Doubly diastereoselective [3,3]-sigmatropic aza-Claisen rearrangements†

Stephen G. Davies,* A. Christopher Garner,‡ Rebecca L. Nicholson, James Osborne, Paul M. Roberts, Edward D. Savory, Andrew D. Smith and James E. Thomson

Received 10th February 2009, Accepted 16th March 2009
First published as an Advance Article on the web 28th April 2009
DOI: 10.1039/b902753j

The doubly diastereoselective [3,3]-sigmatropic aza-Claisen rearrangement of silylketene aminals derived from 5-substituted (3*S*,4*E*,α*R*)-1-benzyloxy-3-[*N*-acyl-*N*-(α-methylbenzyl)amino]pent-4-enes furnishes 2,3-disubstituted (*R*)-*N*-α-methylbenzyl (2*S*,3*R*,4*E*)-7-benzyloxyhept-4-enamides in >90% de under the "matched" control of both stereogenic centres. Rearrangement of the "mismatched" diastereomeric (3*R*,4*E*,α*R*)-substrates proceeds with low diastereoselectivity. The substrate scope of the doubly diastereoselective rearrangement of the "matched" substrates in which two new stereogenic centres are created has been delineated.

Introduction

The potential of [3,3]-sigmatropic rearrangements to create simultaneously two adjacent stereocentres with high levels of diastereoselectivity has been exploited extensively in organic synthesis, notably by application of the Cope[1] and Claisen[2] rearrangements. Aza-Claisen[3] rearrangements of *N*-allyl-*N*,*O*-[4] and *O*-allyl-*N*,*O*-ketene aminals[5] have also been investigated, with the introduction of asymmetry in the former typically achieved *via* the use of either chiral Lewis acids[6] or by a chiral *N*-alkyl substituent.[7] For example, Tsunoda *et al.* have shown that reasonable levels of diastereoselectivity in the rearrangements of *N*-allyl amide enolates may be induced by an *N*-α-methylbenzyl substituent. Deprotonation of amide **1** with LDA and subsequent thermal [3,3]-sigmatropic rearrangement of the lithium (*Z*)-enolate **2** gives the *syn*-amide product **3** in 78% de and 85% yield (Fig. 1).[8]

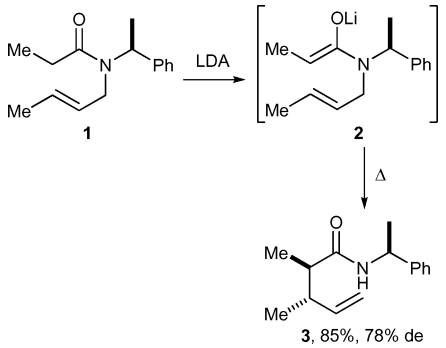


Fig. 1 Diastereoselective [3,3]-sigmatropic aza-Claisen rearrangement.

We envisaged that the diastereoselectivity of this type of rearrangement process could be improved by the synergistic combination of two stereodirecting components within the rearranging substrate structure. For a reaction where there are two stereocontrolling components (*e.g.* the combination of a chiral reagent and chiral substrate, or alternatively in rearrangement/fragmentation reactions of substrates which contain two stereogenic centres), asymmetric induction will arise from the combined influence of the chiral components present: so called *double asymmetric induction.*[9] In the case where the two chiral components offer asymmetric induction towards the same product (are "matched"), high levels of diastereoselectivity are observed, greater than that if only one of the chiral components was present. However if the two chiral components give rise to opposite stereoinduction (are "mismatched") the stereochemistry of the major product will be controlled by the dominant influence. We envisaged that rearrangement of substrates such as benzyl ether **4** (containing both an *N*-α-methylbenzyl group and an adjacent C(3)-stereogenic centre) would be a suitable system in which to probe the effects of double diastereoselectivity in [3,3]-sigmatropic aza-Claisen rearrangements (Fig. 2), and delineate herein our full investigations within this area. Part of this work has been communicated previously.[10]

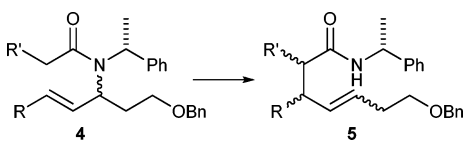


Fig. 2 Doubly diastereoselective [3,3]-sigmatropic aza-Claisen rearrangements.

Results and discussion

Retrosynthetic analysis of aza-Claisen precursors

Retrosynthetic analysis of the required aza-Claisen substrates **6** revealed that a range of differentially substituted precursors could be accessed from allylic amine **7** *via* acylation. Allylic amine **7** is readily accessible from β-amino ester **8**, which in turn may be synthesised from an α,β,γ,δ-unsaturated ester **9** *via* conjugate addition of homochiral lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide **10** (Fig. 3).[11]

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK. E-mail: steve.davies@chem.ox.ac.uk

† Electronic supplementary information (ESI) available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra. CCDC reference numbers 719632, 719633 and 719634. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b902753j

‡ Present address: School of Science and Technology, Nottingham Trent University, Clifton Lane, Nottingham, NG11 8NS, UK.

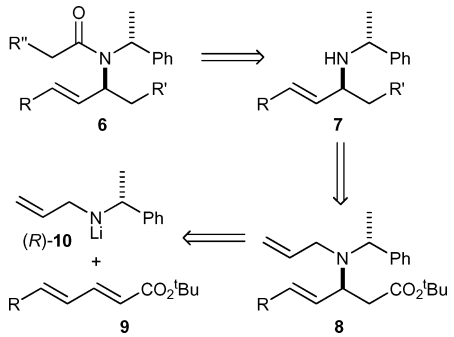
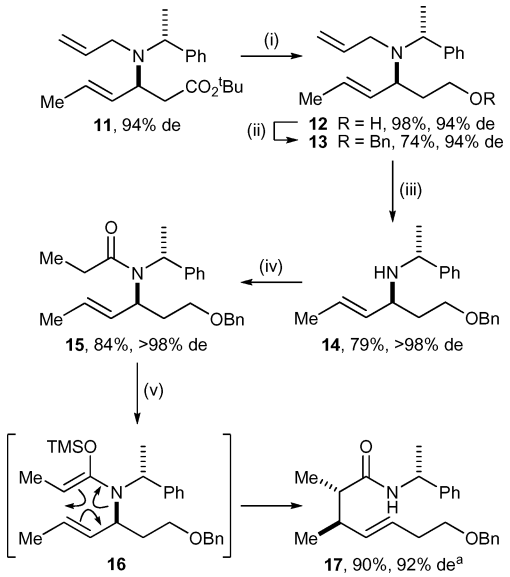


Fig. 3 Retrosynthetic analysis of aza-Claisen precursors **6**.

