Investigations into the [2,3]-aza-Wittig rearrangement of *N*-alkyl *N*-allyl α-amino esters

Iain Coldham,*[a] Mark L. Middleton[a] and Philip L. Taylor[b]

[a] *Department of Chemistry, University of Exeter, Stocker Road, Exeter, UK EX4 4QD*
[b] *ICI Paints, Wexham Road, Slough, Berkshire, UK SL2 5DS*

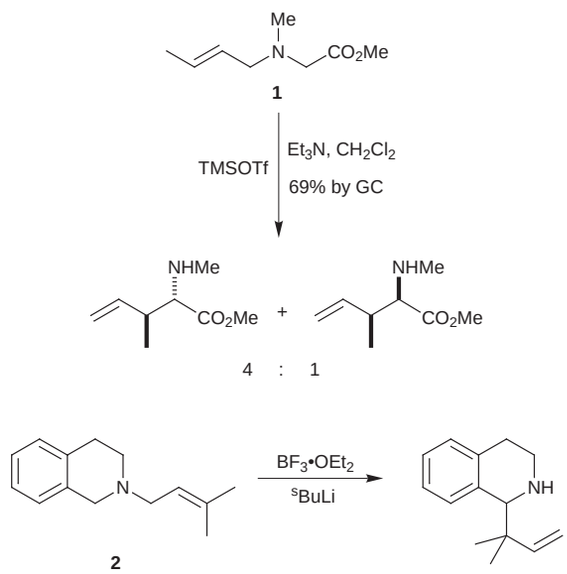
A Lewis acid is needed in order to allow the [2,3]-sigmatropic rearrangement of *N*-alkyl *N*-allyl α-amino esters to give rise to *N*-alkyl *C*-allyl glycine esters. Addition of iodomethane, rather than a Lewis acid, promotes quaternary ammonium salt formation, *in situ* ylide formation and [2,3]-sigmatropic rearrangement to *N,N*-dialkyl *C*-allyl glycine esters.

Of the many methods available to the synthetic chemist for carbon-carbon bond formation, the [2,3]-sigmatropic rearrangement has played an important role, not least in providing allyl-transposed products, which may be difficult to access by other means. In addition, the rearrangement often occurs in high yields and with high levels of stereocontrol, proceeding through a five-membered cyclic transition state.[1] Most popular are the [2,3]-Stevens rearrangement of allylic sulfonium (Scheme 1, X = $^+$SR) or ammonium (Scheme 1, X = $^+$NR$_2$) salts and the [2,3]-Wittig rearrangement of allylic ethers (Scheme 1, X = O).

Scheme 1

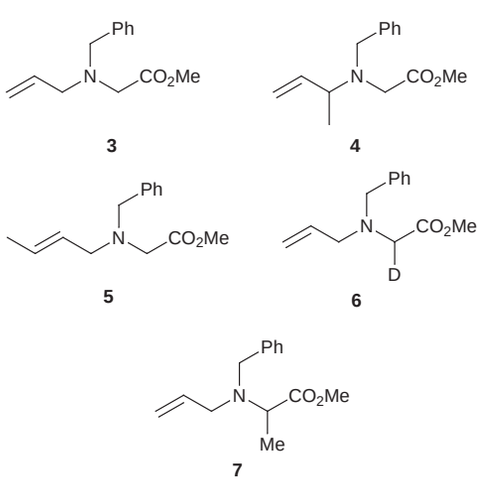
In contrast, the [2,3]-aza-Wittig rearrangement (Scheme 1, X = NR) has received comparatively little attention. This is despite the fact that the quaternary ammonium salts (needed for the Stevens rearrangement) are normally derived from tertiary amines and that the product resulting from rearrangement of the tertiary amine is a secondary amine, which would be more amenable to further manipulation. Successful [2,3]-aza-Wittig rearrangements have been reported using activated tertiary amines, in which the nitrogen atom is incorporated into a β-lactam[2] or aziridine[3] ring system. Alternatively, activation with *N*-Boc[4] or *N*-phosphoramide[5] substituents has allowed the preparation of homoallylic amides. Attempts, however, to promote [2,3]-aza-Wittig rearrangement with tertiary amines normally leads to unreacted starting material or the [1,2]-rearranged products.[6,7] It appears, therefore, that the kinetic barrier to [2,3]-sigmatropic rearrangement of allylic tertiary amines is significantly higher than that of allylic ethers. The intermediate α-amino-organolithium species is therefore more prone to homolytic cleavage (to the allyl radical) than to heterolytic C–N bond cleavage with concomitant [2,3]-sigmatropic rearrangement. There are, however, two reports of successful [2,3]-aza-Wittig rearrangements, using the tertiary amines **1**[8] and **2**[9] (Scheme 2). In both cases, the amine is activated by addition of a Lewis acid, which complexes to the nitrogen atom. The substrate then acts in a way similar to the [2,3]-Stevens rearrangement of ammonium salts and leads, after Lewis acid decomplexation, to the desired secondary amine product.

