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Synthesis of 2-Phenyl- and 2,2-Diarylpyrrolidines through Stevens Rearrangement Performed on Azetidinium Ions

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A set of azetidinium ions substituted at the nitrogen atom either by a benzyl group or a benzhydryl group were synthesized to delineate the scope of their ring expansion into 2-phenyl- or 2,2-diaryl-pyrrolidines through a Stevens rearrangement. Whereas the regioselectivity of the rearrangement is very high, the diastereoselectivity is low when 2,3-disubstituted pyrrolidines are produced, except in one case. The major undesirable side-reaction is a Hofmann elimination leading to ring cleavage.

Introduction

Considering the high number of nitrogen heterocycles in pharmaceuticals, it is quite surprising to note that only two drugs including a pyrrolidine ring are present in the top 200 pharmaceutical products by US retail sales in 2011 (Figure 1): the antiviral Telaprevir (**1**), and the antidiabetic Onglyza (**2**),[1] which probably reflects the difficulties faced by synthetic chemists when substituted pyrrolidines are targets. This analysis is best illustrated when one considers nicotine (**3**), which at first sight is a rather simple molecule. Nonetheless, the search for an efficient route to prepare this drug has stimulated huge amounts of difficult but innovative synthetic work, from which quantities of analogues have been synthesized and evaluated as CNS-focused drugs.[2]

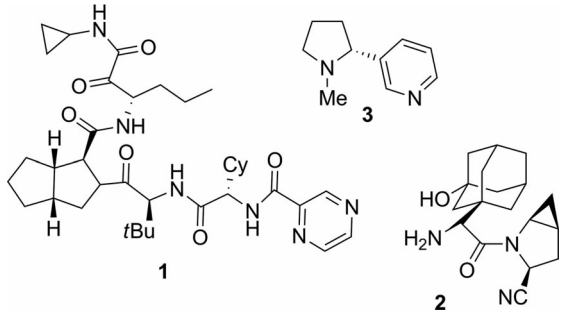

Figure 1. Drugs including a pyrrolidine ring.

Therefore, innovative and robust synthetic routes to pyrrolidines are highly desirable and should be of interest for medicinal chemists wishing to explore chemical diversity derived from this skeleton. In this work, we delineate the scope of the Stevens rearrangement performed on *N*-benzyl-substituted azetidinium ions **4** or *N*-benzhydryl-substituted azetidinium ions **5**, leading to 2-phenylpyrrolidines **8** and 2,2-diarylpyrrolidines **9**, respectively, via ylides **6** and **7** (Figure 2). It is clear from examination of the literature that both of these aryl-substituted pyrrolidines suffer from synthetic routes that are either lengthy and/or lacking in generality,[3] although a major breakthrough has quite recently been reported for the preparation of derivatives of **8** in enantioenriched form.[4]

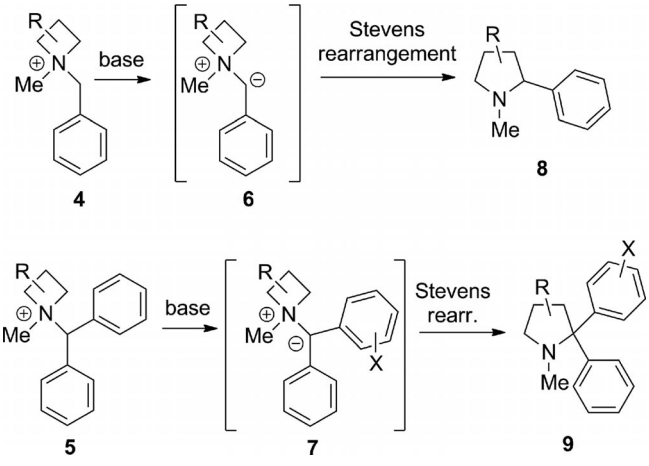

Figure 2. A synopsis of this work.

The Stevens rearrangement of *N*-benzylazetidinium salts has been reported[5] but the scope of this rearrangement has, to the best of our knowledge, not been evaluated apart from isolated issues involving problems of regio- and stereoselectivity.[6] The Stevens rearrangement starting from *N*-benzhydrylazetidinium ions, on the other hand, has not been reported.

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Results and Discussion

Some representative azetidines **10**–**20** (Figure 3) bearing an *N*-benzyl group (**10**–**12**), an *N*-benzhydryl group (**13**–**18**) or a substituted *N*-benzhydryl group (**19** and **20**) were selected for this study. Some of these substrates were either monosubstituted or disubstituted at C-2 on the azetidine ring to address problems of regio- and stereoselectivity during the planned Stevens rearrangement. Among these azetidines, only **13** is commercially available, and other substrates were prepared by three distinct methods.

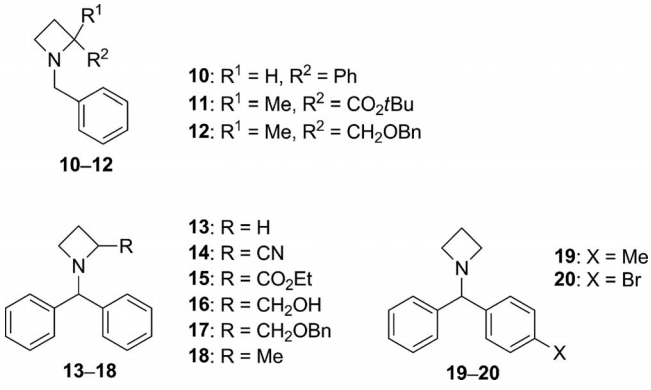
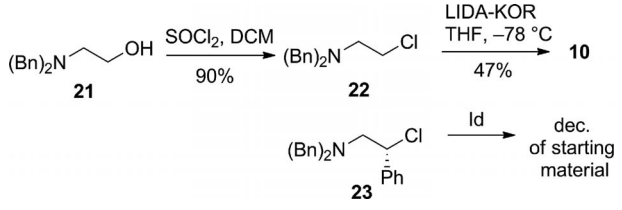


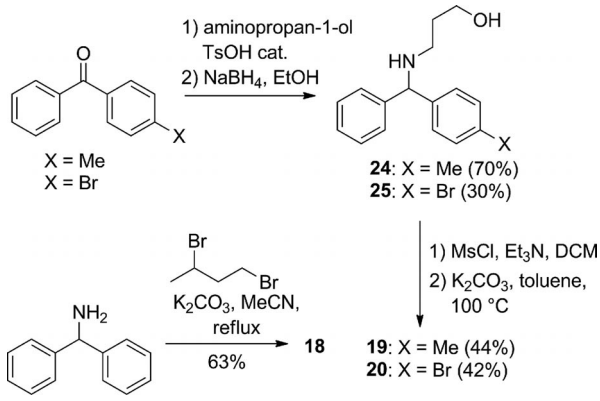
Figure 3. Structures of the *N*-benzyl- and *N*-benzhydrylazetidines selected for this study.