[3,3]-Sigmatropic aza-Claisen rearrangement: model studies

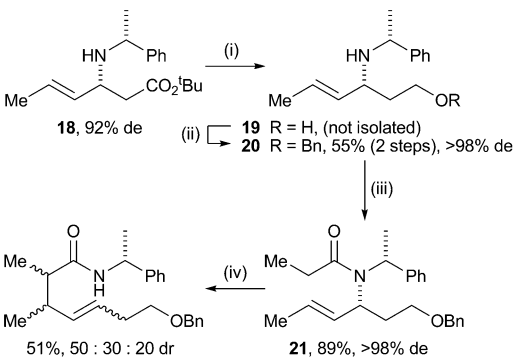
N-Propionyl amide **15** was chosen as a model substrate for initial optimisation of the aza-Claisen rearrangement pathway, and was prepared from the known β-amino ester (3*S*,4*E*,α*R*)-**11** (94% de).[12] It was envisaged that the presence of an acidic CH_2 unit adjacent to an ester functionality would be problematic in a rearrangement process due to competing deprotonation at C(2). The ester functionality within **11** was therefore reduced with $LiAlH_4$ to afford alcohol **12** in 98% yield and 94% de, with subsequent treatment with NaH, BnBr and 15-crown-5 giving benzyl ether **13** in 74% yield and 94% de. *N*-Allyl deprotection of **13** with Wilkinson's catalyst[13] afforded the required secondary amine **14** in 79% yield and >98% de after purification, and subsequent *N*-acylation of amine **14** with propionyl chloride in the presence of DMAP and NEt_3 gave **15** in 84% yield and >98% de. Several conditions were screened in an effort to induce rearrangement,[14] with the optimum conditions being the preparation and *in situ* rearrangement of the (*Z*)-silylketene aminal **16**, derived from *N*-allyl amide **15** by treatment with 1.5 eq of LiHMDS and 2.0 eq of TMSCl: rearrangement under these conditions gave **17** with high diastereoselectivity (92% de), and following chromatographic purification **17** was isolated in 90% yield and 92% de (Scheme 1). Single crystal X-ray analysis unambiguously established the relative configuration within **17**,[15] with the absolute (2*S*,3*R*,4*E*,α*R*)-configuration assigned relative to the known (*R*)-configuration of the α-methylbenzyl stereocentre. ^{1}H NMR ^3J coupling constant analysis of the olefinic protons for the major diastereoisomer **17** confirmed the (*E*)-configuration of the double bond ($J_{4,5}$ >15 Hz), whilst similar analysis of the minor diastereoisomer was indicative of a (*Z*)-configuration of the olefin ($J_{4,5}$ 11.2 Hz).

Having shown that *N*-acyl species **15** undergoes aza-Claisen rearrangement with high diastereoselectivity, attention turned towards evaluation of the C(3)-epimeric substrate to determine whether this highly diastereoselective rearrangement represented the "matched" or "mismatched" reaction manifold. The diastereoisomeric aza-Claisen precursor (3*R*,4*E*,α*R*)-**21** was prepared from the known β-amino ester (3*R*,4*E*,α*R*)-**18** (92% de).[12] Thus, reduction of (3*R*,4*E*,α*R*)-**18** with $LiAlH_4$ gave alcohol **19** which was immediately treated with NaH, BnBr and 15-crown-5 to afford benzyl ether **20** in 55% yield (over two steps) and in >98% de after purification. Subsequent *N*-acylation of **20** gave aza-Claisen precursor **21** in 89% yield and >98% de. Substrate **21** was then treated with 1.5 eq of LiHMDS and 2.0 eq of TMSCl. ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicated that the rearrangement had proceeded to high conversion to give three



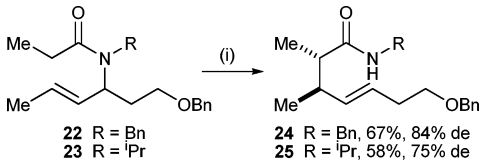
Scheme 1 *Reagents and conditions:* (i) $LiAlH_4$, THF, 0 °C, 16 h; (ii) NaH, BnBr, 15-crown-5, reflux, 16 h; (iii) $Rh(PPh_3)_3Cl$, MeCN–H_2O (85 : 15), reflux, 16 h; (iv) EtCOCl, NEt_3, DMAP, DCM, 16 h; (v) LiHMDS (1.5 eq), TMSCl (2.0 eq), toluene, reflux, 16 h [[a] de refers to both crude and purified material].

diastereoisomeric rearrangement products (50 : 30 : 20 dr). These diastereoisomers proved to be inseparable by chromatography and were therefore isolated as a 50 : 30 : 20 mixture in 51% yield (Scheme 2).[16]



Scheme 2 *Reagents and conditions:* (i) $LiAlH_4$, THF, 0 °C, 16 h; (ii) NaH, BnBr, 15-crown-5, reflux, 16 h; (iii) EtCOCl, NEt_3, DMAP, DCM, 16 h; (iv) LiHMDS (1.5 eq), TMSCl (2.0 eq), toluene, reflux, 16 h.