In order to gain further information on the [2,3]-aza-Wittig rearrangement and to access novel and potentially useful *C*-allyl glycine derivatives, we began an investigation into the rearrangement of *N*-allyl α-amino esters. The closest parallel to

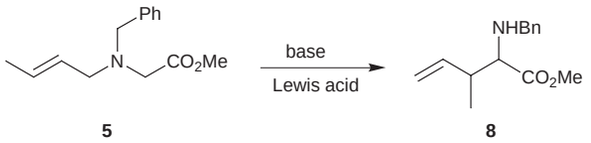


Scheme 2

our studies is the rearrangement of the *N*-allyl α-amino ester **1** using 5 equivalents of trimethylsilyl triflate (TMSOTf) and 4 equivalents of triethylamine, reported by Murata and Nakai.[8] This single example sets the scene for a more detailed investigation of the effect of substituents, different Lewis acids, solvents and conditions for the [2,3]-aza-Wittig rearrangement.



We began our investigations with the allylic amines **3**–**5**, which were prepared by *N*-alkylation of the appropriate *N*-benzyl



5 **8**

Scheme 3

Table 1 Lewis acid catalysed rearrangement of the amine **5**

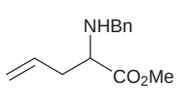
Entry	Base	Solvent	Lewis acid	Conditions	Yield **8** (%)[a]
1	Et_3N	CH_2Cl_2	TMSOTf	room temp.	10
2	Pr^i_2NEt	Et_2O	Bu_2BOTf	−78 to 5 °C	20 (36)[b]
3	LDA	THF	Bu_2BOTf	−78 to 0 °C	22
4	NaH	THF	Bu_2BOTf	−78 to 0 °C	18
5	LDA	THF	$ZnCl_2$	−78 to 0 °C	0
6	LDA	THF	$BF_3{\cdot}OEt_2$	−78 to 0 °C	5
7	LDA	THF	$Sn(OTf)_2$	−78 to 0 °C	0
8	LDA	THF	$[PdCl_2(PPh_3)_2]$	−78 to 0 °C	0
9	LDA	THF	$Cu(OTf)_2$	−78 to 0 °C	0
10	LDA	THF	Cu(OTf)	−78 to 0 °C	28

[a] Yield of the mixture of diastereomers **8** (3:2). [b] Yield in parentheses based on recovered starting material **5**.

allylic amine with methyl bromoacetate (MeCN, K_2CO_3, 75–80%).[10] Treatment of the amine **3** with the base LDA (THF, −78 °C) did not promote rearrangement. Warming to room temperature, addition of HMPA or DMPU, or changing the solvent to Et_2O did not have any affect and the amine **3** could be recovered unchanged, or the enolate could be trapped to give the deuterated product **6** (45%, 100% D) or the methylated product **7** (63%). Likewise, the enolates derived from the amines **4** and **5** could be trapped with iodomethane in reasonable yield.

In order to promote the [2,3]-sigmatropic rearrangement, we turned our attention to the addition of Lewis acids, which would be expected to coordinate to the nitrogen atom of the amine. Somewhat disappointingly, the use of TMSOTf to promote rearrangement of the amine **5** gave only a very low yield of the product **8** (Scheme 3, Table 1, entry 1). In all cases the product **8** was formed as a mixture of diastereoisomers in a ratio 3:2. The [2,3]-Wittig rearrangement has been achieved successfully with the Lewis acid dibutylboron triflate[11] and this reagent (2.2 equivalents) allowed the formation of the allyl glycine derivative **8** using Pr^i_2NEt, LDA or sodium hydride as the base (Table 1, entries 2–4). The low yield of the product **8** was accompanied by recovery of the starting material **5** (up to 45%); however, increasing the amount of dibutylboron triflate was not accompanied by an increase in the yield of the product **8**. We then screened a selection of Lewis acids, as outlined in Table 1. Essentially no rearrangement was observed in all cases, except using Cu^I OTf (entry 10), in which a yield of the rearranged product **8** similar to that using dibutylboron triflate was obtained.

Application of the use of dibutylboron triflate (LDA, THF/DMPU or THF) for rearrangement of the substrates **3** and **4** resulted in the rearranged products **9** and **10** respectively



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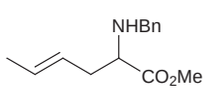

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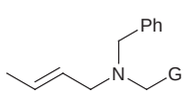

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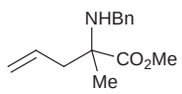

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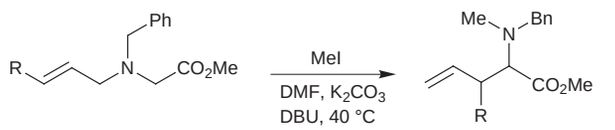
(20–22% yield). Product **10** was formed as predominantly the *E*-isomer (*E*:*Z* = 10:1 by NMR spectroscopy). The use of substrates containing other anion-stabilising groups **11**, G = CO_2Bu^t, CO_2H, CN gave only recovered starting material.

The alanine derivative **7** was subjected to the rearrangement conditions, using LDA and dibutylboron triflate, to give the α-methyl-α-allyl glycine ester **12** (21%). If the yield of this rearrangement could be improved, then this methodology could provide a useful entry to α,α-disubstituted α-amino esters.