Azetidine **10** was prepared through anionic cyclization, by adapting a recently described procedure[7] involving intramolecular alkylation of a benzylic anion by an epoxide. Thus *N*-dibenzyl ethanolamine **21** was first chlorinated to afford **22** and cyclized to give a modest yield of **10** by treatment with LIDA-KOR (a mixture of lithium diisopropylamide (LDA) and potassium *tert*-butoxide) at –78 °C (Scheme 1). It should be noted that attempts to extend this reaction to secondary benzylic chlorides such as **23** failed.



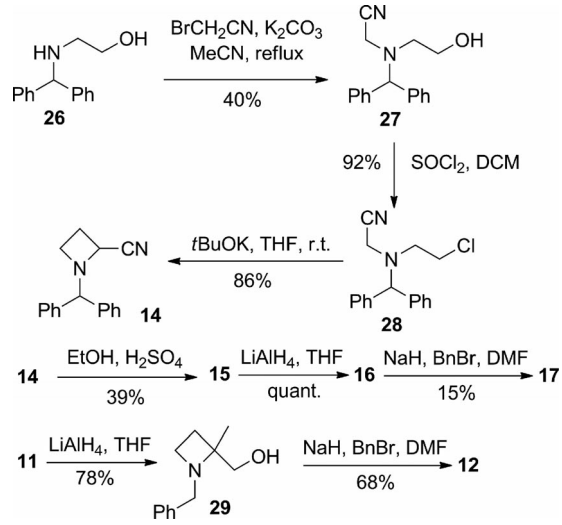
Scheme 1. Synthesis of azetidine **10**.

Azetidines **18**–**20** were prepared through reactions involving the formation of N–C bonds as the key step (Scheme 2), either through a two-step procedure consisting of reductive amination of the corresponding benzophenones with propanolamine followed by mesylation and intramolecular alkylation to produce azetidines **19** and **20** in modest yields, or by double alkylation of 2,4-dibromopropane with benzhydrylamine to afford azetidine **18**.[8]



Scheme 2. Synthesis of azetidines **18**–**20**.

Finally, the other substrates were prepared through our previously reported procedure,[9] involving ring closure of the azetidine ring by intramolecular alkylation of ester or nitrile enolates. Scheme 3 outlines the synthesis of azetidines that have not been described previously by using this methodology.



Scheme 3. Synthesis of azetidines **12** and **14**–**17**.

Next, all of these azetidines were treated with methyl trifluoromethane sulfonate (MeOTf, CH_2Cl_2, 0 °C, then room temp., 3 h) to afford the corresponding azetidinium salts **30**–**39** in good yields, often with high diastereoselectivity, producing single diastereoisomers **33**–**37** in which the relative configurations were not determined but which have already been discussed (Figure 4).[10] In the case of azetidines with a quaternary center, the corresponding ammonium salts were, however, obtained with modest diastereoselectivity (**33** and **39**). Additionally, **13** was also reacted with ethyl trifluoromethanesulfonate to give **40**, however, this required prolonged reaction time (22 h) to complete the alkylation. Only **14** was found to be reluctant to undergo methylation under these conditions, which might be due to deactivation of the nitrogen lone pair by an anomeric effect operating in the amino nitrile moiety.

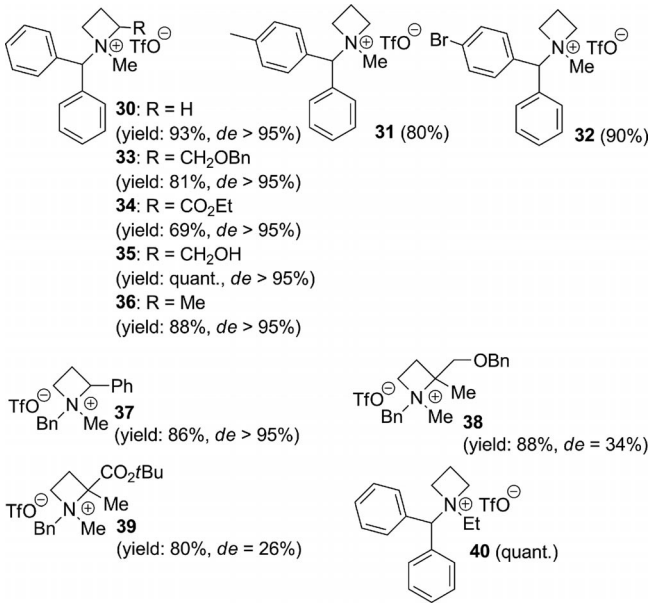
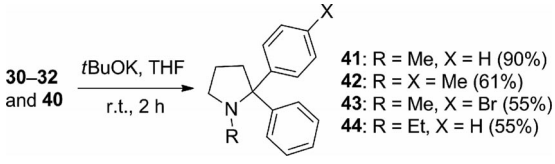


