solution of ylide **16** (2.0 g, 4.8 mmol, 1 equiv) in diethyl ether (30 mL) was added an aqueous solution of formaldehyde (36 mL, 37% in water, 0.48 mmol, 100 equiv). The biphasic reaction mixture was stirred overnight at rt. The aqueous layer was extracted with diethyl ether (3×20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/diethyl ether 95/5) afforded **22** (539 mg, 3.21 mmol, 67%) as a colorless oil. In order to avoid polymerization compound **22** has to be kept in solution (c ~0.2 M in Et_2O or CH_2Cl_2). R_f: 0.85 (petroleum ether/EtOAc 80/20); IR (neat) 2960, 2930, 2870, 1700, 1625, 1400, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.58 (dd, J=17.7, 10.7 Hz, 1H), 6.31 (dd, J=17.6, 1.5 Hz, 1H), 5.77 (dd, J=10.7, 1.5 Hz, 1H), 5.63 (ddd, J=17.3, 10.3, 8.5 Hz, 1H), 5.25 (br dd, J=10.3, 1.8 Hz, 1H), 5.15 (ddd, J=17.3, 1.8, 0.7 Hz, 1H), 4.23 ($d_{syst\ AB}$, J=16.9 Hz, 1H), 4.07 ($d_{syst\ AB}$, J=16.9 Hz, 1H), 3.38 (m, 1H), 1.83 (m, 1H), 0.96 (d, J=7.0 Hz, 3H), 0.87 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.7 (s), 136.1 (d), 132.4 (d), 128.6 (t), 119.0 (t), 87.5 (d), 72.5 (t), 32.3 (d), 18.4 (q), 18.0 (d); EIMS *m/z* (relative intensity) 168 ($M^{+\bullet}$, 1), 125 (100), 99 (24), 83 (40), 70 (14), 69 (61), 67 (12), 55 (84).

5.12.1. 1-(1-Triphenylmethyloxymethylallyloxy)but-3-en-2-one (23). Yield: 70% from **17**; colorless oil. In order to avoid polymerization compound **23** has to be kept in solution (c ~0.2 M in Et_2O or CH_2Cl_2). R_f: 0.70 (petroleum ether/EtOAc 80/20); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51–7.44 (m, 5H), 7.31–7.15 (m, 10H), 6.69 (dd, J=17.3, 10.7 Hz, 1H), 6.33 (dd, J=17.3, 1.5 Hz, 1H), 5.78–5.64 (m, 2H), 5.29–5.19 (m, 2H), 4.31 ($d_{syst\ AB}$, J=16.7 Hz, 1H), 4.19 ($d_{syst\ AB}$, J=16.7 Hz, 1H), 3.93 (m, 1H), 3.35 (dd, J=9.9, 7.0 Hz, 1H), 3.17 (dd, J=9.9, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.6 (s), 143.9 (s, 3C), 135.0 (d), 132.4 (d), 129.0 (t), 128.7 (d, 6C), 127.7 (d, 6C), 127.0 (d, 3C), 118.8 (t), 86.7 (s), 81.3 (d), 73.1 (t), 66.5 (t).

5.12.2. 1-(1-Isopropylbut-3-enyloxy)but-3-en-2-one (24). Yield: 49% from **18**; colorless oil. In order to avoid polymerization compound **24** has to be kept in solution (c ~0.2 M in Et_2O or CH_2Cl_2). R_f: 0.8 (petroleum ether/EtOAc 80/20); IR (neat): 2960, 2920, 2870, 1700, 1680, 1640, 1615, 1465, 1400, 1100, 1065, 990, 915 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.66 (dd, J=17.7, 10.7 Hz, 1H), 6.36 (dd, J=17.7, 1.5 Hz, 1H), 5.94–5.77 (m, 2H), 5.15–5.01 (m, 2H), 4.28 ($d_{syst\ AB}$, J=16.5 Hz, 1H), 4.19 ($d_{syst\ AB}$, J=16.5 Hz, 1H), 3.16 (apparent q, J=5.5 Hz, 1H), 2.34–2.26 (m, 2H), 1.88 (m, 1H), 0.94 (t, J=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.6 (s), 135.1 (d), 132.3 (d), 128.8 (t), 116.7 (t), 85.5 (d), 74.4 (t), 34.9 (t), 30.2 (d), 18.1 (q), 17.8 (q).

5.12.3. 1-(1-Phenylbut-3-enyloxy)but-3-en-2-one (25). Yield: 73% from **19**; colorless oil. In order to avoid polymerization compound **25** has to be kept in solution (c ~0.2 M in Et_2O or CH_2Cl_2). R_f: 0.65 (petroleum ether/EtOAc 80/20); IR (neat): 3060, 3020, 2970, 2860, 1695, 1610, 1400, 1100, 1065, 990, 915 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.26 (m, 5H), 6.55 (dd, J=17.6, 10.7 Hz, 1H), 6.29 (dd, J=17.6, 1.5 Hz, 1H), 5.90–5.74 (m, 2H), 5.11–5.01 (m, 2H), 4.39 (dd, J=7.4, 6.3 Hz, 1H), 4.16 ($d_{syst\ AB}$, J=16.9 Hz, 1H), 4.04 ($d_{syst\ AB}$, J=16.9 Hz, 1H), 2.70 (m, 1H), 2.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.9 (s), 140.5 (s), 134.3 (d), 132.3 (d), 128.8 (t), 128.4 (d, 2C), 127.9 (d), 126.7 (d, 2C), 117.1 (t), 82.4 (d), 72.5 (t), 42.2 (t); EIMS *m/z* (relative intensity) 216 ($M^{+\bullet}$, 1), 175 ($M-C_3H_5^+$, 100), 173 (16), 131 (4), 105 (1), 91 (3), 77 (1), 69 (3).

5.12.4. 1-(1-Dimethylbut-3-enyloxy)but-3-en-2-one (26). Yield: 49% from **20**; colorless oil. In order to avoid polymerization compound **26** has to be kept in solution (c ~0.2 M in Et_2O or CH_2Cl_2). R_f: 0.70 (petroleum ether/EtOAc 80/20); IR (neat): 2970, 2920, 1740, 1700, 1620, 1400, 1100, 915 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.69 (dd, J=17.6, 10.7 Hz, 1H), 6.36 (dd, J=17.6, 1.8 Hz, 1H), 5.93–5.77 (m, 2H), 5.11–5.03 (m, 2H), 4.14 (s, 2H), 2.30 (d, J=7.2 Hz, 2H), 1.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.2 (s), 134.0 (d), 132.2 (d), 128.7 (t), 117.6 (t), 75.9 (s), 67.1 (t), 44.9 (t), 24.9 (q, 2C); EIMS *m/z* (relative intensity) 168 ($M^{+\bullet}$, 1), 127 (100), 113 (8), 95 (2), 85 (8), 83 (56), 69 (99), 67 (11), 59 (8), 55 (92).

5.12.5. 1-(1-Isopropylpent-4-enyloxy)but-3-en-2-one (27). Yield: 54% from **21**; colorless oil. In order to avoid polymerization compound **27** has to be kept in solution (c ~0.2 M in Et_2O or CH_2Cl_2). R_f: 0.60 (petroleum ether/EtOAc 80/20); IR (neat) 3065, 2955, 2870, 1700, 1640, 1610, 1465, 1400, 1105, 1065, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.65 (dd, J=17.6, 10.7 Hz, 1H), 6.35 (dd, J=17.6, 1.5 Hz, 1H), 5.89–5.74 (m, 2H), 5.07–4.93 (m, 2H), 4.26 ($d_{syst\ AB}$, J=16.5 Hz, 1H), 4.20 ($d_{syst\ AB}$, J=16.5 Hz, 1H), 3.13 (apparent dt, J=7.7, 4.4 Hz, 1H), 2.32–2.03 (m, 2H), 1.90 (m, 1H), 1.68–1.48 (m, 2H), 0.92 (d, J=7.0 Hz, 3H), 0.91 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.4 (s), 138.4 (d), 132.3 (d), 128.7 (t), 114.5 (t), 85.1 (d), 74.2 (t), 30.2 (d), 29.7 (t), 29.1 (t),

18.0 (q), 17.5 (q); EIMS *m/z* (relative intensity) 153 (4), 141 (2), 135 (6), 127 (14), 111 (23), 107 (6), 95 (8), 83 (7), 71 (18), 70 (10), 69 (100), 67 (25), 55 (48).

5.12.6. 1-(Hex-5-enyloxy)but-3-en-2-one (56). To a stirred suspension of NaH (1.2 g, 60% in oil, 30 mmol, 5.0 equiv), washed with hexanes, in anhydrous THF (12.5 mL) at rt was slowly added a solution of hex-6-en-1-ol **10** (0.9 g, 7.5 mmol, 1.25 equiv) in anhydrous THF (15 mL). After 30 min at rt, neat triphenylchloroacetonylphosphorane was added in one portion. The reaction mixture was stirred at rt for 14 h and then poured on ice and extracted with EtOAc (3×20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/EtOH 99/1 to 80/20) afforded *1-(hex-5-enyloxy)-3-(triphenyl-λ⁵-phosphoranylidene)propan-2-one* (2.50 g, 6.05 mmol, 80%) as a beige solid; mp 84–86 °C. The obtained ylide was directly treated with aqueous formaldehyde in Et_2O following the general procedure. Purification by flash chromatography (petroleum ether/Et_2O 90/10) afforded **56** (656 mg, 3.90 mmol, 65%) as a colorless oil; R_f: 0.8 (petroleum ether/EtOAc 80/20); IR (neat) 2915, 2850, 1700, 1610, 1400, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.49 (dd, J=17.7, 10.7 Hz, 1H), 6.25 (dd, J=17.7, 1.6 Hz, 1H), 5.78–5.63 (m, 2H), 4.95–4.82 (m, 2H), 4.13 (s, 2H), 3.41 (t, J=6.6 Hz, 2H), 2.04–1.94 (m, 2H), 1.61–1.50 (m, 2H), 1.45–1.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.3 (s), 138.3 (d), 132.2 (d), 128.7 (t), 114.4 (t), 74.8 (t), 65.5 (t), 33.2 (t), 28.7 (t), 25.0 (t); EIMS *m/z* (relative intensity) 168 ($M^{+\bullet}$, 1), 95 (19), 86 (16), 83 (22), 71 (14), 70 (36), 69 (12), 67 (11), 55 (100).