In order to overcome the low yields in the rearrangement of these tertiary amines, we turned our attention from the addition of Lewis acids, to the addition of iodomethane or benzyl bromide. We discovered that the *N*-alkylation of the tertiary amines **3** or **5** was followed spontaneously by [2,3]-sigmatropic rearrangement using the solvent DMF and bases K_2CO_3 and DBU at 40 °C.[12] The product amines **13** (R = H, Me) were formed in good yield for the combined alkylation, formation of the ylide and rearrangement steps (Scheme 4). Alkylation of the

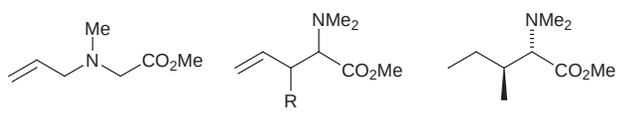


3, R = H
5, R = Me

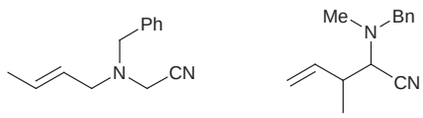
13, R = H 51%
13, R = Me 63%

Scheme 4

corresponding *N*-methyl amines **14** or **1** using benzyl bromide gave the same products **13** (R = H, 52%) or **13** (R = Me, 65%)



14 **15** **16**



17 **18**

respectively. The dimethylamino esters **15** (R = H) or **15** (R = Me) could be prepared by alkylation of the amines **14** or **1** using iodomethane (48 and 53% respectively). In all cases when R = Me, a mixture of the diastereomeric products were obtained. The ratio of the diastereomers was low (60:40). The *anti* diastereomer was found to predominate, as determined by hydrogenation of the product **15**, R = Me, to *N*,*N*-dimethyl isoleucine methyl ester **16** and comparison (NMR) with an authentic sample of ester **16**, prepared from L-isoleucine by *N*,*N*-dimethylation[13] followed by esterification.[14] Finally, it was found that the nitrile **17** acted as a substrate for rearrangement. Treatment with iodomethane gave the product **18** (55%) as a mixture of diastereomers (3:2).

The results suggest that the aza-Wittig rearrangement of tertiary amines with Lewis acids is less effective than the [2,3]-Stevens rearrangement using ylides, generated from quaternary ammonium salts. Both approaches, however, have potential for the formation of novel, substituted allyl glycine derivatives and are being investigated further.

Experimental

Methyl 3-aza-3-benzylhex-5-enoate 3

To *N*-(benzyl)allylamine (2.27 g, 15.44 mmol) was added potassium carbonate (4.15 g, 30.80 mmol) in acetonitrile (40 cm^3) and methyl bromoacetate (2.58 g, 16.94 mmol) in acetonitrile

(40 cm^3), under argon. The solution was stirred at room temperature for 24 h, quenched with $NaHCO_3$ (25 cm^3), extracted with CH_2Cl_2 (3 × 50 cm^3), dried (Na_2SO_4) and evaporated. Purification by column chromatography, eluting with light petroleum (bp 40–60 °C)–EtOAc (5:1) gave the *amine* **3** (2.53 g, 75%) as an oil; R_f [light petroleum (bp 40–60 °C)–EtOAc (5:1)] 0.50; ν_{max}(neat)/cm^{-1} 1735 (C=O), 1640 (C=C), 1495 (Ph); δ_H(400 MHz, $CDCl_3$) 7.30–7.15 (5H, m, Ph), 5.61 (1H, ddt, *J* 17, 10 and 7, CH_2=C*H*), 5.20–5.05 (2H, m, CH_2=CH), 3.73 (2H, s, PhCH_2), 3.55 (3H, s, OCH_3), 3.26 (2H, s, CH_2CO), 3.23 (2H, dt, *J* 7 and 1, C=CCH_2N); δ_C(100 MHz, $CDCl_3$) 171.38 (CO_2), 138.73 (C), 135.64 (CH), 128.87 (CH), 128.22 (CH), 127.08 (CH), 117.73 (CH_2), 57.73 (CH_2), 56.74 (CH_2), 53.31 (CH_2), 50.98 (OCH_3) (Found: M^+, 219.1260. $C_{13}H_{17}NO_2$ requires *M*, 219.1253); *m*/*z* 219 (M^+, 1.4%), 160 (M − CO_2CH_3, 58.0), 128 (M − CH_2Ph, 15.2), 91 ($PhCH_2$, 100).

