Pergamon

Tetrahedron 58 (2002) 1185–1192

TETRAHEDRON

Synthesis of conjugated δ-lactams using ring-closing metathesis

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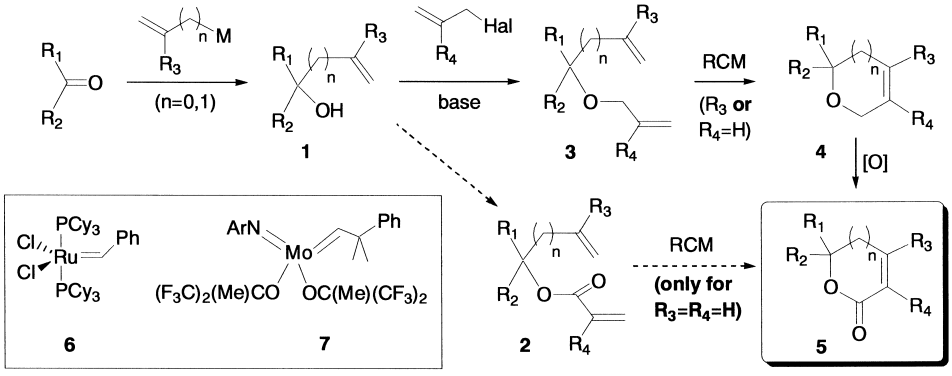
Received 12 November 2001; accepted 13 December 2001

Abstract—Addition of allyl magnesium or metallyl magnesium bromide to the *N*-benzyl imines of benzaldehyde and cyclohexanone, followed by acylation with acryloyl or metacryloyl chloride provided the corresponding α,β-unsaturated amides. Ring-closing metathesis of the latter with ruthenium catalyst $PhCH{=}RuCl_2(PPh_3)_2$ in the presence of $Ti(OiPr)_4$ provided excellent yields of the corresponding conjugated δ-lactams with both disubstituted and trisubstituted C=C bonds. Some specific trisubstitution patterns, however, as well as tetrasubstituted C=C bonds, were not obtained. In these cases, even the use of a second generation, imidazolylidene-substituted ruthenium catalyst at high temperature did not lead to success.

The transition-metal catalyzed olefin metathesis reaction[1] has received a high degree of attention in the last 10 years. At the nonindustrial level, the intramolecular ring-forming version (the 'ring-closing metathesis', RCM)[2] is the most used variant, which has permitted the synthesis of both carbocyclic and heterocyclic ring systems with sizes varying from five to several dozens of atoms.[3] Furthermore, the smooth reaction conditions of metathetic processes are compatible with almost all functional groups, even in sensitive molecules.[4]

Two years ago, we reported on the preparation of conjugated γ- and δ-lactones via a reaction sequence including a RCM.[5] The starting substrates were aldehydes or ketones, which were first subjected to treatment with allyl or alkenyl metal reagents to yield unsaturated alcohols **1**. Attempts at acylation of the latter with acryloyl or metacryloyl chloride (**1**→**2**) gave low yields in the case of tertiary alcohols; furthermore, direct RCM of conjugated esters **2** to α,β-unsaturated lactones **5** worked only for disubstituted C=C bonds ($R_3{=}R_4{=}H$). We circumvented this problem though O-allylation of alcohols **1** and submission of allyl ethers **3** to sequential RCM and allylic oxidation (**3**→**4**→**5**) (Scheme 1).

The RCM catalysts used were the commercially available Grubbs' ruthenium[1b] complex **6** and Schrock's molybdenum[6] complex **7** (Ar=2,6-diisopropylphenyl). With the aid of these catalysts, the preparation of both disubstituted and trisubstituted[7] C=C bonds proved feasible. Lactones having tetrasubstituted olefinic bonds were not obtained, however, under these conditions.



Scheme 1.

Keywords: ring-closing metathesis; ruthenium catalysts; lactams.
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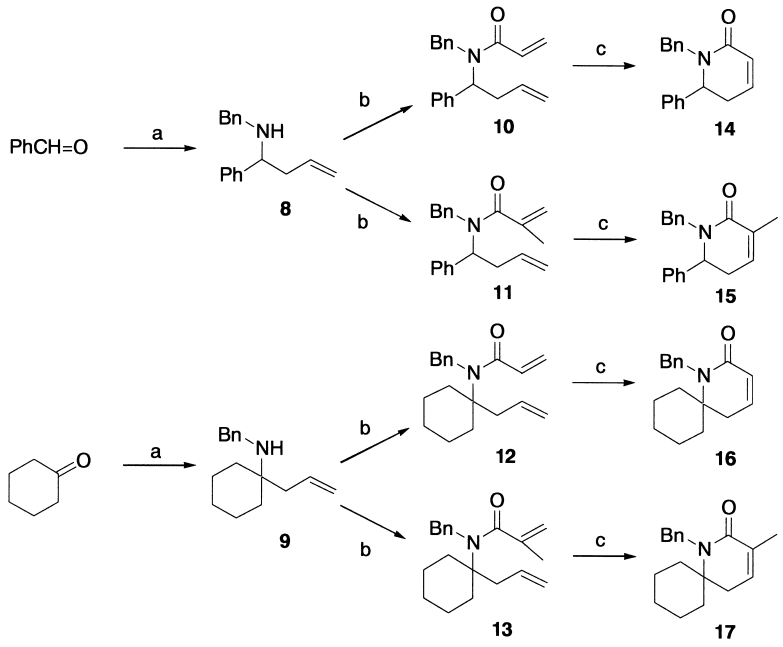
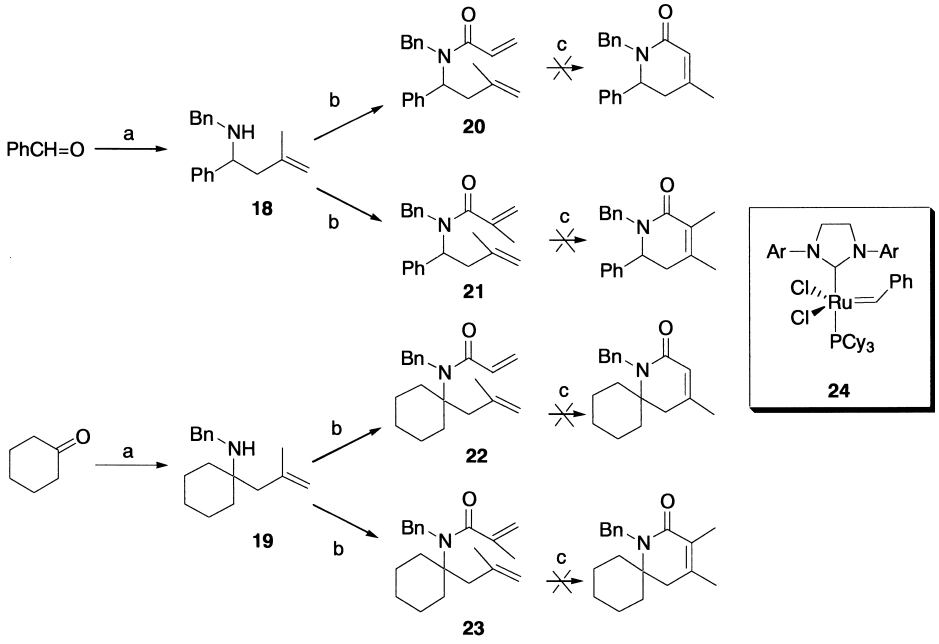