5.13. *N*-(Prop-2-enyl)-4-methylbenzenesulfonamide (28)[33]

To a solution of allylamine (0.5 g, 8.8 mmol, 1 equiv) in anhydrous CH_2Cl_2 (10 mL), at 0 °C, were added successively Et_3N (1.6 mL, 12 mmol, 1.36 equiv) and tosyl chloride (2.00 g, 10.6 mmol, 1.2 equiv). After stirring for 4 h at 0 °C, the reaction mixture was hydrolyzed with water (10 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude solid was purified by recrystallization (hexane/Et_2O 50/50) to afford **28** (1.76 g, 8.36 mmol, 95%) as a pale yellow solid. Physical and spectral data match those previously reported.[33] Mp 60 °C (lit.:[33] mp 59–61 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80–7.73 (m, 2H), 7.36–7.29 (m, 2H), 5.73 (ddt, J=16.2, 10.3, 5.9 Hz, 1H), 5.22–5.06 (m, 2H), 4.65 (br t, J=5.9 Hz, 1H), 3.59 (m, 2H), 2.44 (s, 3H); EIMS *m/z* (relative intensity) 211 ($M^{+\bullet}$, 4), 155 (32), 147 (12), 92 (22), 91 (100), 65 (22), 56 (41).

5.14. *tert*-Butyl allylcarbamate (29)[34]

To a solution of allylamine (2.28 g, 40.0 mmol, 1 equiv) in anhydrous CH_2Cl_2 (200 mL), at rt, was added Et_3N (11.1 mL, 80 mmol, 2 equiv). The solution was cooled to 0 °C and di-*tert*-butyldicarbonate (9.6 g, 44 mmol, 1.1 equiv) was added by small portions. After stirring for 21 h at rt, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc 90/10) afforded **29** (5.98 g, 38.1 mmol, 95%) as a white solid; mp 36 °C; R_f: 0.40 (hexane/EtOAc 90/10); IR (film) 3440, 3350, 2970, 1700, 1500, 1390, 1365, 1265, 1170, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.84 (m, 1H), 5.22–5.07 (m, 2H), 4.74 (br s, 1H), 3.74 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.6 (s), 134.8 (d), 115.4 (t), 79.1 (s), 42.9 (t), 28.2 (q, 3C).

5.15. *tert*-Butyl but-3-enylcarbamate (30)[35]

To a suspension of homoallylamine hydrochloride salt[14] (1.08 g, 10.0 mmol, 1 equiv) in anhydrous CH_2Cl_2 (50 mL), at 0 °C, were added Et_3N (4.2 mL, 30 mmol, 3 equiv) and then di-*tert*-butyldicarbonate (2.4 g, 11 mmol, 1.1 equiv) by small portions. After 15 min of stirring at 0 °C, the reaction mixture was stirred for 60 h at rt and then concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 90/10 and then 80/20) afforded **30** (1.13 g, 6.60 mmol, 66%) as a colorless oil; R_f: 0.60 (hexane/EtOAc 70/30); IR (neat): 3450, 3360, 2985, 1700, 1500, 1390, 1365, 1265, 1170, 920, 745, 735, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.70 (ddt, J=17.4, 10.3, 6.9 Hz, 1H), 5.10–4.95 (m, 2H), 4.65 (br s, 1H), 3.14 (m, 2H), 2.19 (apparent q, J=6.9 Hz, 2H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.7 (s), 135.2 (d), 116.7 (t), 78.8 (s), 39.5 (t), 34.0 (t), 27.7 (q, 3C).

5.16. Benzyl but-3-enylcarbamate (31)[36]

To a suspension of homoallylamine hydrochloride salt[14] (1.07 g, 10.0 mmol, 1 equiv) in anhydrous CH_2Cl_2 (100 mL) was added a solution of sodium carbonate (3.29 g, 31.0 mmol, 3.1 equiv) in water (8 mL). The biphasic mixture was cooled to 0 °C and benzyl chloroformate (2.3 mL, 16 mmol, 1.6 equiv) was added dropwise. After 15 min of stirring at 0 °C, the reaction mixture was stirred for 14 h at rt. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and water (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×100 mL) and the combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 90/1) afforded **31** (1.46 g, 7.12 mmol, 71%) as a colorless oil; R_f: 0.70 (petroleum ether/EtOAc 80/20); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.20 (m, 5H), 5.72 (m, 1H), 5.20–4.90 (m, 3H), 5.08 (s, 2H), 3.22 (m, 2H), 2.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.3 (s), 136.6 (s), 135.0 (d), 128.3 (d, 3C), 127.9 (d, 2C), 117.0 (t), 66.4 (t), 40.0 (t), 34.0 (t).

5.17. *N*-Benzyl-*N*-(but-3-enyl)amine (32)[37]

To a solution of benzylamine (7.71 mL, 70.6 mmol, 5 equiv) and 4-bromobut-1-ene (1.44 mL, 14.2 mmol, 1 equiv) in EtOH (20 mL), degassed by argon bubbling for 20 min, sodium iodide (ca. 80 mg) was added. The reaction mixture was heated at 75 °C for 4 h. After cooling to rt, the reaction mixture was diluted with CH_2Cl_2 (200 mL) and an aqueous solution of KOH (1 M, 200 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×70 mL) and the combined organic layers were dried over K_2CO_3, filtered, and

concentrated under reduced pressure. Purification by flash chromatography on silica gel (hexanes/EtOAc/Et_3N 100/10/02) allowed to isolate **32** (2.08 g, 12.09 mmol, 91%) as a colorless oil; R_f: 0.20 (hexane/EtOAc/Et_3N 100/10/02); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.20 (m, 5H), 5.79 (ddt, J=17.3, 10.3, 7.0 Hz, 1H), 5.13–5.01 (m, 2H), 3.79 (s, 2H), 2.70 (t, J=7.0 Hz, 2H), 2.28 (qt, J=7.0, 1.1 Hz, 2H), 1.50 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.3 (s), 136.3 (d), 128.2 (d, 2C), 128.0 (d, 2C), 126.7 (d), 116.2 (t), 53.7 (t), 48.2 (t), 34.2 (t); EIMS *m/z* (relative intensity) 161 ($M^{+\bullet}$, 1), 120 (54), 91 (100), 65 (8).

5.18. 4-Methyl-*N*-(1-phenylbut-3-enyl)benzenesulfonamide (33)[39]

A solution of benzaldehyde (5.1 mL, 50 mmol, 1 equiv), *p*-TSA (8.55 g, 50 mmol, 1 equiv), and sodium *p*-toluene sulfinate (8.9 g, 50 mmol, 1 equiv) in a mixture of formic acid (75 mL) and water (75 mL) was stirred for 12 h at rt. The resulting white precipitate was filtered, rinsed with water (2× 50 mL) and pentane (50 mL), and then dissolved in CH_2Cl_2 (500 mL). To this solution was added a saturated aqueous $NaHCO_3$ solution (350 mL) and the resulting biphasic mixture was stirred for 2 h at rt. The aqueous layer was then extracted with CH_2Cl_2 (2×200 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford *N*-benzylidene-4-methylbenzenesulfonamide (7.70 g, 29.7 mmol, 59%) as white crystals, which can be recrystallized in a 1/1 mixture of CH_2Cl_2 and petroleum ether. Physical and spectral data of the obtained tosyl imine match those previously reported.[35] Mp 107–108 °C (lit.:[38b] mp 116 °C, lit.:[38a] mp 104 °C).

To a solution of *N*-benzylidene-4-methylbenzenesulfonamide (0.26 g, 1.0 mmol, 1 equiv), in THF (3 mL), cooled at −15 °C was added allylmagnesium chloride (0.75 mL, 2 M in THF, 1.5 mmol, 1.5 equiv). The reaction mixture was stirred for 5 h at −15 °C and quenched by addition of an aqueous saturated NH_4Cl solution (7 mL). The aqueous layer was extracted with EtOAc (3×10 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O 60/40) afforded **33** (282 mg, 0.940 mmol, 94%) as white crystals; mp 77–78 °C (lit.:[39] mp 78 °C); R_f: 0.70 (petroleum ether/Et_2O 20/80); IR ($CHBr_3$) 3250, 2900, 1640, 1600, 1495, 1455, 1320, 1290, 1160, 1090, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61–7.55 (m, 2H), 7.19–7.06 (m, 7H), 5.53 (m, 1H), 5.44 (d, J=7.0 Hz, 1H), 5.08–5.00 (m, 2H), 4.39 (dt, J=7.0, 7.0 Hz, 1H), 2.58–2.39 (m, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.9 (s), 140.3 (s), 137.5 (s), 133.1 (d), 129.2 (d, 2C), 128.2 (d, 2C), 127.1 (d), 127.0 (d, 2C), 126.5 (d, 2C), 118.9 (t), 57.2 (d), 41.7 (t), 21.3 (q); EIMS *m/z* (relative intensity) 262 (6), 261 (18), 260 ($M-C_3H_5^+$, 100), 156 (5), 155 (54), 104 (7), 91 (60), 65 (8).