Methyl 3-aza-3-benzyl-4-methylhex-5-enoate 4

To *N*-benzyl-1-methylallylamine (1.00 g, 6.02 mmol) was added potassium carbonate (1.77 g, 12.4 mmol) in acetonitrile (10 cm^3) and methyl bromoacetate (1.04 g, 6.82 mmol) in acetonitrile (10 cm^3), under argon at room temperature. After 24 h, the mixture was quenched with $NaHCO_3$ (25 cm^3), extracted with CH_2Cl_2 (3 × 10 cm^3), dried (Na_2SO_4) and evaporated. Purification by column chromatography, eluting with light petroleum (bp 40–60 °C)–EtOAc (5:1) gave the *amine* **4** (1.15 g, 80%) as an oil; R_f [light petroleum (bp 40–60 °C)–EtOAc (5:1)] 0.68; ν_{max}(neat)/cm^{-1} 1735 (C=O), 1640 (C=C), 1495 (Ph); δ_H(400 MHz, $CDCl_3$) 7.42–7.18 (5H, m, Ph), 5.85 (1H, ddd, *J* 17, 10 and 7, CH_2=C*H*), 5.19–5.10 (2H, m, CH_2=CH), 3.83 (1H, d, *J* 13, PhCH^AH^B), 3.74 (1H, d, *J* 13, PhCH^AH^B), 3.64 (3H, s, OCH_3), 3.50–3.40 (1H, m, C*H*CH_3), 3.31 (2H, d, *J* 3, CH_2CO), 1.19 (3H, d, *J* 8, CCH_3); δ_C(100 MHz, $CDCl_3$) 172.59 (CO_2), 140.36 (CH), 139.67 (C), 128.73 (CH), 128.21 (CH), 126.91 (CH), 115.74 (CH_2), 58.19 (CH), 54.90 (CH_2), 52.19 (OCH_3), 50.92 (CH_2), 16.74 (C*C*H_3) (Found: M^+, 233.1419. $C_{14}H_{19}NO_2$ requires *M*, 233.1416); *m*/*z* 233 (M^+, 15.0%), 218 (M − CH_3, 24.5), 174 (M − CO_2CH_3, 93.8), 91 ($PhCH_2$, 100).

Methyl 3-aza-3-benzylhept-5-enoate 5

To *N*-(benzyl)crotylamine (1.20 g, 7.45 mmol) was added potassium carbonate (2.01 g, 14.9 mmol) in acetonitrile (30 cm^3) and methyl bromoacetate (1.25 g, 8.21 mmol) in acetonitrile (20 cm^3), under argon at room temperature. After 24 h, the mixture was quenched with $NaHCO_3$ (25 cm^3), extracted with CH_2Cl_2 (3 × 20 cm^3), dried (Na_2SO_4) and evaporated. Purification by column chromatography, eluting with light petroleum (bp 40–60 °C)–EtOAc (5:1) gave the *amine* **5** (1.34 g, 78%) (*E*:*Z* = 10:1) as an oil; R_f [light petroleum (bp 40–60 °C)–EtOAc (5:1)] 0.61; ν_{max}(neat)/cm^{-1} 1735 (C=O), 1639 (C=C), 1495 (Ph); δ_H(400 MHz, $CDCl_3$) 7.26–7.15 (5H, m, Ph), 5.70–5.46 (2H, m, CH=CH), 3.76 (2H, s, PhCH_2), 3.68 (3H, s, OCH_3), 3.30 (2H, s, CH_2CO), 3.20 (2H, dd, *J* 7 and 1, CH_2N), 1.70 (3H, dd, *J* 7 and 1, CH_3); δ_C(100 MHz, $CDCl_3$) 171.94 (CO_2), 138.73 (C), 129.30 (CH), 129.03 (CH), 128.24 (CH), 128.01 (CH), 127.00 (CH), 57.9 (CH_2), 56.15 (CH_2), 53.56 (CH_2), 51.27 (OCH_3), 17.76 (CH_3) (Found: M^+, 233.1419. $C_{14}H_{19}NO_2$ requires *M*, 233.1416); *m*/*z* 233 (M^+, 100%), 218 (M − CH_3, 6.6), 174 (M − CO_2CH_3, 56.1).

Methyl 3-aza-3-benzyl-2-methylhex-5-enoate 7

n-Butyllithium (1.04 cm^3, 2.40 mmol, 2.5 M in hexanes) was added to a solution of diisopropylamine (0.38 cm^3, 2.40 mmol) in THF–HMPA (1.5 cm^3, 4:1) at 0 °C under argon. After 30 min the mixture was cooled to −78 °C and the ester **3** (0.1 g, 0.43 mmol) in THF–HMPA (1 cm^3, 4:1) was added. After 2 h, iodomethane (0.5 cm^3, 8.03 mmol) was added and the mixture was allowed to warm to room temperature, was washed with water (5 cm^3), extracted into CH_2Cl_2 (3 × 10 cm^3), dried (Na_2SO_4) and evaporated. Purification by flash column chromatography, eluting with light petroleum (bp 40–60 °C)–EtOAc (5:1) gave the *amine* **7** as an oil; R_f [light petroleum (bp 40–60 °C)–EtOAc (5:1)] 0.49; ν_{max}(neat)/cm^{-1} 1735 (C=O), 1640 (C=C), 1495 (Ar); δ_H(400 MHz, $CDCl_3$) 7.45–7.21 (5H, m, Ph), 5.88–5.77 (1H, m, CH_2=C*H*), 5.27–5.20 (1H, m, CH=CH^AH^B), 5.15–5.09 (1H, m, CH=CH^AH^B), 3.87 (1H, d, *J* 14, PhCH^AH^B), 3.72 (3H, s, OCH_3), 3.66 (1H, d, *J* 14, PhCH^AH^B), 3.61 (1H, q, *J* 7, C*H*CH_3), 3.30 (1H, ddt, *J* 14, 5 and 2, NCH^AH^B), 3.17 (1H, ddt, *J* 14, 5 and 2, NCH^AH^B), 1.32 (3H, d, *J* 7, CH_3); δ_C(100 MHz, $CDCl_3$) 174.34 (CO_2), 140.12 (C), 136.66 (CH), 128.54 (CH), 128.21 (CH), 126.84 (CH), 117.01 (CH_2), 56.93 (CH), 54.34 (CH_2), 53.65 (CH_2), 51.15 (OCH_3), 15.11 (CH_3) (Found: M^+, 233.1412. $C_{14}H_{19}NO_2$ requires *M*, 233.1416); *m*/*z* 233 (M^+, 4%), 174 (M − CO_2CH_3, 97), 91 ($PhCH_2$, 100).