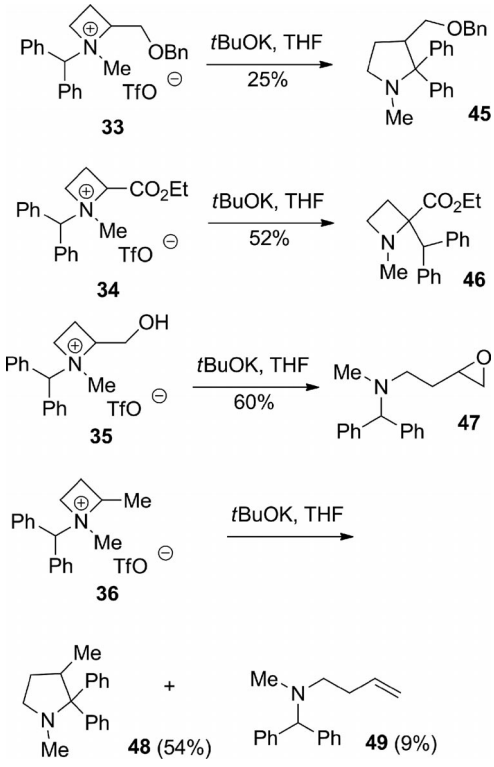
Figure 4. Structures of the *N*-benzyl and *N*-benzhydrylazetidinium salts selected for this study.

A brief screening of the best conditions to induce the Stevens rearrangement of these substrates was carried out by using **30** as substrate; this study led us to identify the use of two equivalents of base (ROK) in tetrahydrofuran (THF) at room temperature for 2 h as best conditions. Using these standardized conditions, *N*-benzhydrylazetidiniums unsubstituted on the azetidine ring **30**–**32** and **40** gave fair to good yields of the expected 2,2-diaryl-substituted pyrrolidines, with no isolable side-products (Scheme 4). No noticeable influence of either the nature of the R group (Me or Et) or of the X group on the *N*-benzhydryl moiety could be detected.



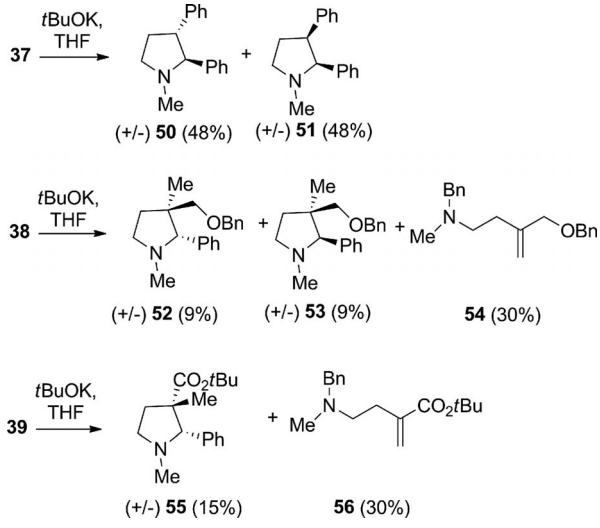
Scheme 4. Stevens rearrangement leading to 2,2-diarylpyrrolidines **41**–**44**.

When *N*-benzhydryl substrates substituted at C-2 (**33**–**36**) were reacted under these conditions, the nature of the C-2 substituent was found to have a strong influence on the outcome of the reaction (Scheme 5). In the case of a Me or CH_2OBn group (**33** and **36**), the Stevens rearrangement was highly regioselective, leading to single regioisomers of **45** or **48**, respectively, resulting from cleavage of the N–C2 bond. However, a side product, **49**, due to competitive Hofmann elimination[11] was isolated in the case of **36**, and the low yield of **48** also reflects similar unwanted processes. When the substituent at C-2 was an ester (**34**), only azetidine **46** was formed, resulting from the regioselective formation of the ylide at C-2 followed by migration of the benzhydryl group without ring expansion. Finally, when the substituent was a primary alcohol (**35**), then alkoxide formation competed, and intramolecular attack led to epoxide **47**, a process that has been observed previously.[12]



Scheme 5. Influence of the nature of the substituent at C-2 for the Stevens rearrangement leading to 2,2-diarylpyrrolidines.

The nature of the substituent at C-2 also had a strong influence on the rearrangement of *N*-benzylazetidinium salts (Scheme 6). In the case of 2-phenyl-substituted azetidinium ion **37**, an excellent yield of 2,3-diphenylpyrrolidines **50** and **51** was produced, demonstrating again the complete regioselectivity for ylide formation and subsequent ring cleavage but low stereoselectivity in the final recombination



Scheme 6. Stevens rearrangement of *N*-benzylazetidinium substrates.

of radicals.[13] These isomers were conveniently separated by flash chromatography, however, in spite of extensive NOESY experiments performed on each compound, we were unable to determine unambiguously their relative configurations. In the case of **38** and **39**, with a quaternary center at C-2, regioselectivity was again total and afforded pyrrolidines **52**, **53** and **55** with low isolated yields because Hofmann elimination becomes severely competitive, with alkenes **54** and **56** isolated as major products. It is worth noting for these examples that whereas **52** and **53** were again produced without stereoselectivity, this was not the case for **55**, which was produced as a single diastereoisomer, which was carefully checked by examination of the crude reaction product by NMR spectroscopy. Relative configurations of **52**, **53** and **55** were assigned on the basis of NOESY experiments (see the Supporting Information).

Conclusions

The set of experiments reported herein demonstrates that Stevens rearrangement of *N*-benzyl and *N*-benzhydrylazetidinium ions constitutes an efficient route to 2-phenyl- and 2,2-diarylpyrrolidines. When 2-substituted and 2,2-disubstituted azetidinium ions are involved, the rearrangement is completely regioselective and often leads to mixtures of diastereoisomeric 2,3-disubstituted pyrrolidines. A major identified side-reaction is Hofmann elimination leading to ring cleavage, and this reaction becomes the major pathway in the case of quaternary azetidinium ions.

Experimental Section

General Comments: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance spectrometer at operating at 200 or 300 and 75 or 50 MHz, respectively; chemical shifts are reported in ppm from TMS. All reactions were carried out under argon. Column chromatography was performed on silica gel 230–400 mesh by using various mixtures of diethyl ether (Et_2O), ethyl acetate (EtOAc), petroleum ether (PE), dichloromethane (CH_2Cl_2), and methanol. TLC analyses were run on Merck Kieselgel 60F_{254} plates. Melting points are uncorrected. THF and toluene were dried by a dehydrating system MB-SPS 800 (Mbraun). Dichloromethane was distilled from calcium hydride. The mention of a "usual workup" means: (i) decantation of the organic layer, (ii) extraction of the aqueous layer with specified solvent, (iii) drying of the combined organic layers over $MgSO_4$, and (iv) solvent evaporation under reduced pressure. Isomeric ratios were determined by NMR analysis of crude reaction mixtures before purification. High-resolution mass spectra (HRMS) were obtained with a Water Micromass Q-Tof Micro instrument. Procedures for the synthesis of azetidines **10**–**20** are provided in the Supporting Information.