These data indicate that aza-Claisen rearrangement of the (3*S*,4*E*,α*R*)-diastereoisomer **15** operates in a synergistically "matched" fashion, whereas rearrangement of the (3*R*,4*E*,α*R*)-diastereoisomer **21** proceeded with low diastereoselectivity in a "mismatched" fashion. In accordance with this hypothesis the corresponding (singly diastereoselective) rearrangements of the racemic *N*-benzyl **22** and *N*-isopropyl **23** substrates proceeded cleanly to give **24** and **25** in 84 and 75% de, respectively, which fall in between the levels of selectivity observed for the "matched" (3*S*,4*E*,α*R*)-diastereoisomer (92% de) and "mismatched" (3*R*,4*E*,α*R*)-diastereoisomer (50 : 30 : 20 dr) (Scheme 3).



Scheme 3 *Reagents and conditions:* (i) LiHMDS (1.5 eq), TMSCl (2.0 eq), toluene, reflux, 16 h [de refers to both crude and purified material].

Stereoselectivity: double diastereoselective induction

There are a number of factors which may combine to influence the overall stereochemical outcome of these rearrangements, namely the enolate geometry, whether the reaction proceeds through a chair- or boat-like transition state, and the interaction of the *N*-α-methylbenzyl group with the C(3)-alkyl substituent. High levels of (*Z*)-selectivity can be assumed in the formation of the enolate upon deprotonation of the *N*-acyl fragment with LiHMDS, which can be rationalised using the Ireland deprotonation model.[18] Subsequent trapping of the enolate with TMSCl will give rise to the (*Z*)-*O*-silyl-*N*,*O*-ketene aminal. Rearrangement of the (*Z*)-*O*-silyl-*N*,*O*-ketene aminal is then expected to proceed *via* either a chair- or boat-like transition state due to the orbital symmetry requirements which apply to all [3,3]-sigmatropic rearrangements, with the chair conformer being inherently favoured over the boat. Furthermore, it is plausible to assume that the nitrogen atom is pyramidalised,[17] with the *N*-α-methylbenzyl substituent preferentially occupying an equatorial site in the transition state. Comparison of the two possible chair transition states **26A** and **26B** (in the "matched" case) indicates that in **26A** all of the alkyl substituents occupy the less sterically demanding equatorial sites. In the alternative chair transition state **26B**, the axial alkyl substituent (R = CH_2CH_2OBn) will experience unfavourable 1,3-diaxial interactions. The final factor to be considered is the preferred conformation of the *N*-α-methylbenzyl substituent and its interaction with the adjacent C(3)-alkyl group. The minimisation of *syn*-pentane interactions between the *N*-α-methylbenzyl group and both the C(3)-alkyl group and silyl ether substituent within transition state **26A** places the C(α)*H* atom *anti* to the nitrogen lone pair; this conformation also places the smaller C(α)*Me* group (*versus* the C(α)*Ph* group) eclipsing the C(3)-alkyl substituent (Fig. 4). Thus, rearrangement of **15** (*via* transition state **26A**) gives **17** as the major product diastereoisomer, as observed experimentally.

From inspection of the corresponding chair-like transition states **28A** and **28B** for rearrangement of the "mismatched" (3*R*,4*E*,α*R*)-diastereoisomer **21** (from which three diastereoisomeric products were isolated in 50 : 30 : 20 dr) it is apparent that the relative difference in energies of the possible transition states is less than those of the "matched" (3*S*,4*E*,α*R*)-diastereoisomeric series: for transition state **28A** the axial C(3)-alkyl group experiences unfavourable 1,3-diaxial interactions with the OTMS group, whereas in transition state **28B** minimisation of *syn*-pentane interactions with the OTMS group places the largest C(α)*Ph* substituent in a position which eclipses the C(3)-alkyl group, resulting in destabilisation of the transition state geometries. The relative instability of chair-like transition states **28A** and **28B** potentially results in boat-like transition states also becoming accessible, thus leading to poor diastereoselectivity in the rearrangement of the "mismatched" diastereoisomer **21** (Fig. 5).

Substrate scope for the "matched" rearrangements

Having established that double asymmetric induction is operating in the aza-Claisen rearrangement of the "matched" diastereoisomer (3*R*,4*E*,α*R*)-**15**, further studies were directed towards assessing the substrate scope of this highly diastereoselective

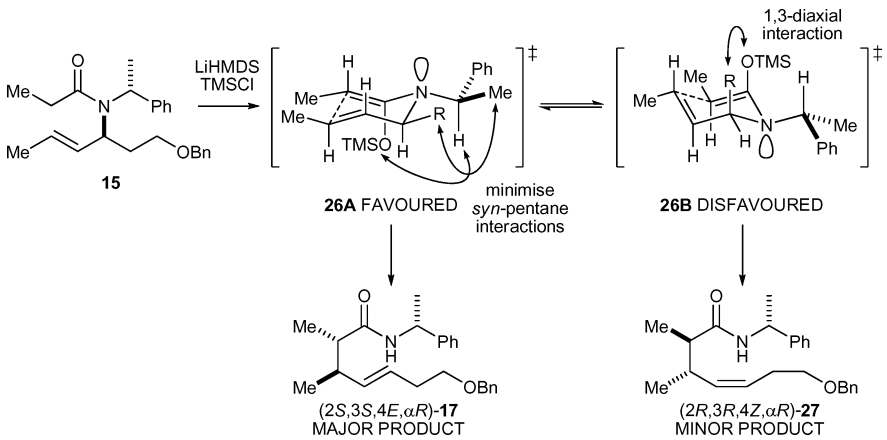


Fig. 4 Proposed transition states for the "matched" aza-Claisen rearrangement of **15** [R = CH_2CH_2OBn].