Methyl 2-*N*-benzylamino-3-methylpent-4-enoate 8

Method A. Dibutylboron triflate (1.0 M in diethyl ether) (0.94 cm^3, 0.94 mmol) was added to allylic amine **5** (0.10 g, 0.43 mmol) and diisopropylethylamine (0.23 cm^3, 1.28 mmol) in anhydrous Et_2O (2 cm^3) at −78 °C under argon. The mixture was allowed to warm to 5 °C over 3 h, quenched with $NaHCO_3$ (5 cm^3), extracted with CH_2Cl_2 (3 × 10 cm^3), dried (Na_2SO_4) and evaporated. Purification by column chromatography, eluting with light petroleum (bp 40–60 °C)–EtOAc (20:1 to 5:1) gave the *amine* **8** (20 mg, 20%) as a mixture of diastereomers a and b (3:2) as an oil; R_f [light petroleum (bp 40–60 °C)–EtOAc (5:1)] 0.58; ν_{max}(neat)/cm^{-1} 1735 (C=O), 1645 (C=C), 1495 (Ph); δ_H(400 MHz, $CDCl_3$) 7.40–7.20 (10H, m, ^{a}Ph and ^{b}Ph), 5.82 (1H, ddd, *J* 17, 10 and 7, $^aCH_2$=C*H*), 5.59 (1H, ddd, *J* 17, 10 and 7, $^bCH_2$=C*H*), 5.08-4.93 (4H, m, $^aCH_2$=CH and $^bCH_2$=CH), 4.05 (1H, d, *J* 7, ^{b}CHCO), 4.02 (1H, d, *J* 7, ^{a}CHCO), 3.74 (3H, s, $^aOCH_3$), 3.68 (3H, s, $^bOCH_3$), 3.37 (1H, d, *J* 12, ^{a}PhCH^AH^B), 3.33 (1H, d, *J* 12, ^{b}PhCH^AH^B), 3.17 (1H, d, *J* 12, ^{a}PhCH^AH^B), 3.08 (1H, d, *J* 12, ^{b}PhCH^AH^B), 2.30 (2H, m, $^aCHCH_3$ and $^bCHCH_3$), 1.60 (2H, s, ^{a}NH and ^{b}NH), 1.07 (3H, d, *J* 7, $^bCH_3$), 0.95 (3H, d, *J* 7, $^aCH_3$); δ_C(100 MHz, $CDCl_3$) 172.36 ($^aCO_2$), 172.18 ($^bCO_2$), 140.61 (^{a}CH), 140.60 (^{b}CH), 140.20 (^{a}C), 140.15 (^{b}C), 128.72 (^{a}CH), 128.51 (^{b}CH), 128.15 (^{a}CH), 128.02 (^{b}CH), 126.72 (^{a}CH), 126.68 (^{b}CH), 115.42 ($^bCH_2$), 114.02 ($^aCH_2$), 67.32 (^{a}CH), 67.20 (^{b}CH), 54.46 ($^aCH_2$), 54.36 ($^bCH_2$), 50.74 ($^aOCH_3$), 50.45 ($^bOCH_3$), 37.77 (^{b}CH), 37.32 (^{a}CH), 13.56 ($^aCH_3$) and 13.39 ($^bCH_3$) (Found: M^+, 233.1416. $C_{14}H_{19}NO_2$ requires *M*, 233.1393); *m*/*z* 233 (M^+, 1.7%), 202 (M − OCH_3, 39.4), 188 (M − CO_2CH_3, 48.3), 91 ($PhCH_2$, 100).

Method B. *n*-Butyllithium (2.5 M hexanes, 0.4 cm^3, 0.96 mmol) was added to a solution of diisopropylamine (1.5 cm^3, 1.07 mmol) in THF (2 cm^3) at 0 °C, under argon. After 30 min, the temperature was lowered to −78 °C, allylic amine **5** (0.1 g, 0.423 mmol) in THF (1 cm^3) was added and the mixture was stirred for 2 h at −78 °C. Dibutylboron triflate (1.0 M in ether, 0.94 cm^3, 0.94 mmol) was added dropwise and the temperature was allowed to warm to 5 °C over 3 h. The reaction was quenched with dilute HCl (5 cm^3, 0.2 M), extracted with CH_2Cl_2 (3 × 10 cm^3), dried (Na_2SO_4) and evaporated. Purification by flash column chromatography eluting with light petroleum (bp 40–60 °C)–EtOAc (20:1 to 5:1) gave the *amine* **8** (22 mg, 22%) as an oil; data as above.