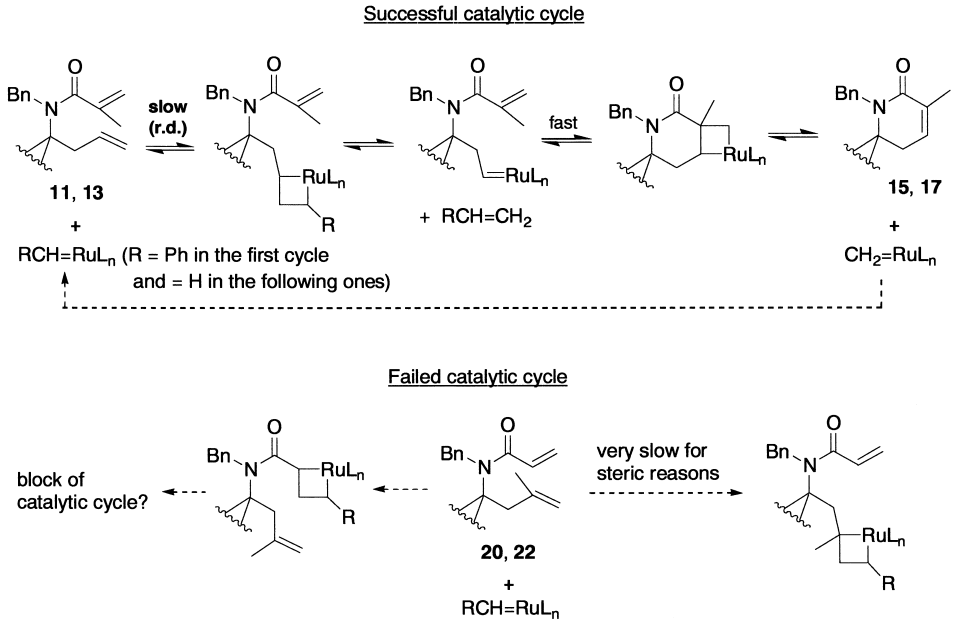
Scheme 2. *Reaction conditions*: (a) $BnNH_2$, toluene, 4 Å MS, rt; allylmagnesium bromide, THF, rt, 3 h. Overall yields: **8** (75%) and **9** (70%); (b) acryloyl or metacryloyl chloride, NEt_3, DMAP, CH_2Cl_2, rt, 12 h. Yields: 88–92%; (c) 4% catalyst **6**, CH_2Cl_2, $Ti(OiPr)_4$, reflux, 12–18 h. Yields: 90–92%.

On the basis of these results, we extended our investigation to the preparation of α,β-unsaturated lactams by means of the same methodology. Heterocyclic nitrogen-containing ring systems have often been obtained via RCM.[2c] As regards lactams,[8] ring sizes from 5 to 14 atoms have been synthesized. In the reported examples with ruthenium catalysts such as **6**, the generated double bond was almost always disubstituted and, in most cases, not conjugated with the amide carbonyl group. As in our previous work with lactones,[5] we wished to establish in the case of conjugated lactams the limits in the degree of substitution at the double bond attainable with the aid of RCM. The present non-commercial availability[6] and the rather uncomfortable use of complex **7** led us to employ catalyst **6** in the initial phase of the work.

The benzylimines of benzaldehyde and cyclohexanone were chosen as the starting model compounds. Addition of allylmagnesium bromide gave the expected addition products **8** and **9**, respectively, which were then acylated with acryloyl



Scheme 3. *Reaction conditions*: (a) $BnNH_2$, toluene, 4 Å MS, rt; metallylmagnesium bromide, THF, rt, 3 h. Overall yields: **18** (70%) and **19** (60%); (b) acryloyl or metacryloyl chloride, NEt_3, DMAP, rt, 12 h. Yields: 88–91%; (c) 4% catalyst **6**, CH_2Cl_2, $Ti(OiPr)_4$, 48 h, refl., or 16% catalyst **24**, toluene, with or without $Ti(OiPr)_4$, 48 h, 80–110°C.