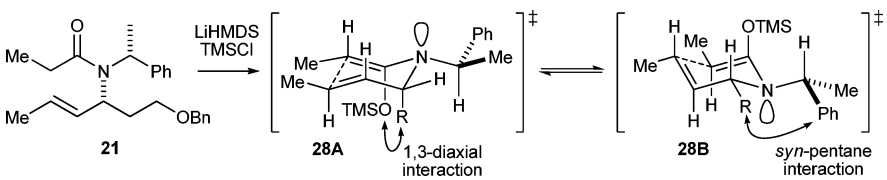
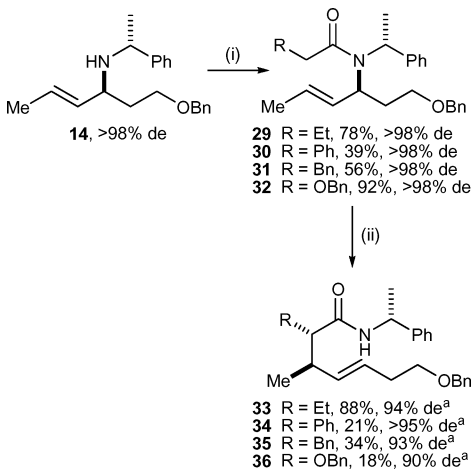


Fig. 5 Possible transition states for the "mismatched" rearrangement of **21** [R = CH_2CH_2OBn].

transformation. It was envisaged that the effect of alternative *N*-acyl functionality could be easily examined by elaboration of amine **14**. *N*-Functionalisation of amine **14** by treatment with butyryl, phenylacetyl, hydrocinnamoyl and benzyloxyacetyl chloride afforded *N*-acyl derivatives **29–32** in 39–92% yield as single diastereoisomers (>98% de) in each case. Treatment of aza-Claisen precursors **29–32** with 1.5 eq of LiHMDS and 2.0 eq of TMSCl promoted rearrangement with high diastereoselectivity: rearrangement of *N*-butyryl **29** gave **33** in 94% de, with subsequent chromatographic purification giving **33** in 88% yield and 94% de.[19] However, treatment of *N*-phenylacetyl **30** afforded a complex mixture of products from which rearrangement product **34** was isolated in 21% yield and >95% de. The corresponding rearrangements of the *N*-hydrocinnamoyl and *N*-benzyloxyacetyl aza-Claisen precursors **31** and **32** proceeded with incomplete conversion to afford **35** and **36** in 34 and 18% isolated yield in 93 and 90% de respectively (Scheme 4). The relative configuration within **35** was unambiguously established by single crystal X-ray analysis, with the absolute (2*S*,3*R*,4*E*,α*R*)-configuration being assigned from the known (*R*)-configuration of the α-methylbenzyl stereocentre (Fig. 6). The configurations within **33**, **34** and **36** were assigned by analogy to those of **17** and **35** which were both unambiguously established by X-ray crystallography.



Scheme 4 *Reagents and conditions:* (i) RCH_2COCl, NEt_3, DMAP, DCM, 16 h; (ii) LiHMDS (1.5 eq), TMSCl (2.0 eq), toluene, reflux, 16 h [[a] de refers to both crude and purified material].

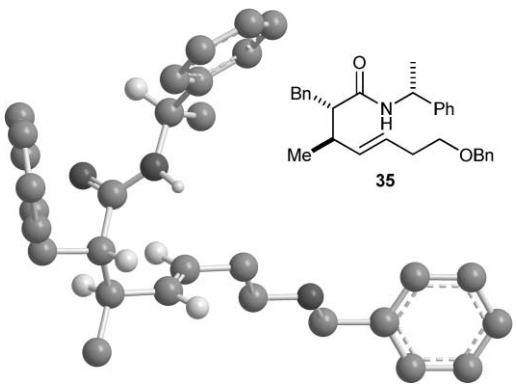
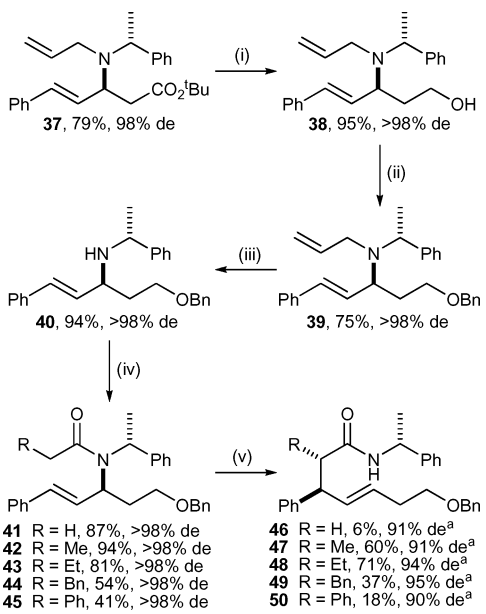


Fig. 6 X-Ray crystal structure of **35** (some H atoms have been omitted for clarity).

The effect of changing the nature of the *N*-allyl fragment was next examined. A range of C(5)-phenyl substrates **41–45** were prepared from the known β-amino ester **37** (98% de).[20] Reduction of **37** with $LiAlH_4$ gave alcohol **38** in 95% yield as a single diastereoisomer (>98% de). Subsequent *O*-benzylation of **38** gave **39** in 75% yield, and *N*-allyl deprotection of **39** with Wilkinson's catalyst gave **40** in 94% yield and >98% de. Finally, treatment of **40** with acetyl, propionyl, butyryl, hydrocinnamoyl and phenylacetyl chloride afforded aza-Claisen precursors **41–45** in moderate to excellent yield (41–94%). Aza-Claisen precursors **41–45** were treated with 1.5 eq of LiHMDS and 2.0 eq of TMSCl to furnish rearranged products **46–50**. Rearrangement of *N*-phenylacetyl **45** afforded a complex mixture of products from which **50** was isolated in 18% yield and 90% de after purification. The rearrangement of *N*-acetyl **41** similarly proceeded in low yield, giving only a 6% yield for the product **46** which was isolated in 91% de. Meanwhile, rearrangement of the precursors **42–44** bearing *N*-propionyl, *N*-butyryl and *N*-hydrocinnamoyl substituents proceeded in high conversion (>80%) with excellent diastereoselectivity (91–95% de). The products **47** and **48** resulting from the *N*-propionyl and *N*-butyryl precursors were isolated in 60 and 71% yield respectively, although the product resulting from rearrangement of the *N*-hydrocinnamoyl precursor **44** was isolated in only 37% yield (Scheme 5). The stereochemistry within **46–50** was initially assigned by analogy to the C(5)-methyl substituted series. In addition, the relative configuration of **47** was unambiguously established by single crystal X-ray analysis, with the absolute (2*S*,3*R*,4*E*,α*R*)-configuration being assigned relative to the known (*R*)-configuration of the *N*-α-methylbenzyl stereocentre (Fig. 7). These data demonstrate that the high levels of diastereoselectivity seen for the aza-Claisen rearrangements in the