5.19. *N*-Allyl-4-methyl-*N*-[2-oxo-3-(triphenyl-λ^5-phosphoranylidene)propyl]benzenesulfonamide (34). Typical procedure

To a solution of protected allylamine **28** (0.15 g, 0.7 mmol, 1.1 equiv) in anhydrous THF (3 mL) was added dropwise a solution of *n*-BuLi (0.28 mL, 2.5 M in hexanes, 0.7 mmol, 1.1 equiv). The reaction mixture was stirred for 10 min at rt and neat triphenylchloroacetonylphosphorane (0.225 g, 0.64 mmol, 1 equiv) was added at once. After stirring at rt for 5 h, the reaction mixture was poured into water (5 mL). The aqueous layer was extracted with EtOAc (3×10 mL) and the combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc and then EtOAc/EtOH 90/10) allowed to isolate phosphorane **34** (285 mg, 0.54 mmol, 85%) as a viscous yellow oil; R_f: 0.25 (EtOAc); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.77–7.42 (m, 17H), 7.24–7.18 (m, 2H), 5.72 (ddt, J=16.5, 9.9, 6.5 Hz, 1H), 5.15 (dd, J=16.5, 1.3 Hz, 1H), 5.09 (m, 1H), 4.13 (br s, 1H), 3.99 (d, J=6.5 Hz, 2H), 3.80 (s, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.0 (s), 142.7 (s), 137.2 (s), 133.0 (d, $^3J_{C-P}$=10.3 Hz, 6C), 132.2 (d), 132.0 (d, $^4J_{C-P}$=2.9 Hz, 3C), 129.3 (d, 2C), 128.7 (d, $^2J_{C-P}$=12.2 Hz, 6C), 127.3 (d, 2C), 126.6 (s, $^1J_{C-P}$= 90.6 Hz, 3C), 118.8 (t), 54.3 (t, $^3J_{C-P}$=14.9 Hz), 51.6 (t), 51.3 (d), 21.3 (q); EIMS *m/z* (relative intensity) 479 (1), 279 (7), 278 (43), 277 (100), 201 (17), 199 (19), 183 (17), 152 (10), 77 (10).

5.19.1. *tert*-Butyl allyl[2-oxo-3-(triphenyl-λ^5-phosphoranylidene)propyl]carbamate (35). Yield: 80% from **29**; viscous yellow oil; R_f: 0.20 (EtOAc); IR (neat) 3050, 2990, 1680, 1420, 1160, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.69–7.41 (m, 15H), 5.84 (m, 1H), 5.22–5.04 (m, 2H), 4.06–3.74 (m, 2H), 3.97 (d, $^2J_{H-P}$=25.8 Hz, 1H), 3.81 (s, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.1 (s), 155.7 (s), 133.8 (d), 132.9 (d, $^3J_{C-P}$=10.1 Hz, 6C), 131.9 (d, 3C), 128.7 (d, $^2J_{C-P}$=12.2 Hz, 6C), 126.8 (s, $^1J_{C-P}$= 90.5 Hz, 3C), 116.4 (t), 79.2 (s), 54.4 (t, $^3J_{C-P}$=13.5 Hz), 50.2 (t), 48.7 (d, $^1J_{C-P}$=109.1 Hz), 28.3 (q, 3C).

5.19.2. *tert*-Butyl but-3-enyl[2-oxo-3-(triphenyl-λ^5-phosphoranylidene)propyl]carbamate (36). Yield: 74% from **30**; viscous yellow oil; R_f: 0.10 (EtOAc); IR (neat) 3050, 2970, 2930, 1680, 1530, 1480, 1440, 1385, 1240, 1170, 1105, 755, 720, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (rotamers) 7.59–7.24 (m, 15H), 5.65 (m, 1H), 4.98–4.81 (m, 2H), 3.89–3.64 (m, 3H), 3.32 (m, 2H), 2.23 (m, 2H), 1.35 and 1.32 (2s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (rotamers) 189.0 and 188.8 (s), 155.6 (s), 135.5 and 135.3 (d), 132.8 (d, $^3J_{C-P}$=10.1 Hz, 6C), 131.9 (d, 3C), 128.6 (d, $^2J_{C-P}$=12.1 Hz, 6C), 126.6 (s, $^1J_{C-P}$=90.6 Hz, 3C), 116.0 (t), 78.9 (s), 55.3 and 54.8 (t, $^3J_{C-P}$=13.7 Hz), 48.8 (d, $^1J_{C-P}$=109.1 Hz), 47.5 (t), 32.8 and 32.3 (t), 28.2 (q, 3C).

5.19.3. Benzyl but-3-enyl[2-oxo-3-(triphenyl-λ^5-phosphoranylidene)propyl]carbamate (37). Yield: 90% from **31**; viscous colorless oil; R_f: 0.25 (EtOAc); IR (neat) 2970, 2930, 1690, 1540, 1435, 1385, 1225, 1105, 735, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (rotamers) 7.70–7.10 (m, 20H), 5.77 (m, 1H), 5.29 and 5.16 (2s, 2H), 5.20–4.94 (m, 2H), 4.02 and 3.93 (2s, 2H), 3.77 (d, $^2J_{H-P}$=24.3 Hz, 1H), 3.49 (m, 2H), 2.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (rotamers) 188.5 and 188.3 (s), 156.3 (s), 137.0 (s), 135.4 (d), 132.9 (d, $^3J_{C-P}$=10.3 Hz, 6C), 132.0 (d, $^4J_{C-P}$= 2.8 Hz, 3C), 128.9 and 128.7 (d, 2C), 128.7 (d, $^2J_{C-P}$= 12.4 Hz, 6C), 128.2 and 128.1 (d, 2C), 127.5 and 127.4 (d), 126.6 (s, $^1J_{C-P}$=91.0 Hz, 3C), 116.5 and 116.4 (t),

66.7 (t), 55.0 (t, $^3J_{C-P}$=14.6 Hz), 49.4 (d, $^1J_{C-P}$=108.5 Hz), 48.1 (t), 32.7 and 32.3 (t).

5.19.4. 4-Methyl-*N*-[2-oxo-3-(triphenyl-λ^5-phosphoranylidene)propyl]-*N*-(1-phenylbut-3-enyl)benzenesulfonamide (39). Yield: 57% from **33**; viscous yellow oil; R_f: 0.30 (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76–7.03 (m, 24H), 5.50 (ddt, J=17.1, 10.3, 6.8 Hz, 1H), 5.07 (dd, J=10.3, 5.3 Hz, 1H), 4.90 (dd, J=17.1, 1.8 Hz, 1H), 4.84 (br d, J=10.3 Hz, 1H), 3.86 ($d_{syst\ AB}$, J=17.6 Hz, 1H), 3.78 ($d_{syst\ AB}$, J=17.6 Hz, 1H), 3.72 (br d, $^2J_{H-P}$=24.0 Hz, 1H), 2.84 (m, 1H), 2.49 (m, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.9 (s), 142.7 (s), 138.1 (s), 137.9 (s), 134.5 (d), 133.0 (d, $^3J_{C-P}$=10.2 Hz, 6C), 131.9 (d, $^4J_{C-P}$=2.2 Hz, 3C), 129.2 (d, 2C), 128.9 (d, 2C), 128.6 (d, $^2J_{C-P}$=12.1 Hz, 6C), 128.3 (d), 127.5 (d, 2C), 127.1 (d, 2C), 126.1 (s, $^1J_{C-P}$=91.1 Hz, 3C), 117.1 (t), 61.2 (d), 51.7 (t, $^3J_{C-P}$=14.8 Hz), 51.2 (d, $^1J_{C-P}$=103.8 Hz), 35.6 (t), 21.3 (q).

5.20. 1-(Benzyl but-3-enylamino)-3-(triphenyl-λ^5-phosphoranylidene)propan-2-one (38)

To a solution of protected homoallylamine **32** (0.5 g, 3.1 mmol, 1.1 equiv) in CH_3CN (30 mL) at rt, were added Et_3N (0.87 mL, 6.2 mmol, 2 equiv), triphenylchloroacetonylphosphorane (1.0 g, 2.8 mmol, 1 equiv), and n-Bu_4NI (0.57 g, 1.5 mmol, 0.5 equiv). The reaction mixture was stirred at rt for 36 h and then heated at 50 °C for 7 h. After cooling to rt, the reaction mixture was hydrolyzed with a saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (3×60 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc/MeOH 98/2) afforded the phosphorane **38** (0.884 g, 1.85 mmol, 60%) as a viscous yellow oil; R_f: 0.30 (EtOAc/MeOH 98/2); IR (neat) 2920, 1730, 1520, 1435, 1390, 1140, 1105, 745, 720, 690, 660, 650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71–7.26 (m, 20H), 5.79 (ddt, J=17.3, 10.3, 7.0 Hz, 1H), 4.99 (dd, J=17.3, 1.8 Hz, 1H), 4.90 (br d, J=10.3 Hz, 1H), 4.44 (br d, $^2J_{H-P}$=25.7 Hz, 1H), 3.78 (s, 2H), 3.18 (s, 2H), 2.66 (t, J=7.0 Hz, 2H), 2.31 (apparent q, J=7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.5 (s), 139.8 (s), 137.1 (d), 132.9 (d, $^3J_{C-P}$=10.2 Hz, 6C), 131.9 (d, $^4J_{C-P}$=2.6 Hz, 3C), 128.7 (d, $^2J_{C-P}$=11.9 Hz, 6C), 128.4 (d, 2C), 128.0 (d, 2C), 127.0 (s, $^1J_{C-P}$=90.6 Hz, 3C), 126.6 (d), 115.1 (t), 63.0 (t, $^3J_{C-P}$=13.5 Hz), 59.0 (t), 53.7 (t), 50.8 (d, $^1J_{C-P}$=108.5 Hz), 31.7 (t).