Methyl 2-*N*-benzylaminopent-4-enoate 9

Using Method B as for amine **8**, *n*-butyllithium (0.4 cm^3, 0.96 mmol, 2.5 M in hexanes), diisopropylamine (1.5 cm^3, 1.07 mmol), allylic amine **3** (0.1 g, 0.46 mmol) in THF–DMPU (1.5 cm^3, 2:1) and dibutylboron triflate (0.94 cm^3, 0.94 mmol, 1.0 M in Et_2O) gave, after purification by flash column chromatography eluting with light petroleum (bp 40–60 °C)–EtOAc (20:1 to 5:1) the *amine* **9** (20 mg, 20%) as an oil; R_f [light petroleum (bp 40–60 °C)–EtOAc (5:1)] 0.50; ν_{max}(neat)/cm^{-1}

1735 (C=O), 1640 (C=C), 1495 (Ph); δ_H(400 MHz, $CDCl_3$) 7.40–7.20 (5H, m, Ph), 5.86–5.75 (1H, m, CH_2=C*H*), 5.25–5.02 (2H, m, CH_2=CH), 3.72 (3H, s, OCH_3), 3.96 (1H, d, *J* 12, PhCH^AH^B), 3.53 (1H, d, *J* 12, PhCH^AH^B), 3.33 (1H, dd, *J* 7 and 6, CHCO), 1.80–1.14 (2H, m, CH_2CH), 1.56 (1H, br s, NH); δ_C(100 MHz, $CDCl_3$) 173.79 (CO_2), 140.07 (C), 136.70 (CH), 128.60 (CH), 128.52 (CH), 128.17 (CH), 117.03 (CH_2), 63.50 (CH), 54.54 (CH_2), 53.54 (CH_2), 50.88 (OCH_3) (Found: M^+, 219.1254. $C_{13}H_{17}NO_2$ requires *M*, 219.1259); *m*/*z* 219 (M^+, 0.2%), 91 ($PhCH_2$, 100), 71 (C_4H_9N, 71.3).

Methyl 2-*N*-benzylaminohex-4-enoate 10

Using Method B, as for amine **8**, *n*-butyllithium (0.4 cm^3, 0.96 mmol, 2.5 M in hexanes), diisopropylamine (1.5 cm^3, 1.07 mmol), allylic amine **4** (0.1 g, 0.423 mmol) in THF (1 cm^3) and dibutylboron triflate (0.94 cm^3, 0.94 mmol, 1.0 M in Et_2O) gave, after purification by flash column chromatography eluting with light petroleum (bp 40–60 °C)–EtOAc (20:1 to 5:1), the *amine* **10** (21 mg, 22%) (*E*:*Z* = 10:1) as an oil; R_f [light petroleum (bp 40–60 °C)–EtOAc (5:1)] 0.54; ν_{max}(neat)/cm^{-1} 1740 (C=O), 1610 (C=C), 1495(Ph); δ_H(400 MHz, $CDCl_3$) 7.45–7.13 (5H, m, Ph), 5.60–5.30 (2H, m, CH=CH), 3.83 (1H, d, *J* 13, PhCH^AH^B), 3.76 (3H, s, OCH_3), 3.67 (1H, d, *J* 13, PhCH^AH^B), 3.30 (1H, t, *J* 6.5, CHCO), 2.42–2.36 (2H, m, CH_2CH), 2.21 (1H, s, NH), 1.66 (3H, dd, *J* 6.5 and 1, CCH_3); δ_C(100 MHz, $CDCl_3$) 175.18 (CO_2), 139.71 (C), 128.83 (CH), 128.37 (CH), 127.18 (CH), 127.06 (CH), 125.82 (CH), 60.58 (CH), 51.99 (CH_2), 51.60 (OCH_3), 36.49 (CH_2), 17.95 (C*C*H_3) (Found M^+, 233.1411. $C_{14}H_{19}NO_2$ requires *M*, 233.1393); *m*/*z* 233 (M^+, 1.2%), 188 (M − CO_2CH_3, 49.2), 91 ($PhCH_2$, 100).

Methyl 2-*N*-benzylamino-2-methylpent-4-enoate 12

Using Method B, as for amine **8**, *n*-butyllithium (0.4 cm^3, 0.96 mmol, 2.5 M in hexanes), diisopropylamine (1.5 cm^3, 1.07 mmol), allylic amine **7** (0.11 g, 0.467 mmol) in THF (1 cm^3) and dibutylboron triflate (1.0 cm^3, 1.0 mmol, 1.0 M in Et_2O) gave, after purification by flash column chromatography eluting with light petroleum (bp 40–60 °C)–EtOAc (20:1 to 5:1), the *amine* **12** (22 mg, 21%) as an oil; characterised in part by the following data: R_f [light petroleum (bp 40–60 °C)–EtOAc (5:1)] 0.51; δ_H(400 MHz, $CDCl_3$) 7.42–7.13 (5H, m, Ph), 5.84–5.71 (1H, m, C*H*=CH_2), 5.05–4.88 (2H, m, CH=CH_2), 3.86 (1H, d, *J* 13, PhCH^AH^B), 3.71 (3H, s, OCH_3), 3.26 (1H, d, *J* 13, PhCH^AH^B), 1.92–1.76 (2H, m, CH_2CH_3), 1.58 (1H, br s, NH), 0.92 (3H, s, CH_3); δ_C(100 MHz, $CDCl_3$) 172.60 (CO_2), 140.36 (CH), 138.96 (C), 129.09 (CH), 128.73 (CH), 126.99 (CH), 115.74 (CH_2), 58.19 (C), 51.30 (OCH_3), 50.93 (CH_2), 30.72 (CH_2), 16.73 (CH_3).