Scheme 5 *Reagents and conditions:* (i) $LiAlH_4$, THF, 0 °C, 16 h; (ii) NaH, BnBr, 15-crown-5, reflux, 16 h; (iii) $Rh(PPh_3)_3Cl$, $MeCN–H_2O$ (85 : 15), reflux, 16 h; (iv) RCH_2COCl, NEt_3, DMAP, DCM, 16 h; (v) LiHMDS (1.5 eq), TMSCl (2.0 eq), toluene, reflux, 16 h [[a] de refers to both crude and purified material].

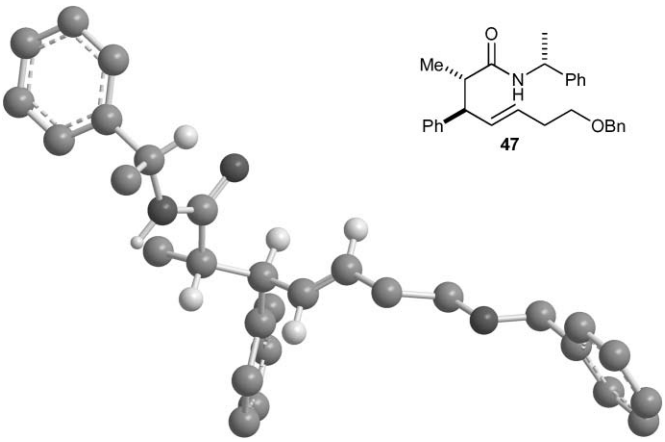


Fig. 7 X-Ray crystal structure of **47** (some H atoms have been omitted for clarity).

C(5)-methyl substituted series is also observed in the C(5)-phenyl substituted series.

Conclusion

In conclusion, [3,3]-sigmatropic aza-Claisen rearrangements of the diastereoisomeric (3*S*,4*E*,α*R*)- and (3*R*,4*E*,α*R*)-substrates proceed under the stereocontrol of both stereogenic centres: the doubly diastereoselective rearrangement of the "matched" (3*S*,4*E*,α*R*)-diastereoisomer proceeds with very high diastereoselectivity, whereas in the "mismatched" rearrangement of the (3*R*,4*E*,α*R*)-diastereoisomer, low levels of diastereoselectivity are observed. Furthermore, rearrangements in the "matched" (3*S*,4*E*,α*R*)-diastereomeric series proceed in good yield, for a range of different substrates, providing useful methodology for the installation of two new stereogenic centres.

Experimental

General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[21] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g per 100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

General procedure 1: reduction with $LiAlH_4$

A solution of $LiAlH_4$ (1.0 eq) was added dropwise to a stirred solution of ester (1.0 eq) in THF at 0 °C and the resultant mixture was allowed to warm to rt over 16 h. The reaction was quenched with ice and EtOAc at 0 °C, then stirred for 1 h, filtered through Celite (eluent Et_2O) and concentrated *in vacuo.*

General procedure 2: *O*-benzylation

A solution of alcohol (1.0 eq) in THF was added dropwise *via* cannula to a suspension of sodium hydride (1.2 eq) in THF at 0 °C. After stirring for 15 min, 15-crown-5 (1.3 eq) and BnBr (2.0 eq) were added and the resultant mixture was heated at reflux. After 16 h the reaction mixture was cooled to rt and sat aq NH_4Cl was added. The resultant mixture was extracted with EtOAc, and the combined organic extracts were dried, filtered and concentrated *in vacuo.*

General procedure 3: *N*-deallylation

Wilkinson's catalyst (0.05 eq) was added in one portion to a stirred solution of amine (1.0 eq) in MeCN–H_2O (85 : 15) at rt. The resultant mixture was heated at reflux for 16 h then cooled to rt and concentrated *in vacuo.*

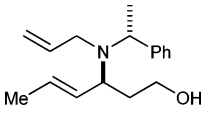
General procedure 4: *N*-acylation

Et_3N (2.5 eq) and the requisite acid chloride (2.0 eq) were added sequentially to a stirred solution of amine (1.0 eq) and DMAP (0.1 eq) in DCM at rt. After stirring for 16 h sat aq NH_4Cl was added. The layers were separated and the organic layer was washed with sat aq $NaHCO_3$, then dried, filtered and concentrated *in vacuo.*

General procedure 5: aza-Claisen rearrangement

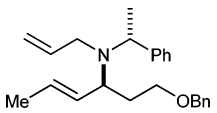
TMSCl (2.0 eq) and LiHMDS (1.5 eq) were added sequentially to a stirred solution of amide (1.0 eq) in toluene at rt. The reaction mixture was heated at reflux for 16 h then allowed to cool to rt. Sat aq NH_4Cl was then added and the aqueous layer was extracted with EtOAc. The combined organic extracts were then dried, filtered and concentrated *in vacuo.*