5.21. Formation of azadienes by Wittig reaction; general procedure

With formaldehyde. To a solution of ylide (1 equiv) in anhydrous Et_2O (c 6–40 mmol L^{-1}) at rt was added a solution of formaldehyde (37% in water, 100 equiv). The biphasic reaction mixture was stirred for 3 h at rt. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel allowed to isolate the corresponding azadiene.

With acetaldehyde. To a solution of ylide (1 equiv) in anhydrous THF (c 0.1–0.2 mol L^{-1}) at rt was added freshly distilled acetaldehyde (10 equiv). The reaction mixture was stirred for 3 h at rt. After concentration of the reaction mixture under reduced pressure, purification of the crude material by flash chromatography on silica gel allowed to isolate the corresponding azadiene.

5.21.1. *N*-Allyl-4-methyl-*N*-(2-oxobut-3-enyl)benzene sulfonamide (40). Yield: 42% from **34**, following the general procedure with formaldehyde; colorless oil. In order to avoid polymerization compound **40** has to be kept in solution (c ~0.2 M in Et_2O or CH_2Cl_2). R_f: 0.40 (petroleum ether/EtOAc 80/20); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76–7.70 (m, 2H), 7.35–7.29 (m, 2H), 6.51 (dd, J=17.6, 10.7 Hz, 1H), 6.32 (dd, J=17.6, 1.3 Hz, 1H), 5.86 (dd, J=10.7, 1.3 Hz, 1H), 5.66 (ddt, J=16.9, 9.9, 6.6 Hz, 1H), 5.19–5.13 (m, 2H), 4.19 (s, 2H), 3.84 (br d, J=6.6 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.4 (s), 143.4 (s), 136.4 (s), 132.8 (d), 132.0 (d), 129.5 (d, 2C), 129.4 (t), 127.3 (d, 2C), 120.0 (t), 53.3 (t), 51.0 (t), 21.4 (q).

5.21.2. *tert*-Butyl allyl(2-oxobut-3-enyl)carbamate (41). Yield: 74% from **35**, following the general procedure with formaldehyde; colorless oil. In order to avoid polymerization compound **41** has to be kept in solution (c ~0.2 M in Et_2O or CH_2Cl_2). R_f: 0.40 (petroleum ether/Et_2O 80/20); IR (neat) 3050, 1685, 1420, 1265, 740, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (rotamers) 6.41 and 6.40 (2dd, J=17.6, 10.3 Hz, 1H), 6.28 (dd, J=17.6, 1.5 Hz, 1H), 5.83 (dd, J=10.3, 1.5 Hz, 1H), 5.75 (m, 1H), 5.17–5.04 (m, 2H), 4.20 and 4.06 (2s, 2H), 3.93 and 3.84 (2d, J=5.7 Hz, 2H), 1.44 and 1.38 (2s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (rotamers) 195.3 (s), 155.5 and 155.0 (s), 133.6 and 133.5 (d), 133.2 (d), 128.7 and 128.6 (t), 117.4 and 116.6 (t), 80.2 (s), 53.7 and 53.3 (t), 50.5 and 50.3 (t), 28.1 and 28.0 (q, 3C); EIMS m/z (relative intensity) 171 (3), 170 (28), 169 (11), 152 (9), 114 (19), 70 (69), 57 (t-Bu$^+$, 100).

5.21.3. *tert*-Butyl but-3-enyl(2-oxopent-3-enyl)carbamate (42). Yield: 87% from **36**, following the general procedure with acetaldehyde; yellow oil; R_f: 0.55 (petroleum ether/EtOAc 70/30); IR (neat) 2975, 2929, 1689, 1639, 1422, 1397, 1365, 1241, 1168, 969, 913, 888, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (rotamers) 6.95 (dq, J=14.6, 7.0 Hz, 1H), 6.19 (m, 1H), 5.76 (m, 1H), 5.05 (m, 2H), 4.16 and 4.03 (2s, 2H), 3.34 and 3.28 (2t, J=7.0 Hz, 2H), 2.27 (m, 2H), 1.91 (apparent t, J=6.0 Hz, 3H), 1.48 and 1.39 (2s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (rotamers) 195.3 and 195.2 (s), 155.8 and 155.2 (s), 143.7 and 143.5 (d), 135.4 (d), 128.8 and 128.3 (d), 116.6 (t), 80.0 (s), 55.6 and 54.8 (t), 48.0 (t), 33.0 and 32.7 (t), 28.3 and 28.2 (q, 3C), 18.4 (q); EIMS m/z (relative intensity) 212 (M−$C_3H_5^+$, 8), 184 (12), 128 (20), 112 (32), 84 (64), 69 (32), 57 (100), 56 (13), 55 (17).

5.21.4. Benzyl but-3-enyl(2-oxopent-3-enyl)carbamate (43). Yield: 85% from **37**, following the general procedure with acetaldehyde; colorless oil; R_f: 0.35 (petroleum ether/Et_2O 70/30); IR (neat) 2920, 1705, 1690, 1640, 1470, 1440, 1425, 1225 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (rotamers) 7.39–7.23 (m, 5H), 6.93 (m, 1H), 6.16 (m, 1H), 5.74 (m, 1H), 5.17 and 5.09 (2s, 2H), 5.07–4.96 (m, 2H), 4.23 and 4.15 (2s, 2H), 3.38 (m, 2H), 2.29 (m, 2H), 1.90 and 1.87 (2dd, J=7.0, 1.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz)

δ (rotamers) 194.5 and 194.4 (s), 156.3 and 155.8 (s), 143.9 (d), 136.5 and 136.4 (s), 135.0 and 134.9 (d), 128.6 (d), 128.3 and 128.2 (d, 2C), 127.8 and 127.7 (d), 127.6 (d, 2C), 116.8 and 116.7 (t), 67.2 and 67.1 (t), 55.0 and 54.9 (t), 48.3 and 47.6 (t), 32.8 and 32.3 (t), 18.3 (q); EIMS *m/z* (relative intensity) 287 ($M^{+\bullet}$, 1), 246 (11), 202 (15), 174 (17), 91 (100), 69 (11).

5.21.5. 1-(Benzylbut-3-enylamino)pent-3-en-2-one (44). Yield: 53% from **38**, following the general procedure with acetaldehyde; bright yellow oil; R_f: 0.30 (petroleum ether/Et_2O 70/30); IR (neat): 2920, 1670, 1450, 1375, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.20 (m, 5H), 6.91 (dq, J=15.6, 6.6 Hz, 1H), 6.37 (dq, J=15.6, 1.6 Hz, 1H), 5.78 (ddt, J=16.9, 10.3, 7.0 Hz, 1H), 5.09–4.95 (m, 2H), 3.66 (s, 2H), 3.31 (s, 2H), 2.61 (m, 2H), 2.26 (m, 2H), 1.86 (dd, J=6.6, 1.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.0 (s), 142.7 (d), 138.6 (s), 136.5 (d), 129.0 (d), 128.9 (d, 2C), 128.1 (d, 2C), 127.0 (d), 115.5 (t), 62.1 (t), 58.6 (t), 53.8 (t), 31.6 (t), 18.1 (q); EIMS *m/z* (relative intensity) 243 ($M^{+\bullet}$, 1), 202 (9), 175 (11), 174 (79), 91 (100), 65 (7).

5.21.6. 4-Methyl-*N*-(2-oxobut-3-enyl)-*N*-(1-phenylbut-3-enyl)benzene sulfonamide (45). Yield: 62% from **39**, following the general procedure with formaldehyde; colorless oil. In order to avoid polymerization compound **45** has to be kept in solution (c ~0.2 M in Et_2O or CH_2Cl_2). R_f: 0.45 (petroleum ether/Et_2O 60/40); IR (neat) 3050, 2980, 2920, 1700, 1425, 1345, 1270, 1150, 1095, 750, 735, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.82–7.78 (m, 2H), 7.37–7.17 (m, 7H), 6.34 (dd, J=17.3, 10.3 Hz, 1H), 6.11 (dd, J=17.3, 1.5 Hz, 1H), 5.61 (dd, J=10.3, 1.5 Hz, 1H), 5.50 (ddt, 1H, J=16.9, 10.3, 6.8 Hz, 1H), 5.03 (dd, J=10.3, 5.5 Hz, 1H), 4.99–4.85 (m, 2H), 4.09 ($d_{syst\ AB}$, J=18.0 Hz, 1H), 3.88 ($d_{syst\ AB}$, J=18.0 Hz, 1H), 2.65 (m, 1H), 2.46 (s, 3H), 2.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.5 (s), 143.5 (s), 137.3 (s), 136.6 (s), 133.8 (d), 131.9 (d), 129.5 (d, 2C), 128.6 (d, 2C), 128.5 (t), 128.1 (d), 127.6 (d, 2C), 124.4 (d, 2C), 117.6 (t), 60.5 (d), 51.4 (t), 34.9 (t), 21.4 (q); EIMS *m/z* (relative intensity) 369 ($M^{+\bullet}$, 1), 329 (14), 328 (68), 314 (21), 184 (10), 155 (35), 132 (12), 131 (100), 91 (68).

5.22. General procedure for the RCM reaction applied to α-alkoxy enones

To a solution of diene (1 equiv) in anhydrous CH_2Cl_2 (c 2×10^{-2} to 5×10^{-3} mol L^{-1}), degassed by argon bubbling for 20 min, Grubbs catalyst **[Ru]-II**[15b] (0.025–0.15 equiv) was added. The reaction mixture was heated at 40 °C for 12 h. After cooling to rt and concentration under reduced pressure, the crude residue was purified by flash chromatography on silica gel.