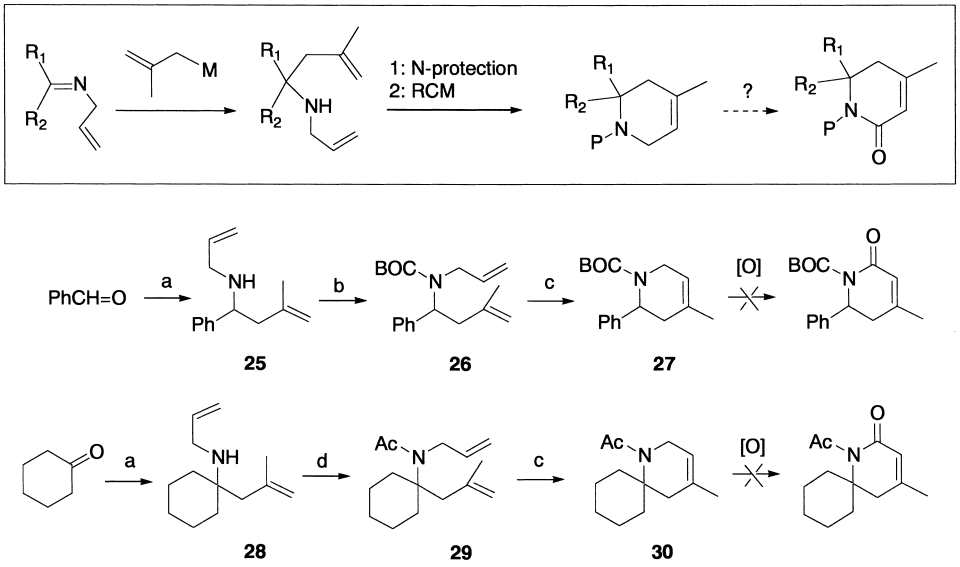


Scheme 4. Chauvin's catalytic cycle in the case of amides **11**, **13**, **20** and **22**.

and metacryloyl chloride to yield the conjugated amides **10**–**13**. These were then subjected to RCM reaction conditions in the presence of 4% of complex **6**. In all four cases, the conjugated amides **14**–**17** were obtained with good yields, provided that Ti(O*i*Pr)$_4$ was added to the reaction mixture.[9] It is interesting to note here that, in contrast to the case of lactones,[5] trisubstituted, conjugated C=C bonds were directly formed (Scheme 2).

In order to check whether other substitution patterns at the double bond were achievable, the previous reaction sequence was repeated using metallylmagnesium bromide in the first step. Acryloyl and metacryloyl chloride were again the acylating reagents. Disappointingly, none of the conjugated amides **20**–**23** underwent cyclization in the presence of catalyst **6**. In view of this failure, we took recourse to the recently developed, second-generation ruthenium complex **24** (Ar=mesityl) containing one imidazolylidene ligand replacing one of the phosphines. Metathesis catalysts of this general type have been shown to perform extremely well, even for the creation of tetrasubstituted C=C bonds.[10] Furthermore, they are much more comfortable to use than **7**, more tolerant to a range of functional groups, and less stringent in their requirements as to purity of solvents and exclusion of air and humidity. In our case, however, this active catalyst failed to promote the cyclization of amides **20**–**23**, even at elevated temperatures (Scheme 3).

RCM processes are reversible and usually characterized by



Scheme 5. *Reaction conditions*: (a) allyl amine, toluene, 4 Å MS, rt; metallylmagnesium bromide, THF, rt, 3 h. Yields: **25** (70%) and **28** (67%); (b) $(BOC)_2O$, NEt_3, DMAP, rt, 12 h. Yield: 85%. (c) 4% catalyst **6**, CH_2Cl_2, Ti(O*i*Pr)$_4$, 18 h, refl. Yields: **27** (70%), **30** (78%); (d) Ac_2O, NEt_3, rt, 7 h. Yield: 80%.

small changes in enthalpy ($\Delta H \sim 0$). Their advance is driven mainly by the favorable entropic factor ($\Delta S > 0$) related to the extrusion of a small volatile molecule (most often, ethylene). RCM rates have been shown to depend on both electronic and steric factors.[1,2] For instance, polar functional groups on the C=C bond may in some cases block the catalytic cycle.[11] Particularly marked is the retarding effect of an increasing degree of substitution, not only on the C=C bond itself, but also in its close proximity.[12] Within Chauvin's mechanistic view,[13] it may be assumed that the first intermolecular metal carbene–olefin [2+2] cycloaddition step of the catalytic cycle (Scheme 4) is rate-determining (r.d.) and takes place on the electronically least deactivated and/or sterically least encumbered C=C bond. The second, and faster, [2+2] cycloaddition is intramolecular and therefore less sensitive to steric hindrance. In amides **10**–**13**, the obvious target for the catalyst in the first cycloaddition is the monosubstituted, unconjugated double bond of the allyl moiety. The second, intramolecular cycloaddition does not find apparently any electronic and/or steric hurdles, even when the reacting C=C bond is both conjugated and disubstituted (amides **11** and **13**). In contrast, the nonconjugated C=C bond in amides **20**–**23** is disubstituted, which makes it much less reactive for steric reasons. Furthermore, initial cycloaddition to the conjugated double bond may be also slow for electronic reasons or perhaps lead to a blockage of the catalytic cycle. It is difficult to decide here, however, which of either pathway is responsible to a major extent of the observed failure (compare with the reactions of Scheme 5).