(3*S*,4*E*,α*R*)-3-[*N*-Allyl-*N*-(α-methylbenzyl)amino]hex-4-en-1-ol 12



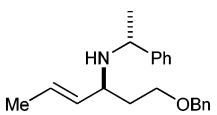
Following *General procedure 1*, **11** (10.5 g, 32.0 mmol, 94% de) and $LiAlH_4$ (32.0 mL, 32.0 mmol) in THF (200 mL) afforded **12** (8.10 g, 98%, 94% de) as a yellow oil; $[\alpha]_D^{21}$ −21.9 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3369 (O–H); δ_H (400 MHz, $CDCl_3$) 1.33–1.43 (1H, m, C(2)H_AH_B), 1.39 (3H, d, *J* 6.9, C(α)CH_3), 1.72 (3H, d, *J* 5.3, C(6)H_3), 1.84–1.90 (1H, m, C(2)H_AH_B), 3.14 (1H, app ddt, *J* 14.4, 8.4, 1.0, C(1′)H_AH_B), 3.37 (1H, ddt, *J* 14.4, 5.2, 1.6, C(1′)H_AH_B), 3.42 (1H, ddd, *J* 10.8, 9.6, 2.8, C(1)H_AH_B), 3.52 (1H, ddd, *J* 10.8, 6.8, 4.4, C(3)*H*), 3.61 (1H, dt, *J* 10.8, 4.4, C(1)H_AH_B), 4.10 (1H, q, *J* 6.9, C(α)*H*), 4.20–4.40 (1H, br s, O*H*), 5.07–5.15 (2H, m, C(3′)H_2), 5.49–5.58 (2H, m, C(4)*H*, C(5)*H*), 5.78–5.84 (1H, m, C(2′)*H*), 7.23–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.9, 18.1, 34.3, 49.5, 57.3, 58.9, 62.4, 116.9, 126.9, 127.0, 128.0, 128.2, 131.0, 137.4, 144.1; *m*/*z* (APCI$^+$) 260 ([M + H]$^+$, 57%), 162 ([M − C_6H_9O]$^+$, 100); HRMS (CI$^+$) $C_{17}H_{26}NO^+$ ([M + H]$^+$) requires 260.2014; found 260.2020.

(3*S*,4*E*,α*R*)-1-Benzyloxy-3-[*N*-allyl-*N*-(α-methylbenzyl)-amino]hex-4-ene 13



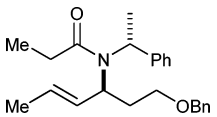
Following *General procedure 2*, **12** (8.03 g, 31.0 mmol), NaH (1.49 g, 37.2 mmol), 15-crown-5 (8.00 mL, 40.3 mmol), and BnBr (7.38 mL, 62.0 mmol) in THF (150 mL) afforded **13** (8.03 g, 74%, 94% de) as a yellow oil after flash column chromatography (eluent pentane–EtOAc, 99 : 1); $[\alpha]_D^{24}$ +10.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1494 (C=C), 1493 (C=C); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.8, C(α)CH_3), 1.60–1.75 (1H, m, C(2)H_AH_B), 1.71 (3H, d, *J* 4.8, C(6)H_3), 1.83–1.95 (1H, m, C(2)H_AH_B), 3.11 (1H, ddt, *J* 14.8, 7.2, 1.2, C(1′)H_AH_B), 3.21 (1H, ddt, *J* 14.8, 5.2, 1.6, C(1′)H_AH_B), 3.37–3.41 (1H, m, C(α)*H*), 3.41 (2H, t, *J* 6.8, C(1)H_2), 4.38 (1H, d, *J* 11.9, OCH_AH_BPh), 4.44 (1H, d, *J* 11.9, OCH_AH_BPh), 5.03 (1H, ddd, *J* 10.4, 2.2, 1.2, C(3′)H_AH_B), 5.09 (1H, ddd, *J* 17.2, 1.8, 1.2, C(3′)H_AH_B), 5.43–5.53 (2H, m, C(4)*H*, C(5)*H*), 5.73–5.83 (1H, m, C(2′)*H*), 7.18–7.39 (10H, m, 2 × *Ph*); δ_C (100 MHz, $CDCl_3$) 17.5, 18.0, 33.3, 49.4, 56.4, 56.5, 68.2, 72.7, 115.3, 126.2, 126.6, 127.4, 127.6, 127.9, 128.2, 131.7, 138.8, 139.1, 145.8; *m*/*z* (APCI$^+$) 350 ([M + H]$^+$, 35%), 162 ([M–C_6H_9O]$^+$, 22), 122 ([$C_8H_{12}N$]$^+$, 100); HRMS (CI$^+$) $C_{24}H_{32}NO^+$ ([M + H]$^+$) requires 350.2484; found 350.2483.

(3*S*,4*E*,α*R*)-1-Benzyloxy-3-[*N*-(α-methylbenzyl)amino]-hex-4-ene 14



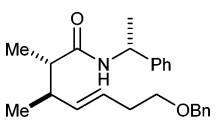
Following *General procedure 3*, **13** (3.12 g, 8.94 mmol, 94% de) and $Rh(PPh_3)_3Cl$ (414 mg, 0.45 mmol) in MeCN–H_2O (85 : 15, 100 mL) afforded **14** (2.12 g, 79%, >98% de) as an orange oil after flash column chromatography (eluent pentane–EtOAc, 7 : 1); $[\alpha]_D^{21}$ +58.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3341 (N–H); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.5, C(α)CH_3), 1.44–1.49 (1H, br s, N*H*), 1.63 (3H, dd, *J* 6.5, 1.6, C(6)H_3), 1.62–1.70 (1H, m, C(2)H_AH_B), 1.82–1.90 (1H, m, C(2)H_AH_B), 3.17–3.22 (1H, m, C(3)*H*), 3.44–3.56 (1H, m, C(1)H_AH_B), 3.56 (1H, dt, *J* 9.2, 6.0, C(1)H_AH_B), 3.85 (1H, q, *J* 6.5, C(α)*H*), 4.46 (1H, d, *J* 11.9, OCH_AH_BPh), 4.51 (1H, d, *J* 11.9, OCH_AH_BPh), 5.19 (1H, ddq, *J* 15.2, 8.4, 1.6, C(4)*H*), 5.45 (1H, dq, *J* 15.2, 6.5, C(5)*H*), 7.20–7.39 (10H, m, 2 × *Ph*); δ_C (100 MHz, $CDCl_3$) 17.7, 23.2, 35.4, 54.6, 55.5, 67.7, 72.9, 126.4, 126.6, 127.4, 127.6, 128.3, 134.1, 138.6, 146.5; *m*/*z* (APCI$^+$) 310 ([M + H]$^+$, 60%), 189 ([M–$C_8H_{11}N$]$^+$, 5), 122 ([$C_8H_{12}N$]$^+$, 5); HRMS (CI$^+$) $C_{21}H_{28}NO^+$ ([M + H]$^+$) requires 310.2171; found 310.2177.