5.22.1. 6*H*-Pyran-3-one (46).[40] Yield: 69% from **7**; colorless oil; R_f: 0.30 (petroleum ether/EtOAc 80/20); IR (neat) 2930, 2850, 1710, 1680, 1440, 1390, 1265, 1160, 1095, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12 (dt, J=10.5, 2.9 Hz, 1H), 6.19 (dt, J=10.5, 1.8 Hz, 1H), 4.39 (apparent t, J=2.6 Hz, 2H), 4.18 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.3 (s), 152.8 (d), 126.8 (d), 72.1 (t), 64.4 (t); EIMS *m/z* (relative intensity) 98 ($M^{+\bullet}$, 37), 69 (6), 68 (100), 53 (2); HRMS (CI^+, CH_4) calcd for $C_5H_7O_2$ ($M+H^+$) 99.0446. Found 99.0441.

5.22.2. 6-Isopropyl-6*H*-pyran-3-one (47). Yield: 87% from **22**; colorless oil; R_f: 0.60 (petroleum ether/EtOAc 80/20); IR (neat) 2960, 2930, 2870, 2810, 1695, 1465, 1385, 1260, 1160, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.99 (dd, J=10.7, 1.8 Hz, 1H), 6.12 (dd, J=10.7, 2.4 Hz, 1H), 4.22 ($d_{syst\ AB}$, J=16.2 Hz, 1H), 4.08–3.99 (m, 2H), 1.95 (m, 1H), 0.97 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.0 (s), 150.7 (d), 127.3 (d), 78.1 (d), 71.4 (t), 32.0 (d), 18.1 (q), 17.4 (q); EIMS *m/z* (relative intensity) 140 ($M^{+\bullet}$, 29), 110 (45), 98 (100), 97 (59), 95 (93), 70 (35), 69 (24), 68 (10), 67 (40), 65 (10), 55 (31); HRMS (CI^+, CH_4) calcd for $C_8H_{13}O_2$ ($M+H^+$) 141.0916. Found 141.0911.

5.22.3. 6-Triphenylmethyloxymethyl-6*H*-pyran-3-one (48). Yield: 68% from **23**; wax; R_f: 0.70 (petroleum ether/EtOAc 80/20); IR (neat) 3050, 2920, 2870, 1695, 1490, 1450, 1265, 1160, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.48–7.42 (m, 5H), 7.33–7.19 (m, 10H), 7.02 (dd, J=10.5, 1.8 Hz, 1H), 6.16 (dd, J=10.5, 2.2 Hz, 1H), 4.44 (m, 1H), 4.31 ($d_{syst\ AB}$, J=16.5 Hz, 1H), 4.10 (dd, J=16.5, 1.8 Hz, 1H), 3.41 (dd, J=9.9, 5.7 Hz, 1H), 3.26 (dd, J=9.9, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.5 (s), 149.3 (d), 143.5 (s, 3C), 128.5 (d, 6C), 127.8 (d, 6C), 127.2 (d), 127.1 (d, 3C), 86.7 (s), 73.1 (d), 71.2 (t), 64.5 (t); EIMS *m/z* (relative intensity) 244 (23), 243 (100), 166 (5), 165 (32), 105 (7), 77 (4); HRMS (ESI) calcd for $C_{25}H_{22}NaO_3$ ($M+Na^+$) 393.14612. Found 393.14636.

5.22.4. 6,7-Dihydrooxepin-3-one (49).[41] Yield: 58% from **8**; yellow oil; R_f: 0.35 (petroleum ether/EtOAc 80/20); IR (neat) 3020, 2920, 2860, 1655, 1265, 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.56 (dt, J=12.5, 4.4 Hz, 1H), 6.03 (dt, J=12.5, 1.8 Hz, 1H), 4.29 (s, 2H), 3.92 (t, J=5.5 Hz, 2H), 2.71–2.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.1 (s), 144.9 (d), 130.2 (d), 78.8 (t), 69.5 (t), 35.0 (t); EIMS *m/z* (relative intensity) 112 ($M^{+\bullet}$, 30), 85 (20), 84 (64), 82 (48), 81 (53), 69 (13), 56 (17), 55 (33), 54 (100), 53 (49), 51 (11); HRMS (CI^+, CH_4) calcd for $C_6H_9O_2$ ($M+H^+$) 113.0603. Found 113.0598.

5.22.5. 7-Isopropyl-6,7-dihydrooxepin-3-one (50). Yield: 90% from **24**; colorless oil; R_f: 0.30 (petroleum ether/Et_2O 80/20); IR (neat): 2960, 2870, 1665, 1630, 1395, 1345, 1275, 1125 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.54 (dt, J=12.3, 4.4 Hz, 1H), 6.00 (d, J=12.3, 1.8 Hz, 1H), 4.41 ($d_{syst\ AB}$, J=18.4 Hz, 1H), 4.15 ($d_{syst\ AB}$, J=18.4 Hz, 1H), 3.31 (apparent q, J=6.3 Hz, 1H), 2.61–2.54 (m, 2H), 1.74 (m, 1H), 0.97 (d, J=6.8 Hz, 3H), 0.93 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.7 (s), 145.3 (d), 129.5 (d), 84.7 (d), 78.1 (t), 37.5 (t), 33.2 (d), 18.5 (q), 17.7 (q); EIMS *m/z* (relative intensity) 154 ($M^{+\bullet}$, 10), 111 (41), 95 (14), 94 (20), 86 (11), 85 (21), 83 (100), 82 (82), 81 (94), 79 (11), 71 (11), 70 (12), 69 (21), 68 (79), 67 (11), 55 (43), 54 (25), 53 (47); HRMS (CI^+, CH_4) calcd for $C_9H_{15}O_2$ ($M+H^+$) 155.1072. Found 155.1068.

5.22.6. 7-Phenyl-6,7-dihydrooxepin-3-one (51). Yield: 93% from **25**; white solid; mp 126–128 °C; R_f: 0.60 (petroleum ether/EtOAc 80/20); IR ($CHBr_3$) 3020, 2880, 1665,

1630, 1395, 1345, 1275, 1125 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42–7.24 (m, 5H), 6.57 (ddd, J=12.5, 4.8, 4.4 Hz, 1H), 6.11 (d, J=12.5 Hz, 1H), 4.69 (dd, J=8.1, 4.8 Hz, 1H), 4.50 ($d_{syst\ AB}$, J=18.4 Hz, 1H), 4.32 ($d_{syst\ AB}$, J=16.9 Hz, 1H), 2.87–2.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.9 (s), 144.3 (d), 141.6 (s), 130.3 (d), 128.5 (d, 2C), 127.8 (d), 125.4 (d, 2C), 81.2 (d), 77.5 (t), 42.0 (t); EIMS m/z (relative intensity) 188 ($M^{+\bullet}$, 8), 157 (2), 129 (100), 104 (2), 82 (5), 77 (2), 54 (2); HRMS (CI^+, CH_4) calcd for $C_{12}H_{13}O_2$ ($M+H^+$) 189.0916. Found 189.0913.

5.22.7. 7,7-Dimethyl-6,7-dihydrooxepin-3-one (52). Yield: 67% from **26**; colorless oil; R_f: 0.40 (petroleum ether/EtOAc 80/20); IR (neat) 2970, 2930, 2870, 1675, 1465, 1390, 1370, 1275, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.64 (dt, J=11.2, 6.8 Hz, 1H), 6.10 (d, J=11.2 Hz, 1H), 4.07 (s, 2H), 2.43 (d, J=6.8 Hz, 2H), 1.24 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.2 (s), 142.5 (d), 133.1 (d), 75.1 (s), 70.2 (t), 39.6 (t), 26.9 (q, 2C); EIMS m/z (relative intensity) 140 ($M^{+\bullet}$, 15), 125 (9), 112 (3), 95 (100), 85 (26), 82 (15), 81 (14), 68 (10), 67 (36), 56 (10), 54 (22); HRMS (CI^+, CH_4) calcd for $C_8H_{13}O_2$ ($M+H^+$) 141.0916. Found 141.0920.

5.22.8. 7,8-Dihydro-6*H*-oxocin-3-one (53). Yield: 66% from **9**; white solid; mp 86–88 °C; R_f: 0.30 (petroleum ether/EtOAc 80/20); IR ($CHBr_3$) 2930, 2880, 1690, 1615, 1430, 1340, 1110, 985 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.00 (dt, J=15.6, 7.3 Hz, 1H), 6.64 (dt, J=15.6, 1.5 Hz, 1H), 4.00 (s, 2H), 3.49 (t, J=5.5 Hz, 2H), 2.54–2.45 (m, 2H), 1.92–1.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.3 (s), 151.0 (d), 125.6 (d), 76.2 (t), 69.3 (t), 28.1 (t), 27.6 (t); CI^+ MS m/z (relative intensity) 127 ($M+H^+$, 10), 109 (100), 106 (13); HRMS (CI^+, CH_4) calcd for $C_7H_{11}O_2$ ($M+H^+$) 127.0759. Found 127.0754.

5.22.9. 8-Isopropyl-7,8-dihydro-6*H*-oxocin-3-one (54) and (*E*,*E*)-8,16-diisopropyl-1,9-dioxacyclohexadeca-4,12-diene-3,11-dione (55). When the RCM reaction was performed on diene **27** following the general procedure, the purification by flash chromatography of the crude residue allowed to isolate **54** in 35% yield and **55** in 14% yield.

*Compound **54***: colorless oil; R_f: 0.60 (petroleum ether/EtOAc 80/20); IR (neat) 1950, 1875, 1720, 1675, 1465, 1385, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.39 (dt, J=12.9, 6.0 Hz, 1H), 5.78 (d, J=12.9 Hz, 1H), 4.34 ($d_{syst\ AB}$, J=18.0 Hz, 1H), 3.95 ($d_{syst\ AB}$, J=18.0 Hz, 1H), 3.19 (m, 1H), 2.56–2.23 (m, 2H), 1.90–1.65 (m, 3H), 1.00 (d, J=6.3 Hz, 3H), 0.94 (d, J=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.8 (s), 155.0 (d), 126.4 (d), 88.6 (d), 76.0 (t), 30.9 (d), 26.6 (t), 26.2 (t), 19.3 (q), 19.0 (q); EIMS m/z (relative intensity) 168 ($M^{+\bullet}$, 3), 125 (8), 111 (19), 108 (12), 97 (16), 96 (15), 95 (15), 87 (12), 82 (13), 81 (21), 79 (13), 69 (17), 68 (100), 67 (23), 55 (12); HRMS (CI^+, CH_4) calcd for $C_{10}H_{17}O_2$ ($M+H^+$) 169.1229. Found 169.1228.