In an attempt to circumvent the problem of the failed synthesis of β-methylsubstituted lactams, and in analogy to our work with lactones,[5] we performed the experiments depicted in Scheme 5. The reaction sequences are in principle the same as those depicted in Schemes 2 and 3 except that the *N*-allyl imines of benzaldehyde and cyclohexanone were the starting materials. The *N*-allyl moiety was intended to provide the necessary material to build up the heterocyclic ring during the metathesis. Allylic oxidation would then create the amide carbonyl group. In the event, reaction of the *N*-allyl imines with metallyl magnesium bromide gave the expected addition products **25** and **28**, which were *N*-protected as their respective BOC derivatives, and then subjected to RCM. The reaction was successful in the case of **26**[14] but not with the corresponding cyclohexanone-derived product (not indicated in the scheme), where a dimer formed by cross metathesis was the main reaction product. However, when acetyl was the *N*-protecting group as in **29**, RCM provided the *N*-acetyl tetrahydropyridine **30**.[14] Unfortunately, tetrahydropyridines **27** and **30** proved useless for our purposes, as we were unable to perform an oxidation in the allylic position contiguous to the nitrogen atom.[15]

In summary, we have reported an efficient method for the preparation of conjugated monocyclic or spirocyclic lactams via RCM. The conjugated C=C bond may be not only disubstituted but also trisubstituted, provided that the additional substituent is bound to the α carbon atom. The present report further points to certain limitations in the catalytic efficiency of the second-generation ruthenium complex **24**.

1. Experimental

NMR spectra (Varian 400 and 500 NMR spectrometers) were measured in $CDCl_3$ solution at 25°C. The NMR spectra of some amides showed very broad signals, due to the presence of slowly interconverting rotamers. For this reason, these NMR spectra were measured at 330 K (57°C), where sharper signals were visible. Mass spectra were run either by the electron impact (EIMS, 70 eV) on a VG AutoSpec mass spectrometer. IR spectra were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Reactions which required inert atmosphere were carried out under argon with flame-dried glassware. Commercial reagents (Aldrich or Fluka) were used as received. THF was freshly distilled from sodium benzophenone ketyl. Dichloromethane was distilled from P_2O_5 and stored over 4 Å molecular sieves. Toluene was freshly distilled from sodium wire. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into brine, extraction with the indicated solvent, additional washing with 5% aq $NaHCO_3$, (if acids had been utilized in the reaction) or with 5% aq HCl (if bases had been utilized), then again with brine, drying over anhydrous Na_2SO_4 or $MgSO_4$ and elimination of the solvent in vacuo. The obtained material was then chromatographed on a silica gel column (Süd-Chemie AG, 60–200 μ) with the indicated eluent.

1.1. General procedure for the preparation of secondary amines 8, 9, 18, 19, 25 and 28 from benzaldehyde or cyclohexanone

The appropriate carbonyl compound (10 mmol) and the primary amine (15 mmol) were dissolved under Ar in dry toluene (20 mL). After addition of activated 4 Å molecular sieves (3 g), the mixture was stirred overnight at room temperature. The solution was then filtered through a pad of anhydrous $MgSO_4$, all volatiles were removed carefully in vacuo and the oily imine was then directly used without purification in the next step.

The crude imine obtained above was dissolved under Ar in dry THF (25 mL) and treated dropwise at 0° with the appropriate Grignard reagent (15 mmol, 1 M solution in THF). The mixture was then stirred for 3 h at room temperature. Work-up (extraction with Et_2O), removal of all volatiles in vacuo and column chromatography of the residue on silica gel (hexane–EtOAc 9:1 and then 4:1) afforded the desired amine. Overall chemical yields (two steps from the starting carbonyl compound): **8** (75%), **9** (70%), **18** (70%), **19** (60%), **25** (70%), **28** (67%).

1.2. General procedure for the preparation of α,β-unsaturated amides 10–13 and 20–23

The appropriate amine (6 mmol), triethyl amine (1.25 mL, ca. 9 mmol) and DMAP (55 mg, 0.45 mmol) were dissolved under Ar in dry CH_2Cl_2 (25 mL), treated with the appropriate acyl chloride (8 mmol) and stirred overnight at room temperature. Work-up (extraction with CH_2Cl_2), removal of all volatiles in vacuo and column chromatography of the residue on silica gel (hexane–EtOAc 7:3) yielded the desired amides. Chemical yields: **10** (90%), **11** (92%), **12** (90%), **13** (89%); **20** (89%), **21** (90%), **22** (88%), **23** (91%).

1.3. General procedure for the ring-closing metathesis with ruthenium catalyst 6

The appropriate α,β-unsaturated amide **10**–**13** (1 mmol) and Ti(O*i*Pr)$_4$ (570 mg, ca. 2 mmol) were dissolved under Ar in dry CH_2Cl_2 (50 mL) and heated at reflux for 1 h. After this time, catalyst **6** (33 mg, 0.04 mmol) was added and the mixture was stirred at reflux for 12–18 h (monitoring by means of TLC). After removal of all volatiles in vacuo, the residue was chromatographed on silica gel (hexane–EtOAc 4:1) to furnish the desired α,β-unsaturated lactams. For compounds **26** and **29**, 10% of catalyst **6** was used and the reflux was maintained for 48 h. Chemical yields: **14** (92%), **15** (90%), **16** (92%), **17** (90%); **27** (70%), **30** (78%). Under these conditions, amides **20**–**23** did not react, even after 48 h.

1.4. Attempts at ring-closing metathesis using ruthenium catalyst 24

The appropriate precursor (1 mmol) and catalyst **24** (68 mg, 0.08 mmol) were dissolved under Ar in dry CH_2Cl_2 (50 mL) and heated at reflux for 24 h. After this time, an additional amount of catalyst (68 mg) was added and the reflux was continued for further 24 h. TLC monitoring revealed that no RCM was taking place, a conclusion confirmed later by means of NMR. When CH_2Cl_2 was replaced by toluene and the reaction was carried out at temperatures from 80 to 110°C for 48 h, the same lack of success was observed. Addition of Ti(O*i*Pr)$_4$ was of no avail, either.