Methyl 2-[*N*-(benzyl)methylamino]pent-4-enoate 13 (R = H)

Iodomethane (0.031 cm^3, 0.50 mmol) was added to the amine **3** (0.1 g, 0.46 mmol) and K_2CO_3 (0.13 g, 0.91 mmol) in DMF (1 cm^3) under argon. After 20 min, the mixture was warmed to 40 °C and DBU (0.14 cm^3, 0.91 mmol) was added. After 24 h, the mixture was quenched with aqueous $NaHCO_3$ (5 cm^3), extracted with $CHCl_3$ (3 × 5 cm^3), washed with brine (2 × 5 cm^3), dried (Na_2SO_4) and evaporated. Purification by flash chromatography eluting with light petroleum (bp 40–60 °C)–EtOAc (5:1 to 1:1) gave the *amine* **13** (R = H) (55 mg, 52%) as an oil; R_f [light petroleum (bp 40–60 °C)–EtOAc (3:1)] 0.61; ν_{max}(neat)/cm^{-1} 1730 (C=O), 1645 (C=C), 1495 (Ph); δ_H(400 MHz, $CDCl_3$) 7.35–7.25 (5H, m, Ph), 5.85 (1H, ddt, *J* 17, 10 and 7, CH_2=C*H*), 5.16–5.06 (2H, m, CH_2=CH), 3.81 (1H, d, *J* 14, PhCH^AH^B), 3.74 (3H, s, OCH_3), 3.62 (1H, d, *J* 14, PhCH^AH^B), 3.43 (1H, t, *J* 8, CHCO), 2.57–2.45 (2H, m, CH_2CH), 2.29 (3H, s, NCH_3); δ_C(100 MHz, $CDCl_3$) 172.44 (CO_2), 139.37 (C), 134.84 (CH), 128.71 (CH), 128.21 (CH), 126.97 (CH), 116.91 (CH_2), 65.72 (CH), 65.71 (CH_2), 50.96 (OCH_3), 37.92 (CH_3), 34.08 (CH_2) (Found: M^+, 233.1414. $C_{14}H_{19}NO_2$ requires *M*, 233.1416); *m*/*z* 233 (M^+, 0.4%), 192 (M − C_3H_5, 49.9) 174 (M − CO_2CH_3, 36.4), 91 ($PhCH_2$, 60.0), 84 (C_4H_6NHMe, 100) (Found: C, 72.06; H, 8.00; N, 5.65. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%).

Methyl 2-[*N*-(benzyl)methylamino]-3-methylpent-4-enoate 13 (R = Me)

In the same way as the amine **13** (R = H), the amine **1** (100 mg, 0.70 mmol), benzyl bromide (0.17 cm^3, 0.77 mmol) and DBU (0.23 cm^3, 1.40 mmol) gave, after purification by flash chromatography, eluting with light petroleum (bp 40–60 °C)–EtOAc (5:1 to 1:1), the *amine* **13** (R = Me) (0.11 g, 65%) as a mixture of diastereomers a and b (3:2) as an oil; R_f [light petroleum (bp 40–60 °C)–EtOAc (3:1)] 0.60; ν_{max}(neat)/cm^{-1} 1730 (C=O), 1645 (C=C), 1495 (Ph); δ_H(400 MHz, $CDCl_3$) 7.40–7.20 (10H, m, ^{a}Ph, ^{b}Ph), 5.89 (1H, ddd, *J* 17, 10 and 8, $^aCH_2$=C*H*), 5.64 (1H, ddd, *J* 17, 10 and 8, $^bCH_2$=C*H*), 5.13–4.95 (4H, m, $^aCH_2$=CH and $^bCH_2$=CH), 3.79 (2H, d, *J* 14, ^{a}PhCH^AH^B and ^{b}PhCH^AH^B), 3.49 (2H, d, *J* 14, ^{a}PhCH^AH^B and ^{b}PhCH^AH^B), 3.75 (3H, s, $^aOCH_3$), 3.70 (3H, s, $^bOCH_3$), 3.11 (1H, d, *J* 11, ^{a}CHCO), 3.05 (1H, d, *J* 11, ^{b}CHCO), 2.85–2.65 (2H, m, $^aCHCH_3$ and $^bCHCH_3$), 2.25 (3H, s, $^aNCH_3$), 2.22 (3H, s, $^bNCH_3$), 1.15 (3H, d, *J* 7, $^aCH_3$), 0.98 (3H, d, *J* 7, $^bCH_3$); δ_C(100 MHz, $CDCl_3$) 171.64 ($^aCO_2$), 171.54 ($^bCO_2$), 141.26 (^{a}CH), 140.45 (^{b}CH), 139.49 (^{a}C), 138.49 (^{b}C), 128.70 (^{a}CH), 128.56 (^{b}CH), 128.22 (^{a}CH), 128.14 (^{b}CH), 126.92 (^{a}CH), 126.88 (^{b}CH), 115.55 ($^aCH_2$), 114.17 ($^bCH_2$), 71.26 (^{a}CH), 70.99 (^{b}CH), 58.67 ($^aCH_2$), 58.10 ($^bCH_2$), 50.71 ($^aOCH_3$), 50.47 ($^bOCH_3$), 38.06 ($^aCH_3$), 37.74 ($^bCH_3$), 37.67 (^{a}CH), 37.23 (^{b}CH), 17.92 ($^aCH_3$), 10.94 ($^bCH_3$) (Found: M^+, 247.1572. $C_{15}H_{21}NO_2$ requires *M*, 247.1577); *m*/*z* (M^+, 0.1%), 192 (M − C_4H_7, 58.8), 188 (M − CO_2CH_3, 18.5), 91 ($PhCH_2$, 100).