General Procedure for the Synthesis of Azetidinium Ions 30–40: To a solution of the required azetidine (1 mmol) in CH_2Cl_2 (10 mL) was added methyl trifluoromethanesulfonate (223 μL, 2 mmol) and the mixture was stirred at room temp. for 3 h. The solvent was evaporated and the oily residue was triturated with small portions of Et_2O. For azetidinium **40**, ethyl trifluoromethanesulfonate was used, and reaction time was prolonged to 22 h. After drying in vacuo, the following azetidinium ions were obtained with yields specified in Figure 4.

Azetidinium 30: Oil; R_f = 0.44 (CH_2Cl_2/MeOH, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.58 (m, 4 H, ArH), 7.47–7.45 (m, 10 H, 2Ph), 6.06 (s, 1 H, $CHPh_2$), 5.00–4.89 (m, 2 H, H-2), 4.18–4.09 (m, 2 H, H-2′), 3.37 (s, 3 H, Me), 2.85–2.75 (m, 1 H, H-3), 2.24–2.14 (m, 1 H, H-3′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.3 (CqAr), 130.1, 130.0, 129.7 (CHAr), 78.2 (CH), 63.4 (CH_2), 49.0 (CH_3), 14.2 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 3035, 1497, 1452, 1259, 1221, 1145 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{17}H_{20}N$ [M – TfO^-]$^+$ 238.1596; found 238.1598.

Azetidinium 31: Oil; R_f = 0.11 (CH_2Cl_2/MeOH, 98:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, J = 6 Hz, 2 H, ArH), 7.40–7.32 (m, 5 H, ArH), 7.14 (d, J = 8 Hz, 2 H, ArH), 5.88 (s, 1 H, $CHPh_2$), 4.86–4.74 (m, 2 H, H-2), 3.99 (br. s, 2 H, H-2′), 3.23 (s, 3 H, Me), 2.77–2.61 (m, 1 H, H-3), 2.24 (s, 3 H, Me), 2.09–2.05 (m, 1 H, H-3′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.3, 132.6 (CqAr), 130.3, 130.0, 129.9, 129.7, 129.6 (CHAr), 129.2 (CqAr), 78.0 (CH), 63.3, 63.2 (CH_2), 48.7 (CH_3), 21.1 (CH_3), 14.1 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 3036, 1455, 1253, 1223, 1151, 1028 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{18}H_{22}N$ [M – TfO^-]$^+$ 252.1752; found 252.1749.

Azetidinium 32: Oil; R_f = 0.26 (CH_2Cl_2/MeOH, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.44 (m, 9 H, 2Ph), 6.07 (s, 1 H, $CHPh_2$), 4.92–4.75 (m, 2 H, H-2), 4.12 (br. s, 2 H, H-2′), 3.35 (s, 3 H, Me), 2.82–2.68 (m, 1 H, H-2), 2.19 (br. s, 1 H, H-2′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.8 (CHAr), 131.8 (CqAr), 131.6 (CHAr), 131.3 (CqAr), 130.3, 129.9, 129.8 (CHAr), 124.6 (CqBr), 76.6 (N*C*HPh_2), 63.6 (CH_2), 48.9 (CH_3), 14.2 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 3037, 2981, 2248, 1590, 1492, 1456, 1251, 1223, 1153, 1076, 1027, 1010 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{16}H_{19}NBr$ [M – TfO^-]$^+$ 316.0701; found 316.0698.

Azetidinium 33: Oil; R_f = 0.62 (EtOAc/*n*BuOH/AcOH/H_2O, 1:1:1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.60 (m, 4 H, ArH), 7.42–7.23 (m, 11 H, 3Ph), 5.87 (s, 1 H, $CHPh_2$), 5.20–5.12 (m, 1 H, H-2), 4.91–4.81 (m, 1 H, H-4), 4.49–4.39 (m, 2 H, OCH_2Ph), 3.92–3.84 (m, 1 H, H-4′), 3.79–3.72 (m, 1 H, C*H*HO), 3.44 (d, J = 15 Hz, 1 H, CH*H*O), 3.21 (s, 3 H, Me), 2.77–2.64 (m, 1 H, H-3), 2.29–2.18 (m, 1 H, H-3′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.6, 132.4, 131.8 (CqAr), 131.0, 130.2, 130.0, 129.9, 129.7, 129.6, 128.6, 128.2, 128.1, 128.0, 127.8 (CHAr), 79.9 (CH), 73.4 (CH_2), 72.5 (CH), 65.8, 60.9 (CH_2), 42.5 (CH_3), 17.1 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 3478, 3058, 2355, 1455, 1394, 1254, 1223, 1151, 1027 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{25}H_{28}NO$ [M – TfO^-]$^+$ 358.2172; found 358.2171.

Azetidinium 34: Oil; R_f = 0.62 (EtOAc/*n*BuOH/AcOH/H_2O, 1:1:1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (br. s, 4 H, ArH), 7.46 (m, 6 H, ArH), 6.12 (s, 1 H, $CHPh_2$), 5.61 (t, J = 8.3 Hz, 1 H, H-2), 5.08–4.98 (m, 1 H, H-4), 4.15–4.07 (m, 2 H, CH_2O), 3.92–3.85 (m, 1 H, H-4′), 3.35 (s, 3 H, Me), 3.08–2.95 (m, 1 H, H-3), 2.76–2.66 (m, 1 H, H-3′), 1.14 (t, J = 8.5 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.2 (CO), 131.3, 131.0 (CqAr), 130.9, 130.6, 130.4, 129.9, 129.7 (CHAr), 80.9, 69.4 (CH), 63.2, 62.2 (CH_2), 43.5 (CH), 18.8 (CH_2), 13.7 ppm. HRMS (ESI, +ve): calcd. for $C_{20}H_{24}NO_2$ [M – TfO^-]$^+$ 310.1807; found 310.1799.