*Compound **55***: white solid; mp 90–92 °C; R_f: 0.40 (petroleum ether/EtOAc 80/20); IR ($CHBr_3$) 2950, 1685, 1615, 1140, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98–6.85 (m, 2H), 6.50 (d, J=15.8 Hz, 2H), 4.20 ($d_{syst\ AB}$, J=16.5 Hz, 2H), 3.98 ($d_{syst\ AB}$, J=16.5 Hz, 2H), 3.05–2.96 (m, 2H), 2.64–2.48 (m, 2H), 2.37–2.25 (m, 2H), 2.00–1.86 (m, 2H), 1.80–1.58 (m, 4H), 0.88 (d, J=6.6 Hz, 6H), 0.83 (d, J=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.9 (s, 2C), 194.2 (d, 2C), 126.2 (d, 2C), 84.8 (d, 2C), 74.3 (t, 2C), 29.8 (d, 2C), 28.6 (t, 2C), 28.0 (t, 2C), 18.7 (q, 2C), 16.5 (q, 2C); EIMS m/z (relative intensity) 336 ($M^{+\bullet}$, 45), 294 (18), 293 (100), 275 (34), 189 (15), 161 (12), 147 (12), 135 (11), 133 (15), 121 (15), 119 (10), 109 (18), 107 (21), 105 (13), 95 (30), 93 (17), 91 (15), 83 (15), 82 (19), 81 (22), 79 (25), 77 (11), 71(11), 70 (10), 69 (35), 67 (19), 55 (33); HRMS (CI^+, CH_4) calcd for $C_{20}H_{33}O_2$ ($M+H^+$) 337.2379. Found 337.2370.

5.22.10. (*E*,*E*)-1,10-Dioxacyclooctadeca-4,13-diene-3,12-dione (57). Yield: 75% from **56**; white solid; mp 90–92 °C; R_f: 0.30 (petroleum ether/EtOAc 80/20); IR ($CHBr_3$) 2925, 2860, 1690, 1665, 1615, 1140, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.23 (apparent dt, J=15.8, 5.5 Hz, 2H), 6.57 (apparent dt, J=15.8, 1.8 Hz, 2H), 4.04 (s, 4H), 3.49 (t, J=5.1 Hz, 4H), 2.35–2.25 (m, 4H), 1.80–1.62 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.7 (s, 2C), 149.5 (d, 2C), 124.4 (d, 2C), 76.0 (t, 2C), 71.2 (t, 2C), 32.1 (t, 2C), 29.5 (t, 2C), 24.7 (t, 2C); EIMS m/z (relative intensity) 280 ($M^{+\bullet}$, 2), 141 (13), 140 (12), 125 (20), 124 (13), 123 (14), 122 (12), 111 (12), 109 (33), 108 (20), 107 (19), 98 (11), 97 (18), 96 (10), 95 (32), 85 (11), 83 (20), 82 (16), 81 (100), 80 (23), 79 (42), 69 (11), 68 (27), 67 (41), 66 (13), 55 (26), 54 (21), 53 (24); HRMS (CI^+, CH_4) calcd for $C_{16}H_{25}O_4$ ($M+H^+$) 281.1753. Found 281.1759.

5.23. General procedure for the RCM reaction applied to α-amino enones

To a solution of diene (1 equiv) in anhydrous CH_2Cl_2 (c 5×10^{-3} mol L^{-1}), degassed by argon bubbling for 20 min, Grubbs catalyst **[Ru]-II**[15b] (0.025–0.05 equiv) was added. The reaction mixture was heated at 40 °C for 12 h. After cooling to rt and concentration under reduced pressure, the crude residue was purified by flash chromatography on silica gel.

5.23.1. 1-[(4-Methylphenyl)-1-sulfonyl]-1,6-dihydro-2*H*-pyridine-3-one (60).[42] Yield: 65% from **40**; colorless oil; R_f: 0.30 (petroleum ether/EtOAc 70/30); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.70 (m, 2H), 7.39–7.65 (m, 2H), 6.93 (dt, J=10.5, 3.7 Hz, 1H), 6.07 (dt, J=10.5, 2.2 Hz, 1H), 3.98 (m, 2H), 3.81 (s, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.9 (s), 144.7 (d), 144.3 (s), 132.8 (s), 129.9 (d, 2C), 127.8 (d), 127.5 (d, 2C), 52.7 (t), 44.3 (t), 21.4 (q); EIMS m/z (relative intensity) 251 ($M^{+\bullet}$, 7), 155 (4), 96 (29), 91 (18), 68 (100), 65 (9); HRMS (ESI) calcd for $C_{12}H_{13}NNaO_3S$ ($M+Na^+$) 274.05084. Found 274.05094.

5.23.2. *tert*-Butyl 3-oxo-3,6-dihydro-2*H*-pyridine-1-carboxylate (61).[43] Yield: 80% from **41**; colorless oil; R_f: 0.45 (petroleum ether/EtOAc 70/30); IR (neat) 3050, 2980, 1690, 1420, 1380, 1265, 740, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.00 (m, 1H), 6.13 (dt, J=10.3, 2.2 Hz, 1H), 4.20 (m, 2H), 4.07 (s, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.2 (s), 154.1 (s), 147.1 (br d), 127.5 (d), 81.0 (s), 51.9 (br t), 42.7 (br t), 28.3 (q, 3C); EIMS m/z (relative intensity) 197 ($M^{+\bullet}$, 12), 142 (13), 141

(33), 128 (28), 97 (27), 68 (45), 57 (*t*-Bu$^+$, 100), 56 (12); HRMS (ESI) calcd for $C_{10}H_{15}NNaO_3$ (M+Na$^+$) 220.09441. Found 220.09442.

5.23.3. *tert*-Butyl 3-oxo-2,3,6,7-tetrahydroazepin-1-carboxylate (62). Yield: 90% from **42**; colorless oil; R_f: 0.45 (petroleum ether/EtOAc 70/30); IR (neat) 2970, 1690, 1420, 1370, 1265, 1165, 740, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (rotamers) 6.45 (m, 1H), 5.97 (dt, J=12.5, 1.8 Hz, 1H), 4.24 and 4.12 (2s, 2H), 3.55 (m, 2H), 2.66 (m, 2H), 1.45 and 1.40 (2s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (rotamers) 201.6 and 201.5 (s), 154.4 (s), 144.3 and 143.5 (d), 130.3 and 130.2 (d), 80.5 and 80.3 (s), 58.0 and 57.8 (t), 45.3 and 44.9 (t), 32.5 and 30.9 (t), 28.2 and 28.1 (q, 3C); EIMS *m/z* (relative intensity) 211 (M$^{+\bullet}$, 1), 155 (8), 138 (12), 111 (60), 110 (20), 83 (15), 82 (13), 81 (26), 68 (13), 57 (*t*-Bu$^+$, 100); HRMS (ESI) calcd for $C_{11}H_{17}NNaO_3$ (M+Na$^+$) 234.11006. Found 234.11013.

5.23.4. Benzyl 3-oxo-2,3,6,7-tetrahydroazepin-1-carboxylate (63). Yield: 97% from **43**; colorless oil; R_f: 0.45 (petroleum ether/EtOAc 60/40); IR (neat): 2970, 1700, 1660, 1460, 1425, 1260, 1215, 1180, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (rotamers) 7.40–7.28 (m, 5H), 6.51 and 6.43 (2dt, J=12.5, 4.6 Hz, 1H), 6.01 (m, 1H), 5.17 and 5.13 (2s, 2H), 4.35 and 4.28 (2s, 2H), 3.65 (m, 2H), 2.77–2.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (rotamers) 200.9 and 200.7 (s), 155.3 and 154.9 (s), 144.3 and 143.6 (d), 136.2 and 136.0 (s), 130.3 and 130.2 (d, 2C), 128.5 and 128.4 (d), 128.1 and 128.0 (d), 127.8 and 127.7 (d, 2C), 67.5 and 67.4 (t), 58.2 and 57.7 (t), 45.6 and 45.2 (t), 32.5 and 31.1 (t); EIMS *m/z* (relative intensity) 245 (M$^{+\bullet}$, 13), 217 (5), 173 (11), 91 (100), 81 (13), 65 (11); HRMS (ESI) calcd for $C_{14}H_{15}NNaO_3$ (M+Na$^+$) 268.09441. Found 268.09431.

5.23.5. 1-[(4-Methylphenyl)-1-sulfonyl]-7-phenyl-2,3,6,7-tetrahydroazepin-3-one (64). Yield: 99% from **45**; colorless oil; R_f: 0.45 (petroleum ether/EtOAc 70/30); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56–7.51 (m, 2H), 7.35–7.17 (m, 7H), 6.62 (ddd, J=11.8, 8.1, 5.5 Hz, 1H), 5.90 (br d, J=11.8 Hz, 1H), 5.40 (dd, J=10.7, 5.5 Hz, 1H), 4.37 (m, 1H), 3.83 ($d_{syst\ AB}$, J=18.4 Hz, 1H), 2.96 (ddd, J=16.2, 8.1, 5.5 Hz, 1H), 2.78 (m, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.6 (s), 143.5 (s), 140.9 (d), 139.7 (s), 136.8 (s), 133.1 (d), 129.4 (d, 2C), 128.8 (d, 2C), 127.8 (d), 127.2 (d, 2C), 126.1 (d, 2C), 58.4 (d), 53.9 (t), 35.2 (t), 31.3 (q); EIMS *m/z* (relative intensity) 341 (M$^{+\bullet}$, 3), 186 (31), 158 (21), 157 (21), 130 (46), 129 (36), 128 (14), 118 (27), 115 (13), 105 (10), 104 (100), 91 (84), 65 (13); HRMS (ESI) calcd for $C_{19}H_{19}NNaO_3S$ (M+Na$^+$) 364.09779. Found 364.09817.