3-Aza-3-benzylhept-5-enenitrile 17

In the same way as amine **5**, *N*-crotyl(benzyl)amine (0.73 g, 4.51 mmol) and bromoacetonitrile (0.35 cm^3, 4.96 mmol) gave the amine **17** (0.74 mg, 80%) as an oil; R_f [light petroleum (bp 40–60 °C)–EtOAc (5:1)] 0.62; ν_{max}(neat)/cm^{-1} 2230 (CN), 1670 (C=C), 1495 (Ph); δ_H(400 MHz, $CDCl_3$) 7.35–7.26 (5H, m, Ph), 5.78–5.47 (2H, m, CH=CH), 3.66 (2H, s, CH_2CN), 3.44 (2H, s, $PhCH_2$), 3.18 (2H, d, *J* 2, =CCH_2N), 1.74 (3H, d, *J* 6.5, CH_3); δ_C(100 MHz, $CDCl_3$) 137.27 (C), 130.71 (CH), 128.97 (CH), 128.58 (CH), 127.65 (CH), 126.80 (CH), 114.77 (CN), 58.09 (CH_2), 56.51 (CH_2), 40.55 (CH_2), 17.78 (CH_3) (Found: M^+, 200.1307. $C_{13}H_{16}N_2$ requires *M*, 200.1313); *m*/*z* 200 (M^+, 13.7%), 109 (M − $PhCH_2$, 25.2), 91 ($PhCH_2$, 100), 83 (M − C_8H_7N, 33.6).

2-[*N*-(Benzyl)methylamino]-3-methylpent-4-enenitrile 18

In the same way as amine **13**, the amine **17** (100 mg, 0.50 mmol) and iodomethane (0.04 cm^3, 0.55 mmol) gave the *amine* **18** (59 mg, 55%) as a mixture of diastereomers a and b (3:2) as an oil; R_f [light petroleum (bp 40–60 °C)–EtOAc (3:1)] 0.64; ν_{max}(neat)/cm^{-1} 2225 (CN), 1640 (C=C), 1495 (Ph); δ_H(400 MHz, $CDCl_3$) 7.35–7.26 (10H, m, ^{a}Ph and ^{b}Ph), 5.82–5.63 (2H, m, $^aCH_2$=C*H* and $^bCH_2$=C*H*), 5.29–5.09 (4H, m, $^aCH_2$=CH and $^bCH_2$=CH), 3.80 (2H, d, *J* 13, ^{a}PhCH^AH^B and ^{b}PhCH^AH^B), 3.49 (2H, d, *J* 13, ^{a}PhCH^AH^B and ^{b}PhCH^AH^B), 3.28 (1H, d, *J* 11, ^{a}CHCN), 3.20 (1H, d, *J* 11, ^{b}CHCN), 2.74–2.50 (2H, $^aCHCH_3$ and $^bCHCH_3$), 2.31 (3H, s, $^aNCH_3$), 2.30 (3H, s, $^bNCH_3$), 1.18 (3H, d, *J* 7, $^aCCH_3$), 1.11 (3H, d, *J* 7, $^bCCH_3$); δ_C(100 MHz, $CDCl_3$) 139.00 (^{a}CH), 138.58 (^{b}CH), 137.54 (^{a}C), 137.49 (^{b}C), 128.97 (^{a}CH), 128.89 (^{b}CH), 128.81 (^{a}CH), 128.59 (^{b}CH), 127.58 (^{a}CH), 127.55 (^{b}CH), 117.54 ($^aCH_2$), 116.30 (^{a}CN), 116.15 (^{b}CN), 115.44 ($^bCH_2$), 61.92 (^{a}CH), 61.71 (^{b}CH), 59.94 ($^aCH_2$), 59.59 ($^bCH_2$), 39.30 (^{a}CH), 38.71 (^{b}CH), 38.17 ($^aCH_3$), 37.99 ($^bCH_3$), 18.08 ($^aCH_3$), 16.65 ($^bCH_3$) (Found: M^+, 214.1468. $C_{14}H_{18}N_2$ requires *M*, 214.1470); *m*/*z* 214 (M^+, 0.1%), 159 (M − C_4H_7, 68.6), 91 ($PhCH_2$, 100).

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