1.4.1. Benzyl-(1-phenylbut-3-enyl)-amine, 8. Oil, physical data in agreement with published data.[16]

1.4.2. (1-Allylcyclohexyl) benzyl amine, 9. Oil, ^{1}H NMR (500 MHz): δ 7.45–7.25 (5H, m), 5.95 (1H, m), 5.15 (2H, m), 3.69 (2H, s), 2.29 (2H, d, *J*=7.5 Hz), 1.70–1.30 (10H, br m); ^{13}C NMR (125 MHz): δ 141.4, 134.4, 128.2, 128.1, 126.5, 117.2, 53.9, 45.4, 41.9, 35.5, 26.2, 21.8. Other data in agreement with published data.[17]

1.4.3. *N*-Benzyl-*N*-(1-phenylbut-3-enyl)acrylamide, 10. Oil, IR ν_{max} cm^{-1}: 3064, 3031, 2979, 2874, 1651 (amide C=O), 1614, 1423, 1222, 1163, 978, 919, 795, 752, 731, 700; EIMS, *m/z* 291.1616 (M$^+$, 3), 250 (34), 196 (70), 91 (100). Calc. for $C_{20}H_{21}NO$, *M*=291.1623; ^{1}H NMR (400 MHz, 57°C): δ 7.40–7.00 (10H, br m), 6.40 (2H, m), 6.00 (1H, very br m), 5.70 (1H, m), 5.60 (1H, br m), 5.05–5.00 (2H, m), 4.55 (1H, very br s), 4.30 (1H, very br s), 2.70 (2H, br m); ^{13}C NMR (100 MHz, 57°C): δ 167.6, 139.2, 138.3, 134.7, 129.0, 128.5, 128.3, 128.2*, 127.8, 127.0, 117.6, 57.5*, 47.3, 35.7 (the starred signals are low and broad).

1.4.4. *N*-Benzyl-2-methyl-*N*-(1-phenylbut-3-enyl)acrylamide, 11. Oil, IR ν_{max} cm^{-1}: 3064, 3031, 2975, 2925, 1640sh, 1625 (amide C=O), 1452, 1412, 1338, 1195, 1156, 1048, 915, 731, 700; EIMS, *m/z* 305.1776 (M$^+$, 7), 264 (100), 91 (72). Calc. for $C_{21}H_{23}NO$, *M*=305.1779; ^{1}H NMR (400 MHz, 57°C): δ 7.40–7.00 (10H, br m), 5.70 (1H, m), 5.55 (1H, br m), 5.16 (2H, br s), 5.05–5.00 (2H, m), 4.63, 4.19 (2H, broadened AB system, *J*=15.5 Hz), 2.70 (2H, br m), 1.92 (3H, br s); ^{13}C NMR (100 MHz, 57°C): δ 173.7, 141.7, 139.1, 138.5, 134.9, 128.6, 128.4, 128.2, 127.8, 127.7, 127.0, 117.6, 115.2, 59.5*, 47.2*, 36.3, 20.7 (the starred signals are low and broad).

1.4.5. *N*-(1-Allylcyclohexyl)-*N*-benzylacrylamide, 12. Oil, IR ν_{max} cm^{-1}: 3071, 3033, 2933, 2863, 1655 (amide C=O), 1611, 1495, 1451, 1411, 1301, 1226, 1200, 994, 913, 797, 725; EIMS, *m/z* 283.1932 (M$^+$, 3), 242 (100), 188 (84), 91 (80). Calc. for $C_{19}H_{25}NO$, *M*=283.1936; ^{1}H NMR (500 MHz): δ 7.40–7.20 (5H, br m), 6.34 (1H, dd, *J*=16.5, 9.5 Hz), 6.28 (1H, dd, *J*=16.5, 3 Hz), 5.77 (1H, br m), 5.50 (1H, dd, *J*=9.5, 3 Hz), 5.15–5.00 (2H, m), 4.58 (2H, s), 2.93 (2H, br d, *J*=7.5 Hz), 2.50 (2H, m), 1.60–1.40 (8H, br m); ^{13}C NMR (125 MHz): δ 168.9, 139.8, 134.6, 132.0, 128.7, 127.1, 127.0, 125.7, 118.0, 63.6, 49.1, 35.7, 33.5, 25.4, 22.7.

1.4.6. *N*-(1-Allylcyclohexyl)-*N*-benzyl-2-methylacrylamide, 13. Oil, IR ν_{max} cm^{-1}: 3074, 3031, 2932, 2873, 1631 (amide C=O), 1451, 1386, 1296, 1183, 1049, 911, 729, 700; EIMS, *m/z* 297.2091 (M$^+$, 4), 256 (100), 176 (22), 91 (93). Calc. for $C_{20}H_{27}NO$, *M*=297.2092; ^{1}H NMR (400 MHz): δ 7.35–7.20 (5H, br m), 5.79 (1H, ddt, *J*=16, 11, 7.5 Hz), 5.10–5.04 (2H, m), 5.00 (1H, quint, *J*=1.5 Hz), 4.89 (1H, quint, *J*=1.5 Hz), 4.62 (2H, s), 2.84 (2H, d, *J*=7.5 Hz), 2.30 (2H, m), 1.85 (3H, t, *J*=1.5 Hz), 1.70 (3H, m), 1.55–1.45 (4H, br m), 1.10 (1H, m); ^{13}C NMR (100 MHz): δ 175.2, 143.5, 140.7, 134.5, 128.5, 126.9, 126.5, 117.9, 113.6, 63.6, 50.7, 36.7, 33.7, 25.6, 22.7, 20.8.

1.4.7. 1-Benzyl-6-phenyl-5,6-dihydro-1*H*-pyridin-2-one, 14. Oil, physical data in agreement with published data.[18]

1.4.8. 1-Benzyl-3-methyl-6-phenyl-5,6-dihydro-1*H*-pyridin-2-one, 15. Oil, IR ν_{max} cm^{-1}: 3070, 3030, 2924, 1672 (amide C=O), 1629, 1495, 1452, 1358, 1222, 1078, 1030, 835, 736, 700; EIMS, *m/z* 277.1471 (M$^+$, 100), 200 (12), 186 (33), 173 (40), 91 (80). Calc. for $C_{19}H_{19}NO$, *M*=277.1466; ^{1}H NMR (400 MHz): δ 7.35–7.10 (10H, br m), 6.02 (1H, br d, *J*=6.5 Hz), 5.62 (1H, d, *J*=15 Hz), 4.54 (1H, dd, *J*=8, 1.5 Hz), 3.50 (1H, d, *J*=15 Hz), 2.86 (1H, br m), 2.36 (1H, br ddq, *J*=15, 6, 1 Hz), 1.97 (3H, quint, *J*=1 Hz); ^{13}C NMR (100 MHz): δ 166.0, 140.4, 138.1, 131.5, 130.5, 128.6, 128.5, 128.0, 127.6, 127.3, 126.5, 57.6, 48.2, 31.9, 17.3.