5.24. Synthesis of the inhibitor of cathepsin K, 65

5.24.1. (2-Pyridyl)sulfonyl chloride.[44] To a solution of 2-mercaptopyridine (2.0 g, 18 mmol, 1 equiv) in concentrated sulfuric acid (50 mL), at 0 °C, was added dropwise an aqueous sodium hypochlorite solution (112 mL, 12%). At the end of the addition, the reaction mixture was stirred for a further 30 min at 0 °C and then diluted with water (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2×22 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford (2-pyridyl)sulfonyl chloride as a colorless oil. Physical and spectral data match those previously reported.[19] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.85 (m, 1H), 8.25–8.10 (m, 2H), 7.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.8 (s), 150.6 (d), 139.2 (d), 129.3 (d), 121.9 (d).

5.24.2. *N*-(But-3-enyl)-2-pyridine sulfonamide (67). To a suspension of but-3-enylammonium chloride **66**[14] (0.87 g, 8.13 mmol, 1 equiv) in CH_2Cl_2 (40 mL), at 0 °C, was added triethylamine (3.42 mL, 24.4 mmol, 3 equiv). A solution of (2-pyridyl)sulfonyl chloride (1.59 g, 8.95 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) was then added dropwise. After 20 min at 0 °C, the reaction mixture was stirred for 14 h at rt and then hydrolyzed with a saturated aqueous NH_4Cl solution (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 70/30 and then 80/20) allowed to isolate **67** (1.43 g, 7.14 mmol, 88%) as a colorless oil; R_f: 0.25 (petroleum ether/EtOAc 70/30); IR (neat) 3270 (broad, NH), 3070, 2980, 2925, 1730, 1640, 1580, 1565, 1425, 1325, 1165, 1120, 1080, 980, 920, 780, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.74 (m, 1H), 8.15–7.90 (m, 2H), 7.60 (m, 1H), 6.00 (m, 1H), 5.70 (m, 1H), 5.10–4.95 (m, 2H), 3.35 (m, 2H), 2.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.2 (s), 149.8 (d), 138.1 (d), 134.2 (d), 126.6 (d), 122.1 (d), 117.4 (t), 42.5 (t), 33.7 (t); EIMS *m/z* (relative intensity) 172 (8), 171 (100), 107 (18), 79 (12), 78 (63), 51 (13); HRMS (ESI) calcd for $C_9H_{12}N_2NaO_2S$ (M+Na$^+$) 235.05117. Found 235.05115.

5.24.3. *N*-But-3-enyl-*N*-[2-oxo-3-(triphenyl-λ^5-phosphoranylidene)]-2-pyridine sulfonamide (68). To a solution of protected homoallylamine **67** (1.3 g, 6.5 mmol, 1.1 equiv) in anhydrous THF (35 mL), at 0 °C, was added dropwise a solution of *n*-BuLi (2.6 mL, 2.5 M in hexanes, 6.5 mmol, 1.1 equiv). The reaction mixture was stirred for 5 min at rt and solid triphenylchloroacetonylphosphorane (2.06 g, 5.85 mmol, 1 equiv) was added in one portion. After stirring for 22 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with EtOAc (3×30 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc 98/2 to 95/5) allowed to isolate phosphorane **68** (2.83 g, 5.48 mmol, 94%) as a pale yellow solid, which decomposed at $T \leq 50$ °C; R_f: 0.15 (EtOAc/EtOH 98/2); IR (neat) 3050, 2980, 1735, 1575, 1565, 1540, 1435, 1425, 1395, 1340, 1265, 1170, 1110, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.54 (m, 1H), 7.96 (m, 1H), 7.77 (m, 1H), 7.64–7.41 (m, 15H), 7.30 (m, 1H), 5.72 (ddt, J=17.3, 10.3, 7.0 Hz, 1H), 5.05–4.92 (m, 2H), 4.04 (br d, $^2J_{H-P}$=24.3 Hz, 1H), 3.98 (s, 2H), 3.61 (m, 2H), 2.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.2 (s, $^2J_{C-P}$=3.6 Hz), 158.1 (s), 149.7 (d), 137.5 (d), 134.9 (d), 132.9 (d, $^3J_{C-P}$=10.3 Hz, 6C), 132.1 (d, $^4J_{C-P}$=2.7 Hz, 3C), 128.7 (d, $^2J_{C-P}$=12.3 Hz, 6C), 126.4 (s, $^1J_{C-P}$=91.0 Hz, 3C), 126.0 (d), 122.2 (d), 116.6 (t), 56.0 (t, $^3J_{C-P}$=15.0 Hz), 50.8 (d, $^1J_{C-P}$=109.8 Hz), 49.5 (t), 32.9 (t). Anal. Calcd for

$C_{30}H_{29}N_2O_3PS$: C, 68.16; H, 5.53; N, 5.30. Found: C, 67.98; H, 5.51; N, 5.11.

5.24.4. *N*-But-3-enyl-*N*-(2-oxopent-3-enyl)-2-pyridine sulfonamide (69). The Wittig reaction was performed on ylide **68** (0.57 g, 1.1 mmol, 1 equiv) in THF (10 mL) with acetaldehyde (0.52 mL, 11 mmol, 10 equiv) according to the general procedure. Purification of the crude residue by flash chromatography on silica gel (petroleum ether/EtOAc 70/30) afforded diene **69** (304 mg, 1.03 mmol, 94%) as a colorless oil. In order to avoid polymerization compound **69** has to be kept in solution ($c \sim 0.2$ M in CH_2Cl_2). R_f: 0.35 (petroleum ether/EtOAc 70/30); IR (neat) 2979, 2920, 1710, 1685, 1640, 1575, 1425, 1340, 1170, 1115, 920, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.64 (m, 1H), 7.92–7.82 (m, 2H), 7.46 (m, 1H), 6.92 (m, 1H), 6.25 (m, 1H), 5.63 (m, 1H), 5.20–4.90 (m, 2H), 4.32 (s, 2H), 3.40 (t, J=7.5 Hz, 2H), 2.22 (m, 2H), 1.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.0 (s), 157.7 (s), 149.7 (d), 144.5 (d), 137.7 (d), 134.3 (d), 128.0 (d), 126.5 (d), 121.9 (d), 117.0 (t), 55.7 (t), 48.9 (t), 32.6 (t), 18.3 (q); EIMS *m*/*z* (relative intensity) 253 ($M-C_3H_5^+$, 22), 226 (12), 225 (91), 211 (16), 171 (100), 152 (18), 144 (12), 133 (12), 110 (39), 107 (23), 82 (13), 79 (14), 78 (92), 69 (34), 67 (14), 55 (29), 51 (15).

5.24.5. 1-(Pyridine-2-sulfonyl)-2,3,6,7-tetrahydroazepin-3-one (70). The RCM reaction was performed on diene **69** (0.44 g, 1.5 mmol, 1 equiv) in anhydrous degassed CH_2Cl_2 (150 mL, 0.01 M) in the presence of Grubbs catalyst **[Ru]-II**[15b] (32 mg, 0.037 mmol, 0.025 equiv) following the general procedure. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc 50/50) afforded azepanone **70** (363 mg, 1.44 mmol, 96%) as a yellowish gray solid; mp 98–100 °C; R_f: 0.30 (petroleum ether/EtOAc 50/50); IR (neat) 2900, 1660, 1425, 1340, 1175, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.63 (m, 1H), 7.93–7.86 (m, 2H), 7.48 (m, 1H), 6.42 (dt, J=12.5, 4.6 Hz, 1H), 5.96 (dt, J=12.5, 1.9 Hz, 1H), 4.25 (s, 2H), 3.65 (t, J=5.7 Hz, 2H), 2.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.1 (s), 157.2 (s), 149.9 (d), 143.8 (d), 138.0 (d), 130.2 (d), 126.8 (d), 122.1 (d), 59.7 (t), 47.9 (t), 33.7 (t); EIMS *m*/*z* (relative intensity) 188 (3), 171 (8), 120 (17), 110 (100), 82 (30), 81 (55), 80 (23), 78 (42), 55 (13), 54 (20), 53 (22), 52 (12), 51 (26). Anal. Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10. Found: C, 52.34; H, 4.61; N, 11.03.