(3*S*,4*E*,α*R*)-1-Benzyloxy-3-[*N*-propionyl-*N*-(α-methylbenzyl)amino]hex-4-ene 15



Following *General procedure 4*, **14** (200 mg, 0.65 mmol), propionyl chloride (0.11 mL, 1.29 mmol), Et_3N (0.23 mL, 1.62 mmol) and DMAP (8 mg, 0.07 mmol) in DCM (10 mL) afforded **15** as a colourless oil (198 mg, 84%, >98% de) after flash column chromatography (eluent pentane–EtOAc, 7 : 1); $[\alpha]_D^{24}$ +32.4 (*c* 1.4 in $CHCl_3$); ν_{max} (film) 1643 (C=O); δ_H (500 MHz, DMSO-d_6, 363 K) 1.04 (3H, t, *J* 7.2, C(3′)H_3), 1.57 (3H, d, *J* 7.0, C(α)CH_3), 1.67 (3H, d, *J* 6.5, C(6)H_3), 1.61–1.69 (1H, m, C(2)H_AH_B), 1.99–2.06 (1H, m, C(2)H_AH_B), 2.32 (1H, dq, *J* 15.5, 7.2, C(2′)H_AH_B), 2.40 (1H, dq, *J* 15.5, 7.2, C(2′)H_AH_B), 3.01–3.11 (2H, m, C(1)H_2), 3.92–4.04 (1H, br s, C(3)*H*), 4.24 (2H, s, OCH_2Ph), 5.07 (1H, q, *J* 7.0, C(α)*H*), 5.56 (1H, dq, *J* 14.5, 6.5, C(5)*H*), 5.75–5.83 (1H, m, C(4)*H*), 7.17–7.41 (10H, m, 2 × *Ph*); δ_C (100 MHz, DMSO-d_6, 363 K) 10.4, 18.2, 19.4, 28.4, 34.3, 55.7, 68.0, 72.6, 127.5, 127.6, 128.0, 128.1, 128.9, 132.4, 139.6, 173.5; *m*/*z* (APCI$^+$) 366 ([M + H]$^+$, 8%), 189 ([M − C_8H_7]$^+$, 17), 122 ([M − $C_{13}H_{15}O$]$^+$, 100); HRMS (CI$^+$) $C_{24}H_{32}NO_2^+$ ([M + H]$^+$) requires 366.2433; found 366.2432.

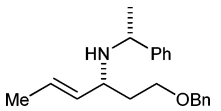
(*R*)-*N*-α-Methylbenzyl (2*S*,3*R*,4*E*)-2,3-dimethyl-7-benzyloxy-hept-4-enamide 17



Following *General procedure 5*, **15** (196 mg, 0.54 mmol), LiHMDS (0.80 mL, 0.80 mmol) and TMSCl (0.14 mL, 1.07 mmol) in toluene (10 mL) afforded the crude product in 92% de. Purification by flash column chromatography (eluent petroleum–EtOAc, 5 : 1) afforded **17** as a white crystalline solid (153 mg, 90%, 92% de). Purification of an aliquot by recrystallisation from petroleum–Et_2O gave an analytical sample of the major diastereoisomer **17** as a white crystalline solid; Found C, 78.7; H, 8.4; N, 3.9%; $C_{24}H_{31}NO_2$ requires C, 78.9; H, 8.55; N, 3.8%; mp 83–85 °C (petroleum–Et_2O); $[\alpha]_D^{21}$ +75.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3285 (N–H), 1641 (C=O),

1547 (C=O); δ_H (400 MHz, $CDCl_3$) 1.00 (3H, d, *J* 6.8, C(3)CH_3), 1.10 (3H, d, *J* 6.9, C(2)CH_3), 1.43 (3H, d, *J* 6.9, C(α)CH_3), 2.02 (1H, dq, *J* 7.0, 6.9, C(2)*H*), 2.32 (2H, m, C(6)H_2), 2.37 (1H, m, (3)*H*), 3.48 (2H, t, *J* 6.9, C(7)H_2), 4.51 (2H, s, OCH_2Ph), 5.12 (1H, m, C(α)*H*), 5.44–5.46 (2H, m, C(4)*H*, C(5)*H*), 5.60 (1H, d, *J* 7.0, N*H*), 7.24–7.38 (10H, m, 2 × *Ph*); δ_C (100 MHz, $CDCl_3$) 14.7, 17.2, 21.6, 33.0, 39.9, 47.2, 48.3, 70.0, 72.8, 126.2, 126.4, 127.3, 127.5, 127.6, 128.3, 128.6, 135.4, 138.5, 143.5, 174.4; *m/z* (APCI$^+$) 366 ([M + H]$^+$, 100%).