1.4.9. 1-Benzyl-1-azaspiro[5.5]undec-3-en-2-one, 16. Oil, IR ν_{max} cm^{-1}: 3061, 2930, 2864, 1667 (amide C=O), 1614, 1494, 1453, 1415, 1340, 1268, 1253, 1124, 842, 731; EIMS, *m/z* 255.1619 (M$^+$, 67), 212 (49), 164 (22), 91 (100). Calc. for $C_{17}H_{21}NO$, *M*=255.1623; ^{1}H NMR (400 MHz): δ 7.30–7.15 (5H, br m), 6.46 (1H, dt, *J*=9.7, 4.5 Hz), 6.06 (1H, dt, *J*=9.7, 2 Hz), 4.73 (2H, br s), 2.50 (2H, dd, *J*=4.5, 2 Hz), 1.75–1.50 (6H, br m), 1.30–1.10 (4H, br m); ^{13}C NMR (100 MHz): δ 165.5, 140.2, 136.9, 128.3, 126.8, 126.5, 125.2, 59.8, 43.2, 34.1, 31.8, 25.2, 22.6.

1.4.10. 1-Benzyl-3-methyl-1-azaspiro[5.5]undec-3-en-2-one, 17. Oil, IR ν_{max} cm^{-1}: 3029, 2923, 1672 (amide C=O), 1628, 1494, 1452, 1358, 1220, 1076, 1029, 736, 700; EIMS, *m/z* 269.1776 (M$^+$, 48), 226 (42), 178 (31), 91 (100). Calc. for $C_{18}H_{23}NO$, *M*=269.1779; ^{1}H NMR (400 MHz): δ 7.30–7.15 (5H, br m), 6.22 (1H, tq, *J*=4,

2 Hz), 4.73 (2H, br s), 2.45 (2H, sext, J=2 Hz), 1.92 (3H, q, J=2 Hz), 1.75–1.50 (6H, br m), 1.35–1.00 (4H, br m); ^{13}C NMR (100 MHz): δ 166.7, 140.5, 131.2, 131.1, 128.3, 126.8, 126.4, 59.7, 43.7, 34.2, 31.6, 25.3, 22.6, 17.4.

1.4.11. Benzyl-(3-methyl-1-phenylbut-3-enyl)-amine, 18. Oil, IR ν_{max} cm^{-1}: 3450 (br, NH), 3026, 2933, 1492, 1453, 1115, 1028, 894, 700; EIMS, m/z 196.1102 ($M^+-C_4H_7$, 100), 91 (72). Calc. for $C_{18}H_{21}N-C_4H_7$, M=196.1126; ^{1}H NMR (500 MHz): δ 7.50–7.25 (10H, br m), 4.88 (1H, br s), 4.84 (1H, br s), 3.84 (1H, dd, J=9.5, 4.7 Hz), 3.78 (1H, d, J=13.5 Hz), 3.56 (1H, d, J=13.5), 2.45 (1H, dd, J=14, 9.5 Hz), 2.37 (1H, dd, J=14, 4.7 Hz), 1.85 (1H, br s), 1.72 (3H, s); ^{13}C NMR (125 MHz): δ 144.3, 142.7, 140.6, 128.4, 128.3, 128.1, 127.3, 127.0, 126.8, 113.4, 59.3, 51.5, 47.6, 22.1.

1.4.12. Benzyl-[1-(2-methylallyl)cyclohexyl]amine, 19. Oil, IR ν_{max} cm^{-1}: 3400 (br, NH), 3070, 3048, 2940, 2853, 1494, 1451, 1373, 1262, 1184, 1143, 1091, 1068, 889, 742, 699; EIMS, m/z 242.1912 (M^+-H, 5), 188 (100), 91 (60). Calc. for $C_{17}H_{25}N-H$, M=242.1908; ^{1}H NMR (500 MHz): δ 7.50–7.25 (5H, br m), 4.93 (1H, br s), 4.73 (1H, br s), 3.70 (2H, s), 2.23 (2H, s), 1.88 (3H, s), 1.80–1.20 (10H, br m); ^{13}C NMR (125 MHz): δ 143.1, 141.6, 128.3, 128.2, 126.7, 114.1, 54.6, 45.4, 45.1, 35.9, 26.2, 25.6, 21.8.

1.4.13. *N*-Benzyl-*N*-(3-methyl-1-phenylbut-3-enyl)acrylamide, 20. Oil, IR ν_{max} cm^{-1}: 3065, 3031, 2931, 1651 (amide C=O), 1611, 1451, 1420, 1212, 977, 893, 794, 731, 700; EIMS, m/z 305.1790 (M^+, 10), 250 (60), 196 (77), 91 (100). Calc. for $C_{21}H_{23}NO$, M=305.1779; ^{1}H NMR (400 MHz, 57°C): δ 7.40–6.90 (10H, br m), 6.40–6.20 (2H, br m), 5.56 (1H, br s), 4.77 (1H, br s), 4.72 (1H, br s), 4.52 (1H, br m), 4.37 (1H, br d, J=17 Hz), 2.66 (2H, d, J=7.5 Hz), 1.69 (3H, s); ^{13}C NMR (100 MHz, 57deg;C): δ 167.3, 141.7*, 139.4, 138.3*, 129.0, 128.4, 128.3, 128.1, 128.0, 127.7, 127.0, 126.6*, 113.2, 55.3*, 47.3, 39.2*, 22.4 (the starred signals are low and broad).