Azetidinium 35: Oil; R_f = 0.54 (EtOAc/*n*BuOH/AcOH/H_2O, 1:1:1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.39 (m, 10 H, 2Ph), 5.75 (s, 1 H, $CHPh_2$), 5.11–4.99 (m, 1 H, H-2), 4.86–4.76 (m, 1 H, H-4), 4.06–3.88 (m, 1 H, H-4′), 3.75–3.70 (m, 1 H, C*H*HOH), 3.46–3.10 (m, 1 H, CH*H*OH), 3.28 (s, 3 H, Me), 2.75–2.65 (m, 1 H, H-3), 2.18–2.12 (m, 1 H, H-3′) ppm. ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 132.9 (CqAr), 131.6, 131.5, 131.2, 130.3, 130.0, 129.8, 129.7, 129.5, 129.2 (CHAr), 79.9, 73.4 (CH), 59.5, 59.0 (CH_2), 43.0 (CH_3), 17.3 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 3432, 3060, 2357, 1450, 1244, 1223, 1156, 1027 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{18}H_{22}NO$ [M – TfO^-]$^+$ 268.1701; found 268.1701.

Azetidinium 36: Oil; R_f = 0.2 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.77–7.68 (m, 4 H, ArH), 7.49–7.41 (m, 6 H, ArH), 6.17 (s, 1 H, $CHPh_2$), 5.33–5.25 (m, 1 H, H-2), 5.01–4.91 (m, 1 H, H-4), 3.77–3.70 (m, 1 H, H-4′), 3.13 (s, 3 H, Me), 2.68–2.58 (m, 1 H, H-3), 2.48–2.41 (m, 1 H, H-3′), 1.09 (d, J = 6 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.7, 131.6 (CqAr), 130.6, 130.4, 130.2, 129.7, 129.6 (CHAr), 79.6, 72.1 (CH), 62.3 (CH_2), 39.3 (CH_3), 22.8 (CH_2), 15.7 (CH_3) ppm. IR (film): $\tilde{\nu}_{max}$ = 3432, 3060, 2357, 1450, 1244, 1223, 1156, 1027 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{18}H_{22}N$ [M – TfO^-]$^+$ 252.1752; found 252.1752.

Azetidinium 37: Oil; R_f = 0.4 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.35 (m, 10 H, 2Ph), 6.16 (t, J = 9 Hz, 1 H, H-2), 5.01 (d, AB syst., J = 12 Hz, NC*H*HPh), 4.96 (m, 1 H, H-4), 4.38 (d, AB syst., J = 12 Hz, NCH*H*Ph), 3.66–3.60 (m, 1 H, H-4), 3.24–3.14 (m, 1 H, H-3), 2.87–2.84 (m, 1 H, H-3′), 2.49 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.0, 131.6 (CqAr), 130.8, 129.9, 129.7, 129.6, 128.7, 127.5 (CHAr), 77.2 (CH), 67.2, 59.9 (CH_2), 42.8 (CH_3), 19.0 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 3579, 3065, 2363, 1471, 1254, 1224, 1145, 1028 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{17}H_{20}N$ [M – TfO^-]$^+$ 238.1596; found 238.1592.

Azetidinium 38: Obtained as a mixture of stereoisomers (63:37) as an oil; R_f = 0.6 (EtOAc/*n*BuOH/AcOH/NEt_3, 1:1:1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.28 (m, 10 H, 2Ph), 4.82 (d, AB syst., J = 12 Hz, 1 H, NC*H*HPh minor), 4.68 (s, 2 H, OCH_2Ph, minor), 4.72–4.59 (m, 3 H, H-4 both isomers, NCH*H*Ph major), 4.57 (s, 2 H, OCH_2Ph, major), 4.42 (d, AB syst., J = 12 Hz, 1 H, NCH*H*Ph minor), 4.10 (d, AB syst., J = 12 Hz, 1 H, NCH*H*Ph major), 4.05 (s, 2 H, $CqCH_2O$ major), 3.97 (d, AB syst., J = 12 Hz, 1 H, CqC*H*HO minor), 3.72 (d, AB syst., J = 12 Hz, 1 H, CqCH*H*O minor), 3.58–3.50 (m, 1 H, H-4′ major), 3.40–3.39 (m, 1 H, H-4′ minor), 2.96 (s, 3 H, Me major), 2.92 (s, 3 H, Me minor), 2.85–2.69 (m, 3 H, 2H-3 major, H-3 minor), 2.46–2.39 (m, 1 H, H-3′ minor), 1.97 (s, 3 H, Me major), 1.67 (s, 3 H, Me minor) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.5, 136.3 (Cq Ar), 132.1, 131.8, 130.4, 129.4, 129.3, 128.7, 128.7, 128.4, 128.3, 128.2, 128.0, 127.8, 127.6 (CH Ar), 84.1, 83.6 (Cq), 73.6, 73.4, 71.6, 71.5, 62.2, 61.0, 59.5, 58.7 (CH_2), 44.6, 43.4 (CH_3), 25.3, 24.7 (CH_2), 20.1, 19.7 (CH_3) ppm. IR (film): $\tilde{\nu}_{max}$ = 3064, 2868, 1455, 1391, 1255, 1123, 1153, 1095, 1012 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{20}H_{26}NO$ [M – TfO^-]$^+$ 296.2014; found 296.2018.