5.24.6. 4-Bromo-1-(pyridine-2-sulfonyl)azepan-3-one (71). To a suspension of copper cyanide (269 mg, 3.0 mmol, 2 equiv) in THF (14 mL), at −20 °C, was added dropwise a solution of *n*-BuLi (1.31 mL, 2.28 M in hexanes, 3.0 mmol, 2 equiv). The resulting brown solution was stirred for 30 min at −20 °C and then cooled to −50 °C. A DIBAL-H solution (4.96 mL, 1.21 M in toluene, 6.0 mmol, 4 equiv) was added dropwise. After 1 h stirring, at −50 °C, a solution of enone **70** (378 mg, 1.5 mmol, 1 equiv) in THF (5 mL) was added dropwise. After stirring for 2 h at −50 °C, HMPA (780 μL, 4.5 mmol, 3 equiv) and a solution of methyllithium (0.95 mL, 1.6 M in Et_2O, 1.5 mmol, 1 equiv) were added successively, and the solution was stirred for 15 min at −50 °C. Bromine (0.8 mL, 15.5 mmol, 10.3 equiv) was added dropwise and the reaction mixture was warmed to −20 °C over 1 h. The reaction was quenched with water (20 mL) and EtOAc (30 mL) was added to the reaction mixture. The aqueous layer was separated and extracted with EtOAc (2×30 mL). The combined organic layers were washed with saturated aqueous sodium metabisulfite (30 mL), water (2×30 mL), and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture (0.77 g) was used without purification in the next step. R_f: 0.50 (petroleum ether/EtOAc 60/40); IR (neat) 2923, 2853, 1732, 1339, 1172, 1116, 1036, 898, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.68 (m, 1H), 7.99–7.92 (m, 2H), 7.53 (m, 1H), 5.11 (m, 1H), 4.43 (dd, J=18.5, 1.1 Hz, 1H), 4.18 ($d_{syst\ AB}$, J=18.5 Hz, 1H), 3.69 (m, 1H), 3.16 (m, 1H), 2.38 (m, 1H), 2.16–1.99 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.9 (s), 157.0 (s), 150.2 (d), 138.3 (d), 127.1 (d), 122.4 (d), 58.1 (t), 54.8 (d), 50.7 (t), 34.1 (t), 27.8 (t); EIMS *m*/*z* (relative intensity) 253 (1), 225 (16), 189 (100), 171 (9), 162 (15), 133 (14), 110 (10), 96 (10), 84 (21), 83 (25), 82 (22), 80 (22), 79 (64), 78 (75), 55 (26), 51 (23).

5.24.7. 4-Azido-1-(pyridine-2-sulfonyl)azepan-3-one (72). To a suspension of sodium azide (487.5 mg, 7.5 mmol, 5 equiv) in DMF (9 mL) at rt, was added a solution of crude bromoketone **71** (0.77 g) in DMF (15 mL). The reaction mixture was stirred for 2.5 h at rt, then hydrolyzed with water (40 mL) and diluted with EtOAc (80 mL). The aqueous layer was extracted with EtOAc (80 mL) and the combined organic layers were washed with brine (3×40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 60/40) afforded the azidoketone **72** (198.5 mg, 0.67 mmol, 45% from **70**) as an oil; R_f: 0.50 (petroleum ether/EtOAc 50/50); IR (neat) 2923, 2853, 2100, 1727, 1337, 1172, 1116, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.69 (m, 1H), 7.98–7.93 (m, 2H), 7.53 (m, 1H), 4.75–4.59 (m, 2H), 4.10 (m, 1H), 3.78 ($d_{syst\ AB}$, J=18.8 Hz, 1H), 2.77 (m, 1H), 2.24–1.88 (m, 3H), 1.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.4 (s), 157.0 (s), 150.1 (d), 138.3 (d), 127.1 (d), 122.4 (d), 66.3 (d), 58.5 (t), 50.8 (t), 30.3 (t), 28.2 (t); EIMS *m*/*z* (relative intensity) 267 ($M-N_2^+$, 18), 207 (26), 171 (29), 125 (100), 124 (65), 97 (44), 79 (61), 69 (35), 51 (25).

5.24.8. *tert*-Butyl 4-methyl-1-oxo-1-[3-oxo-1-(pyridine-2-sulfonyl)azepan-4-ylamino]pentan-2-ylcarbamate (74). To a solution of azidoketone **72** (197.7 mg, 0.64 mmol, 1 equiv) in MeOH (40 mL), at rt, were added 37% aqueous HCl (170 μL) and Pd/C (58 mg, 10% w/w, 0.05 mmol, 8.4 mol %). The reaction mixture was then stirred for 16 h at rt, and filtered through Celite. After concentration under reduced pressure, the crude hydrochloride salt **73** was used directly in the next step.

To a solution of the crude hydrochloride salt **73** (0.64 mmol, 1 equiv) in CH_2Cl_2 (8.6 mL), at 0 °C, were added successively *N*-Boc-L-leucine (219.1 mg, 0.95 mmol, 1.5 equiv), HOBt (129.7 mg, 0.96 mmol, 1.5 equiv), and EDCI (184 mg, 0.96 mmol, 1.5 equiv). After being stirred for 10 min at 0 °C, Et_3N (0.27 mL, 1.92 mmol, 2 equiv) was added. After 1.5 h at 0 °C, the reaction mixture was stirred for 18 h at rt, then diluted with EtOAc (40 mL) and hydrolyzed with aqueous 1 M HCl (30 mL). The organic layer was separated and washed with a saturated aqueous K_2CO_3 solution (30 mL), water (30 mL), and brine (30 mL), dried

over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (CH_2Cl_2/MeOH 99/1) afforded the azepanone **74** (156.9 mg, 0.33 mmol, 51%) as a colorless amorphous solid; R_f: 0.45 (CH_2Cl_2/MeOH 97/3); IR (neat) 3306, 2926, 1692, 1655, 1505, 1339, 1170, 1117, 1040, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (diastereoisomers) 8.69 (m, 1H), 8.02–7.90 (m, 2H), 7.53 (m, 1H), 7.14 and 7.06 (2d, J=6.0 Hz, 1H), 5.11 (m, 1H), 4.99 and 4.95 (2d, J=7.5 and 8.0 Hz, 1H), 4.78 and 4.74 (2dd, J=19.1, 1.5 and 1.0 Hz, 1H), 4.23–4.04 (m, 2H), 3.83 (dd, J=19.1, 1.5 Hz, 1H), 2.71 (m, 1H), 2.27–2.07 (m, 2H), 1.90–1.80 (m, 1H), 1.75–1.58 (m, 2H), 1.54–1.36 (m, 2H), 1.46 and 1.45 (2s, 9H), 0.98–0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (diastereoisomers) 205.8 (s), 171.7 (s), 157.2 (s), 155.5 (s), 150.2 (d), 138.2 (d), 127.0 (d), 122.4 (d), 80.1 (s), 58.7 (t), 57.7 (d), 53.1 (d), 51.3 (t), 41.6 and 41.3 (t), 31.8 and 31.6 (t), 28.4 (t), 28.3 (3q), 24.8 and 24.7 (d), 23.0 (q), 22.9 (q); MS (CI^+, CH_4) m/z (relative intensity) 483 ($M+H^+$, 85), 427 (67), 383 (30), 342 (100), 329 (37), 314 (56), 286 (86), 268 (23), 224 (28), 175 (14); HRMS (CI^+, CH_4) calcd for $C_{22}H_{35}N_4O_6S$ ($M+H^+$) 483.2199. Found 483.2271.

5.24.9. *N*-{(2*S*)-4-Methyl-1-oxo-1-[(4*RS*)-3-oxo-1-(pyridine-2-sulfonyl)azepan-4-ylamino]pentan-2-yl}benzofuran-2-carboxamide (65 and 65′). To a solution of carbamate **74** (97.7 mg, 0.20 mmol, 1 equiv) in MeOH (1 mL), at rt, was added 4 M HCl in dioxane (1 mL). The reaction mixture was then stirred for 2.5 h at rt. After concentration under reduced pressure, the crude hydrochloride salt was used directly in the next step.

To a solution of the crude hydrochloride salt (0.20 mmol, 1 equiv) in CH_2Cl_2 (5 mL), at 0 °C, were added successively benzofuran-2-carboxylic acid (32.4 mg, 0.20 mmol, 1 equiv), HOBt (27.0 mg, 0.20 mmol, 1 equiv), and EDCI (38.3 mg, 0.20 mmol, 1 equiv). After 5 min at 0 °C, Et_3N (60 μL, 0.43 mmol, 2.1 equiv) was added. The reaction mixture was stirred for 18 h at rt, then diluted with EtOAc (20 mL) and hydrolyzed with aqueous 1 M HCl (15 mL). The organic layer was separated and washed with a saturated aqueous K_2CO_3 solution (15 mL), water (15 mL), and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (CH_2Cl_2/MeOH 99/1) afforded a 1/1 mixture of azepanones **65** and **65′** (54.2 mg, 0.10 mmol, 52%) as a colorless amorphous solid; R_f: 0.60 (CH_2Cl_2/MeOH 97/3); IR (neat) 3293, 2955, 2923, 2869, 1727, 1645, 1509, 1338, 1173, 1117, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (**65**+**65′**) 8.68 (m, 1H), 8.00–7.88 (m, 2H), 7.66 (d, J=8.0 Hz, 1H), 7.55–7.46 (m, 3H), 7.43 (t, J=8.0 Hz, 1H), 7.29 (t, J=8.0 Hz, 1H), 7.14 (d, J=6.5 Hz, 1H), 7.10 and 7.04 (d, J=8.5 and 6.5 Hz, 1H), 5.15 (m, 1H), 4.82–4.67 (m, 2H), 4.11 (m, 1H), 3.86 and 3.81 (2d, J=10.0 and 10.0 Hz, 1H), 2.73 (m, 1H), 2.32–1.38 (m, 7H), 1.04–0.96 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (**65**+**65′**) 205.7 (s), 170.8 and 170.7 (s), 158.8 and 158.6 (s), 157.2 (s), 154.9 (s), 150.2 (d), 148.2 and 148.1 (s), 138.2 (d), 127.5 (s), 127.0 (d), 126.8 (d), 123.7 (d), 122.7 (d), 122.5 and 122.4 (d), 111.9 (d), 111.1 and 110.9 (d), 58.6 (t), 57.9 (d), 51.5 (t), 51.3 (d), 41.9 and 41.5 (t), 31.7 and 31.5 (t), 28.4 (t), 24.9 (d), 23.0 and 22.9 (q), 22.2 and 22.1 (q); MS (CI^+, CH_4) m/z (relative intensity) 527 ($M+H^+$, 100), 386 (51), 358 (6), 340 (20), 308 (6), 270 (6), 258 (8), 176 (7); HRMS (CI^+, CH_4) calcd for $C_{26}H_{31}N_4O_6S$ ($M+H^+$) 527.1886. Found 527.1969.

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