1.4.14. *N*-Benzyl-2-methyl-*N*-(3-methyl-1-phenylbut-3-enyl)acrylamide, 21. Oil, IR ν_{max} cm^{-1}: 3065, 3031, 2979, 2929, 1625 (broad, amide C=O), 1451, 1420, 1181, 1048, 910, 731, 700; EIMS, m/z 319.1944 (M^+, 8), 264 (100), 91 (68). Calc. for $C_{22}H_{25}NO$, M=319.1936; ^{1}H NMR (400 MHz, 57°C): δ 7.40–6.90 (10H, br m), 5.80 (1H, br m), 5.12 (2H, br s), 4.79 (1H, br s), 4.70 (1H, br s), 4.59, 4.29 (2H, broadened AB system, J=15.7 Hz), 2.70 (2H, br m), 1.84 (3H, br s), 1.70 (3H, s); ^{13}C NMR (100 MHz, 57°C): δ 173.7, 141.9, 141.8, 139.3, 138.5, 128.6, 128.4, 128.2, 127.8, 127.6, 126.9, 115.1, 113.4, 57.3*, 47.6*, 40.1, 22.4, 20.5 (the starred signals are low and broad).

1.4.15. *N*-Benzyl-*N*-[1-(2-methylallyl)cyclohexyl]acrylamide, 22. Oil, IR ν_{max} cm^{-1}: 3064, 3031, 2931, 2864, 1655 (amide C=O), 1611, 1451, 1412, 1353, 1192, 993, 729, 700; EIMS, m/z 297.2093 (M^+, 4), 242 (100), 188 (76), 91 (81). Calc. for $C_{20}H_{27}NO$, M=297.2092; ^{1}H NMR (400 MHz, 57°C): δ 7.40–7.20 (5H, br m), 6.35 (1H, dd, J=16.6, 10.2 Hz), 6.24 (1H, dd, J=16.6, 2.3 Hz), 5.47 (1H, dd, J=10.2, 2.3 Hz), 4.92 (1H, br s), 4.72 (1H, br s), 4.58 (2H, s), 2.90 (2H, s), 2.60 (2H, m), 1.79 (3H, s), 1.65–1.40 (7H, br m), 1.10 (1H, m); ^{13}C NMR (100 MHz, 57°C): δ 169.2, 143.1, 140.1, 132.5, 128.8, 127.0, 126.6, 125.9, 64.0, 49.5, 38.1, 34.3, 25.6, 24.8, 23.0.

1.4.16. *N*-Benzyl-2-methyl-*N*-[1-(2-methylallyl)cyclohexyl]acrylamide, 23. Oil, IR ν_{max} cm^{-1}: 3070, 3030, 2925, 2863, 1650 (amide C=O), 1455, 1182, 1155, 1030, 902, 729, 700; EIMS, m/z 311.2247 (M^+, 3), 256 (100), 176 (14), 91 (89). Calc. for $C_{21}H_{29}NO$, M=311.2249; ^{1}H NMR (400 MHz, 57°C): δ 7.35–7.20 (5H, br m), 5.03 (1H, quint, J=1.5 Hz), 4.90 (1H, quint, J=1.5 Hz), 4.87 (1H, sext, J=1.5 Hz), 4.72 (1H, m), 4.65 (2H, s), 2.79 (2H, s), 2.30 (2H, m), 1.84 (3H, t, J=1.5 Hz), 1.80 (3H, t, J=1.5 Hz), 1.60–1.40 (7H, br m), 1.20 (1H, m); ^{13}C NMR (100 MHz, 57°C): δ 175.2, 143.4, 142.7, 140.6, 128.4, 126.8, 126.6, 64.1, 50.9, 39.9, 34.1, 25.6, 25.1, 22.9, 20.7.

1.4.17. Allyl-(3-methyl-1-phenylbut-3-enyl)amine, 25. Oil, IR ν_{max} cm^{-1}: 3330 (br, NH), 3074, 3027, 2934, 2878, 1492, 1455, 1375, 1113, 1029, 893, 756, 700; EIMS, m/z 146.0964 ($M^+-C_4H_7$, 100), 91 (22). Calc. for $C_{14}H_{19}N-C_4H_7$, M=146.0969; ^{1}H NMR (400 MHz): δ 7.40–7.20 (5H, br m), 5.83 (1H, dddd, J=17.3, 10.3, 7, 5.3 Hz), 5.08 (1H, dq, J=17.3, 1.5 Hz), 5.06 (1H, dq, J=10.3, 1.5 Hz), 4.81 (1H, quint, J=1.5 Hz), 4.76 (1H, br s), 3.80 (1H, dd, J=9.2, 5 Hz), 3.12 (1H, ddt, J=14, 5.3, 1.5 Hz), 2.98 (1H, ddt, J=14, 7, 1.2 Hz), 2.39 (1H, dd, J=13.7, 9.2 Hz), 2.30 (1H, dd, J=13.7, 5 Hz), 1.73 (3H, s); ^{13}C NMR (100 MHz): δ 144.0, 142.6, 136.7, 128.3, 127.3, 127.1, 116.0, 113.5, 59.6, 50.0, 47.3, 22.2.