Azetidinium 39: Obtained as a mixture of stereoisomers (70:30) as an oil; R_f = 0.6 (EtOAc/*n*BuOH/AcOH/H_2O, 1:1:1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.43 (m, 5 H, Ph), 5.04–4.94 (m, 1 H, H-4 major), 4.82 (d, AB syst., J = 12 Hz, NC*H*HPh), 4.11 (d, AB syst., J = 12 Hz, NCH*H*Ph), 3.58–3.51 (m, 1 H, H-4′ major), 3.46–3.40 (m, 1 H, H-4 minor), 3.28–3.17 (m, 1 H, H-3), 2.94 (s, 3 H, Me, major), 2.89 (s, 3 H, Me, minor), 2.40–2.33 (m, 1 H, H-3′), 2.15 (s, 3 H, Me, major), 2.12 (s, 3 H, Me, minor), 1.51 (s, 9 H, *t*Bu, major), 1.27 (s, 9 H, *t*Bu, minor) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9 (CO minor), 166.8 (CO major), 131.8, 131.7, 130.7, 129.6, 126.5 (CHAr), 86.3, 81.8 (Cq major), 81.7 (Cq minor), 62.0 (CH_2 major), 61.5 (CH_2 minor), 58.9 (CH_2 major), 58.7 (CH_2 minor), 46.3 (CH_3), 30.8 (CH_3 minor), 27.6 (CH_3 major), 25.4 (CH_2 major), 25.2 (CH_2 minor), 20.6 (CH_3 major), 20.1 (CH_3 minor) ppm. IR (film): $\tilde{\nu}_{max}$ = 2983, 1736, 1456, 1373, 1250, 1221, 1144, 1027 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{17}H_{26}NO_2$ [M – TfO^-]$^+$ 276.1969; found 276.1964.

Azetidinium 40: Oil; R_f = 0.6 (EtOAc/*n*BuOH/AcOH/H_2O, 1:1:1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.43 (m 10 H, 2Ph), 5.60 (s, 1 H, $NCHPh_2$), 4.86–4.76 (m, 2 H, H-2), 4.46–4.37 (m, 2 H, H-2′), 3.74–3.67 (m, 2 H, C$H_2$$CH_3$), 2.59–2.47 (m, 1 H, H-3), 1.74–1.66 (m, 1 H, H-3′), 1.37 (t, J = 11 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.3 (CqAr), 130.0, 129.9, 129.7, 129.5, 127.4 (CHAr), 74.4 (CH), 59.8, 57.5, 54.5, 14.3 (CH_2), 8.2 (CH_3) ppm. IR (film): $\tilde{\nu}_{max}$ = 3478, 3058, 2984, 1455, 1254, 1223, 1027 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{18}H_{22}N$ [M – TfO^-]$^+$ 252.1753; found 252.1752.

General Procedure for the Stevens Rearrangement: To a solution of the required azetidinium salt (1 mmol) in anhydrous THF (10 mL) at 0 °C was added *t*BuOK (224 mg, 2 mmol) and the mixture was stirred at room temp. for 2 h. At this time, the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the reaction mixture was partitioned between water and EtOAc. Usual workup was followed by purification by flash chromatography, yielding the following compounds.

Pyrrolidine 41 (from 30): Oil; R_f = 0.6 (PE/EtOAc, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.25 (m, 10 H, 2Ph), 2.79 (dd, J = 7, 7 Hz, 2 H, H-5), 2.47–2.41 (m, 2 H, H-3), 2.10–2.00 (m, 2 H, H-4), 2.06 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.9 (CqAr), 128.3, 127.5, 1263 (CHAr), 73.1 (Cq), 53.4, 41.9 (CH_2), 36.6 (Me), 22.1 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 3035, 1497, 1452, 1259, 1221, 1145 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{17}H_{20}N$ [M + H]$^+$ 238.1593; found 238.1596.

Pyrrolidine 42 (from 31): Oil; R_f = 0.25 (PE/EtOAc, 95:5). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.24 (m, 9 H, 2Ph), 2.79–2.72 (m, 2 H, H-5), 2.43–2.39 (m, 2 H, H-3), 2.36 (s, 3 H, Me), 2.07–2.00 (m, 2 H, H-4), 2.02 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.2, 140.5, 135.7 (Cq Ar), 128.3, 128.2, 128.1, 127.4, 126.2 (CH Ar), 72.9 (Cq), 53.3, 41.9 (CH_2), 36.6 (CH_3), 22.0 (CH_2), 21.0 (CH_3) ppm. IR (film): $\tilde{\nu}_{max}$ = 2967, 2921, 1693, 1444, 1230 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{18}H_{22}N$ [M + H]$^+$ 252.1750; found 252.1752.

Pyrrolidine 43 (from 32): Oil; R_f = 0.25 (PE/EtOAc, 95:5). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, J = 8 Hz, 2 H, ArH), 7.33–7.27 (m, 4 H, ArH), 7.22–7.13 (m, 4 H, ArH), 2.82–2.68 (m, 2 H, H-5), 2.49–2.27 (m, 2 H, H-3), 2.07–1.97 (m, 5 H, Me and H-4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.3, 142.9 (CqAr), 130.6, 129.9, 128.2, 127.5, 126.5 (CHAr), 120.1 (CqBr), 72.7, 53.3, 41.8 (CH_2), 36.4 (CH_3), 22.0 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 3051, 2970, 2929, 2782, 1687, 1597, 1483, 1463, 1444, 1392, 1228, 1157, 1071, 1108 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{17}H_{18}NBr$ [M + H]$^+$ 316.0701; found 316.0704.

Pyrrolidine 44 (from 40): Oil; R_f = 0.49 (PE/Et_2O, 98:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.23 (m, 10 H, 2Ph), 2.81 (t, J = 12 Hz, 2 H, H-5), 2.42–2.37 (m, 2 H, H-3), 2.10–2.03 (m, 4 H, H-4 and NC$H_2$$CH_3$), 1.15 (t, J = 9 Hz, 3 H, NCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6 (CqAr), 128.2, 127.4, 126.2 (CHAr), 73.7 (Cq), 49.3, 44.5, 42.0, 22.1 (CH_2), 14.3 (CH_3) ppm. IR (film): $\tilde{\nu}_{max}$ = 3051, 2967, 2800, 2365, 1598, 1488, 1443, 1227, 1161, 1074, 1059 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{18}H_{22}N$ [M + H]$^+$ 252.1748; found 252.1752.

Pyrrolidine 45 (from 33): Oil; R_f = 0.64 (PE/EtOAc, 95:5). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.12 (m, 15 H, 3Ph), 4.21 (s, 2 H, OCH_2Ph), 3.14–2.97 (m, 3 H, H-3, H-5 and CHC*H*HO), 2.82–2.78 (m, 1 H, CHCH*H*O), 2.38–2.26 (m, 2 H, H-4 and H-5′), 2.11–2.06 (m, 1 H, H-4′), 1.97 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 142.1, 140.0, 138.5 (CqAr), 129.3, 129.2, 128.2, 127.6, 127.6, 127.4, 127.3, 127.0, 126.5, 126.4 (CHAr), 75.1 (Cq), 74.4, 72.9, 52.2 (CH_2), 48.0, 36.2 (CH), 27.8 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 3027, 2931, 2844, 2789, 2353, 2493, 1443, 1363, 1027, 1090 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{25}H_{28}NO$ $[M + H]^+$ 358.2168; found 358.2171.

Azetidine 46 (from 34): Oil; R_f = 0.8 (CH_2Cl_2/MeOH, 98:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.05 (m, 10 H, 2Ph), 4.37 (s, 1 H, $CHPh_2$), 4.03–3.86 (m, 2 H, O*C*H_2CH$_3$), 2.98–2.91 (m, 2 H, H-4), 2.61–2.54 (m, 1 H, H-3), 2.21 (s, 3 H, Me), 2.18–2.08 (m, 1 H, H-3′), 0.90 (t, J = 6 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4 (CO), 141.4, 140.9 (CqAr), 130.9, 128.9, 128.3, 127.4, 126.4, 126.2 (CHAr), 76.5 (Cq), 60.1 (CH_2), 54.5 (CH), 52.6 (CH_2), 38.5 (CH_3), 23.7 (CH_2), 14.0 (CH_3) ppm. IR (film): $\tilde{\nu}_{max}$ = 2921, 1693, 1444, 1230, 1074 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{20}H_{23}NO_2$ $[M + H]^+$ 252.1752; found 252.1750.

Epoxide 47 (from 35): Oil; R_f = 0.29 (PE/EtOAc, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, J = 7 Hz, 4 H, ArH), 7.32–7.27 (m, 4 H, ArH), 7.23–7.18 (m, 2 H, ArH), 4.40 (s, 1 H, $CHPh_2$), 2.99 (br. s, 1 H, CC*H*O), 2.78–2.75 (m, 1 H, C*H*HO), 2.58–2.53 (m, 2 H, CH_2N), 2.47–2.45 (m, 1 H, CH*H*O), 2.19 (s, 3 H, Me), 1.82–1.69 (m, 2 H, NCH_2CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1, 143.0 (CqAr), 128.4, 127.9, 126.9 (CHAr), 75.8 (CH), 51.9 (CH_2), 51.0 (CH), 47.1 (CH), 40.1 (CH_3), 30.5 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 3023, 2962, 2786, 1593, 1490, 1451, 1266, 1078, 1027, 1010 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{18}H_{22}NO$ $[M + H]^+$ 268.1701; found 268.1701.

Pyrrolidine 48 and Alkene 49 (from 36); Compound 48: Oil; R_f = 0.45 (PE/EtOAc, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.09 (m, 10 H, 2Ph), 2.82–2.75 (m, 1 H, H-5), 2.69–2.59 (m, 1 H, H-3), 2.42–2.34 (m, 1 H, H-5′), 2.28–2.17 (m, 1 H, H-4), 1.86 (s, 3 H, Me), 1.64–1.52 (m, 1 H, H-4′), 0.59 (d, J = 9 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.2, 141.7 (CqAr), 129.7, 129.2, 127.1, 127.0, 126.3, 126.0 (CHAr), 52.3 (CH_2), 43.8 (CH), 36.5 (CH_3), 31.9 (CH_2), 20.1 (CH_3) ppm. IR (film): $\tilde{\nu}_{max}$ = 2958, 1695, 1487, 1443, 1233, 1217 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{18}H_{22}N$ $[M + H]^+$ 252.1755; found 252.1752.

Compound 49: Oil; R_f = 0.54 (PE/EtOAc, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, J = 7 Hz, 4 H, ArH), 7.22–7.17 (m, 6 H, ArH), 7.12–7.07 (m, 2 H, ArH), 5.75–5.61 (m, 1 H, C*H*=CH_2), 4.95–4.86 (m, 2 H, CH=C*H*$_2$), 4.30 (s, 1 H, $CHPh_2$), 2.37–2.33 (m, 2 H, NCH_2), 2.23–2.17 (m, 2 H, C*H*$_2$CH), 2.09 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 128.3, 128.0, 126.7 (CHAr), 75.6 (CH), 54.7 (CH_2), 40.1 (CH_3), 31.6 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 2958, 1695, 1487, 1443, 1233, 1217 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{18}H_{22}N$ $[M + H]^+$ 252.1755; found 252.1752.

Pyrrolidine 50 and 51 (from 37); Compound 50 (or 51): Oil; R_f = 0.52 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.95–6.84 (m, 10 H, 2Ph), 3.57–3.44 (m, 3 H, H-2, H-3 and H-5), 2.52–2.44 (m, 1 H, H-5′), 2.38–2.27 (m, 1 H, H-4), 2.23 (s, 3 H, Me), 2.19–2.13 (m, 1 H, H-4′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 129.0, 128.3, 127.4, 127.3, 126.3, 125.6 (CHAr), 75.9 (CH), 56.3 (CH_2), 50.7 (CH), 41.0 (CH_3), 30.9 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 3023, 2924, 2776, 1678, 1601, 1493, 1447, 1197, 1153, 1071, 1027 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{17}H_{20}N$ $[M + H]^+$ 238.1596; found 238.1596.