1.4.18. *N*-Allyl-*N*-(*tert*-butyloxycarbonyl)-*N*-(3-methyl-1-phenylbut-3-enyl)amine, 26. Amine **25** (503 mg, 2.5 mmol), $(BOC)_2O$ (590 mg, 2.7 mmol) and NEt_3 (420 μL, ca. 3 mmol) were dissolved in dry CH_2Cl_2 (5 mL) and stirred under Ar at room temperature for 4 h. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexane–EtOAc 7:3) furnished 562 mg (75%) of **26** as an oil, IR ν_{max} cm^{-1}: 3076, 2979, 2932, 1683 (uretane C=O), 1453, 1400, 1367, 1251, 1168, 1120, 1075, 912, 734, 700; EIMS, m/z 301.2029 (M^+, 1), 246 (29), 190 (100), 146 (88), 57 (55). Calc. for $C_{19}H_{27}NO_2$, M=301.2042; ^{1}H NMR (400 MHz, 57°C): δ 7.35–7.20 (5H, br m), 5.55 (2H, br m), 4.90 (2H, m), 4.82 (1H, br s), 4.78 (1H, br s), 3.70–3.50 (2H, br m), 2.68 (2H, m), 1.79 (3H, s), 1.46 (9H, s); ^{13}C NMR (100 MHz, 57°C): δ 155.7*, 142.3, 140.9, 136.0, 128.3, 128.0, 127.3, 115.4, 113.1, 79.7, 56.5*, 46.5, 39.5, 28.5, 22.5 (the starred signals are low and broad).

1.4.19. 1-*tert*-Butyloxycarbonyl-4-methyl-2-phenyl-1,2,3,6-tetrahydropyridine, 27. Oil, IR ν_{max} cm^{-1}: 3030, 2977, 2885, 1695 (uretane C=O), 1455, 1368, 1253, 1168, 1027, 885, 858, 764, 700; EIMS, m/z 273.1724 (M^+, 1), 217 (25), 57 (100). Calc. for $C_{17}H_{23}NO_2$, M=273.1728; ^{1}H NMR (500 MHz): δ 7.35–7.25 (5H, br m), 5.55 (1H, br m), 5.34 (2H, br s), 4.19 (1H, br d, J=18 Hz), 3.30 (1H, br d, J=18 Hz), 2.62 (1H, br d, J=17 Hz), 2.2.37 (1H, br d, J=17 Hz), 1.78 (3H, br s), 1.49 (9H, s); ^{13}C NMR (125 MHz): δ 155.0, 141.3, 128.2, 126.8, 126.6, 118.3, 79.7, 40.2, 32.5, 28.4, 27.9, 23.2.

1.4.20. Allyl-[1-(2-methylallyl)cyclohexyl]amine, 28. Oil, IR ν_{max} cm^{-1}: 3360 (br, NH), 3074, 2929, 2854, 1642, 1449, 1373, 1147, 1092, 995, 916, 889; EIMS, *m/z* 192.1744 (M^+-H, 1), 178 (1), 150 (3), 138 (100). Calc. for $C_{13}H_{23}N-H$, M=192.1752; ^1H NMR (500 MHz): δ 5.90 (1H, ddd, J=17, 10, 6 Hz), 5.14 (1H, br d, J=17 Hz), 5.00 (1H, br d, J=10 Hz), 4.86 (1H, br s), 4.60 (1H, br s), 3.12 (2H, d, J=6 Hz), 2.10 (2H, s), 1.80 (3H, s), 1.60–1.30 (10H, br m); ^{13}C NMR (125 MHz): δ 142.9, 137.7, 114.9, 114.1, 54.4, 44.0, 37.9, 35.8, 26.1, 25.5, 21.9.

1.4.21. *N*-Allyl-*N*-[1-(2-methylallyl)cyclohexyl]acetamide, 29. Amine **28** (387 mg, ca. 2 mmol) was dissolved under Ar in dry CH_2Cl_2 (2 mL) and treated with acetic anhydride (1 mL) and NEt_3 (560 μL, ca. 4 mmol). The reaction mixture was stirred overnight at room temperature. Work-up (extraction with EtOAc) and column chromatography on silica gel (hexane–EtOAc 7:3) afforded 376 mg (80%) of acetamide **29** as an oil, IR ν_{max} cm^{-1}: 3073, 2929, 2861, 1642 (amide C=O), 1392, 1242, 1193, 891; EIMS, *m/z* 235.1938 (M^+, 1), 180 (64), 138 (100). Calc. for $C_{15}H_{25}NO$, M=235.1936; ^1H NMR (400 MHz): δ 5.82 (1H, ddt, J=17, 10.5, 4.5 Hz), 5.21 (1H, dq, J=17, 1.5 Hz), 5.18 (1H, dq, J=10.5, 1.5 Hz), 4.84 (1H, sext, J=1.5 Hz), 4.64 (1H, m), 3.86 (2H, m), 2.80 (2H, br s), 2.40 (2H, br d, J=12 Hz), 2.06 (3H, s), 1.71 (3H, t, J=1 Hz), 1.70–1.20 (8H, br m); ^{13}C NMR (100 MHz): δ 172.6, 143.1, 136.6, 115.8, 114.6, 63.4, 48.4, 38.3, 34.3, 25.7, 25.6, 24.6, 23.0.

1.4.22. 1-Acetyl-4-methyl-1-azaspiro[5.5]undec-3-ene, 30. Oil, IR ν_{max} cm^{-1}: 2928, 2850, 1655 (amide C=O), 1444, 1391, 1342, 1223, 1191, 1172, 700; EIMS, *m/z* 207.1624 (M^+, 100), 164 (94), 150 (66), 122 (98), 105 (60). Calc. for $C_{13}H_{21}NO$, M=207.1623; ^1H NMR (400 MHz): δ 5.38 (1H, m), 3.75 (2H, m), 2.68 (2H, m), 2.07 (3H, s), 1.66 (5H, br s), 1.60–1.20 (8H, m); ^{13}C NMR (100 MHz): δ 171.6, 134.5, 117.9, 58.6, 44.5, 40.6, 34.8, 26.1, 25.7, 23.1, 22.6.

Acknowledgements

The authors wish to acknowledge financial support by the DGICYT (Project PB98-1438), by Fundació Caixa Castellò-Univ. Jaume I (P1B99-18) and by the Conselleria de Cultura de la Generalitat Valenciana (project GV-99-77-1-02). E. C. thanks the latter institution for a pre-doctoral fellowship.

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