Compound 51 (or 50): Oil; R_f = 0.35 (CH_2Cl_2/MeOH, 9:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.11 (m, 8 H, ArH), 7.04–7.01 (m, 2 H, ArH), 3.43–3.38 (m, 1 H, H-5), 3.22–3.14 (m, 1 H, H-3), 3.07–3.04 (m, 1 H, H-2), 2.64–2.56 (m, 1 H, H-5′), 2.53–2.39 (m, 1 H, H-4), 2.18 (s, 3 H, Me), 2.03–1.93 (m, 1 H, H-4′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 128.5, 128.4, 128.0, 127.7, 126.6 (CHAr), 80.0 (CH), 56.2 (CH_2), 53.4 (CH), 39.9 (CH_3), 31.3 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 3399, 2952, 2449, 2671, 1456, 1419, 1157, 1095 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{17}H_{20}N$ $[M + H]^+$ 238.1596; found 238.1596.

Pyrrolidine 52, 53 and Alkene 54 (from 38); Compound 52: Oil; R_f = 0.43 (PE/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.27 (m, 10 H, 2Ph), 4.65–4.56 (m, 2 H, OCH_2Ph), 3.32–3.18 (m, 5 H, H-2 H-5 CH_2O), 2.41–2.32 (m, 1 H, H-5′), 2.21 (s, 3 H, Me), 2.14–2.07 (m, 1 H, H-4), 1.71–1.61 (m, 1 H, H-4′), 0.63 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.8, 138.8 (Cq Ar), 128.7, 128.3, 127.8, 127.5, 127.4, 126.7 (CHAr), 76.8 (CH_2), 73.2 (CH), 55.2 (CH_2), 46.2 (Cq), 41.3 (CH_3), 35.2 (CH_2), 22.9 (CH_3) ppm. IR (film): $\tilde{\nu}_{max}$ = 3027, 2962, 2936, 2837, 2776, 1491, 1452, 1361, 1249, 1092, 1027 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{20}H_{26}NO$ $[M + H]^+$ 296.2017; found 296.2014.

Compound 53: Oil; R_f = 0.17 (PE/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.17 (m, 10 H, 2Ph), 4.29–4.18 (m, 2 H, OCH_2Ph), 3.25–3.19 (m, 1 H, H-5), 3.16 (d, AB syst., J = 9 Hz, 1 H, C*H*HO), 2.92 (s, 1 H, H-2), 2.65 (d, AB syst., J = 9 Hz, 1 CH*H*O), 2.40–2.31 (m, 1 H, H-5′), 2.19 (s, 3 H, Me), 2.15–2.09 (m, 1 H, H-4), 1.65–1.58 (m, 1 H, H-4′), 1.21 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9, 138.7 (CqAr), 128.1, 127.9, 127.7, 127.3, 127.1, 126.9 (CHAr), 81.2 (CH), 77.2, 73.0, 55.0 (CH_2), 45.9 (CH_3), 35.0 (CH_2), 24.5 (CH_3) ppm. IR (film): $\tilde{\nu}_{max}$ = 3027, 2950, 2836, 2772, 1602, 1492, 1450, 1360, 1250, 1201, 1096, 1027 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{20}H_{26}NO$ $[M + H]^+$ 296.2017; found 296.2014.

Compound 54: Oil; R_f = 0.30 (PE/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.17 (m, 10 H, 2Ph), 5.00 (s, 1 H, C=C*H*H), 4.87 (s, 1 H, C=CH*H*), 4.39 (s, 2 H, OCH_2Ph), 3.87 (s, 2 H, CCH_2O), 3.42 (s, 2 H, NCH_2Ph), 2.49–2.44 (m, 2 H, NCH_2), 2.27–2.22 (m, 2 H, CH_2C=C), 2.19 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.5 (Cq), 139.1, 138.4 (CqAr), 129.0, 128.4, 128.2, 127.7, 127.5, 126.9 (CHAr), 112.7, 73.1, 71.9, 62.2, 55.8 (CH_2), 42.0 (CH_3), 30.9 (CH_2) ppm. IR (film): $\tilde{\nu}_{max}$ = 3027, 2839, 1452, 1364, 1093, 1073 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{20}H_{26}NO$ $[M + H]^+$ 296.2016; found 296.2014.

Pyrrolidine 55 and Alkene 56 (from 39); Compound 55: Oil; R_f = 0.75 (PE/EtOAc, 8:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 5 H, Ph), 3.31–3.25 (m, 1 H, H-5), 3.02 (s, 1 H, H-2), 2.80–2.69 (m, 1 H, H-4), 2.47–2.39 (m, 1 H, H-5′), 2.19 (s, 3 H, Me), 1.59–1.49 (m, 1 H, H-4′), 1.37 (s, 3 H, Me), 1.00 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9 (CO), 139.6 (Cq), 128.6, 127.8, 127.1 (CHAr), 82.0 (CH), 79.6 (Cq), 55.0 (Cq), 54.9 (CH_2), 40.8 (CH_3), 35.6 (CH_2), 27.3, 25.8 (CH_3) ppm. IR (film): $\tilde{\nu}_{max}$ = 2975, 2777, 1720, 1452, 1365, 1247, 1144, 1120 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{17}H_{26}NO_2$ $[M + H]^+$ 276.1976; found 276.1964.

Compound 56: Oil; R_f = 0.41 (PE/EtOAc, 8:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 5 H, Ph), 6.09 (d, J = 1 Hz, 1 H, C=C*H*H), 5.49 (d, J = 1 Hz, 1 H, C=CH*H*), 3.54 (s, 2 H, NCH_2Ph), 2.57–2.52 (m, 4 H, NCH_2CH_2), 2.25 (s, 3 H, Me), 1.49 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4 (CO), 140.6, 139.1 (Cq), 129.0, 128.2, 126.9 (CHAr), 124.6 (CH_2), 80.5 (Cq), 62.1, 56.5 (CH_2), 42.0 (CH_3), 29.8 (CH_2), 28.0 (CH_3) ppm. IR (film): $\tilde{\nu}_{max}$ = 2976, 2786, 1708, 1453, 1366, 1310, 1147 cm^{-1}. HRMS (ESI, +ve): calcd. for $C_{17}H_{26}NO_2$ $[M + H]^+$ 276.1962; found 276.1964.

Supporting Information (see footnote on the first page of this article): Procedures for the synthesis of azetidines **10**–**20**. Copies of ^1H and ^{13}C NMR spectra for all new compounds. NOESY data for **52**, **53**, and **55**.

Acknowledgments

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