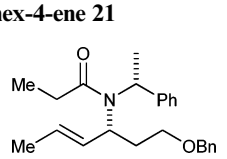
(3*R*,4*E*,α*R*)-1-Benzyloxy-3-[*N*-(α-methylbenzyl)amino]hex-4-ene 20



Following *General procedure 1*, **18** (210 mg, 1.03 mmol, 92% de) and $LiAlH_4$ (1.03 mL, 1.03 mmol) in THF (30 mL) afforded alcohol **19** as a yellow oil (164 mg) which was used immediately in the next step; $[\alpha]_D^{24}$ +103 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 3284 (N–H, O–H), 1108 (C–O); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.6, C(α)CH_3), 1.46–53 (1H, m, C(2)H_AH$_B$), 1.57–1.67 (1H, m, C(2)H$_A$$H_B$), 1.71 (3H, dd, *J* 6.3, 1.5, C(6)H_3), 2.91 (1H, ddd, *J* 10.2, 8.5, 3.7, C(3)*H*), 3.60–3.72 (2H, m, C(1)H_2), 3.87 (1H, q, *J* 6.6, C(α)*H*), 5.22 (1H, ddq, *J* 15.2, 8.5, 1.5, C(4)*H*), 5.36 (1H, dq, *J* 15.2, 6.3, C(5)*H*), 7.20–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.7, 25.2, 37.6, 54.7, 58.8, 62.8, 127.0, 127.1, 127.6, 128.6, 132.6, 144.7; *m/z* (APCI$^+$) 220 ([M + H]$^+$, 11%), 105 ([C_8H_9]$^+$, 100); HRMS (CI$^+$) $C_{14}H_{22}NO^+$ ([M + H]$^+$) requires 220.1701; found 220.1398.

Following *General procedure 2*, **19** (164 mg), NaH (35 mg, 0.87 mmol), 15-crown-5 (0.19 mL, 0.95 mmol), and BnBr (0.17 mL, 1.45 mmol) in THF (15 mL) afforded benzyl ether **20** as a yellow oil (124 mg, 55% over two steps, >98% de) after flash column chromatography (eluent petroleum–EtOAc, 1 : 2); $[\alpha]_D^{24}$ +34.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3310 (N–H), 1103 (C–O); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.8, C(α)CH_3), 1.58 (1H, br s, N*H*), 1.68 (3H, dd, *J* 6.0, 1.2, C(6)H_3), 1.59–1.78 (2H, m, C(2)H_2), 2.84–2.89 (1H, m, C(3)*H*), 3.41–3.52 (2H, m, C(1)H_2), 3.82 (1H, q, *J* 6.8, C(α)*H*), 4.39 (1H, d, *J* 11.9, OCH_AH$_B$Ph), 4.46 (1H, d, *J* 11.9, OCH$_A$$H_B$Ph), 5.19 (1H, ddq, *J* 15.2, 8.4, 1.2, C(4)*H*), 5.29 (1H, dq, *J* 15.2, 6.0, C(5)*H*), 7.20–7.36 (10H, m, 2 × *Ph*); δ_C (100 MHz, $CDCl_3$) 17.2, 25.1, 36.3, 54.6, 54.8, 68.1, 72.9, 126.6, 126.7, 127.5, 127.6, 128.3, 128.3, 128.8, 133.7, 138.5, 145.9; *m/z* (APCI$^+$) 310 ([M + H]$^+$, 100%), 122 ([M – $C_{13}H_{15}O$]$^+$, 46); HRMS (CI$^+$) $C_{21}H_{28}NO^+$ ([M + H]$^+$) requires 310.2171; found 310.2170.

(3*R*,4*E*,α*R*)-1-Benzyloxy-3-[*N*-propionyl-*N*-(α-methylbenzyl)amino]hex-4-ene 21



Following *General procedure 4*, **20** (59 mg, 0.19 mmol), propionyl chloride (0.03 mL, 0.38 mmol), Et_3N (0.07 mL, 0.48 mmol) and DMAP (2 mg, 0.02 mmol) in DCM (5 mL) afforded **21** (62 mg, 89%, >98% de) as a colourless oil after flash column chromatography (eluent petroleum–EtOAc, 7 : 1); $[\alpha]_D^{24}$ –26.0 (*c* 0.7 in $CHCl_3$); ν_{max} (film) 1643 (C=O), 1098 (C–O); δ_H (500 MHz, DMSO-d_6, 363 K) 1.02 (3H, t, *J* 7.2, C(3′)H_3), 1.42 (3H, d, *J* 6.0, C(6)H_3), 1.60 (3H, d, *J* 7.0, C(α)CH_3), 1.91–1.98 (1H, m, C(2)H_AH$_B$), 2.10–2.20 (1H, m, C(2)H$_A$$H_B$), 2.28–2.42 (2H, m, C(2′)H_2), 3.38 (1H, ddd, *J* 10.4, 8.5, 5.2, OCH_AH$_B$Ph), 3.48 (1H, dt, *J* 10.4, 5.2, C(1′)H$_A$$H_B$), 3.98–4.08 (1H, m, C(3)*H*), 4.42 (1H, d, *J* 11.7, C(1)H_2), 4.50 (1H, d, *J* 11.7, OCH$_A$$H_B$Ph), 4.88–5.00 (1H, m, C(5)*H*), 5.08 (1H, q, *J* 7.0, C(α)*H*), 5.55 (1H, dd, *J* 15.2, 7.0, C(4)*H*), 7.22–7.38 (10H, m, 2 × *Ph*); δ_C (100 MHz, $CDCl_3$) 9.6, 17.5, 17.7, 27.8, 34.2, 54.9, 55.4, 67.6, 72.8, 127.3, 127.4, 127.7, 128.0, 128.1, 128.3, 129.1, 138.4, 140.2, 176.7; *m/z* (APCI$^+$) 365 ([M + H]$^+$, 100%), 178 ([$C_{13}H_{16}$]$^+$, 100); HRMS (CI$^+$) $C_{24}H_{32}NO_2^+$ ([M + H]$^+$) requires 366.2433; found 366.2437.

References and notes

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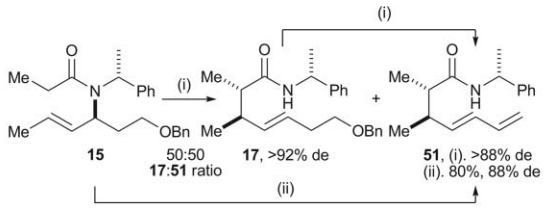
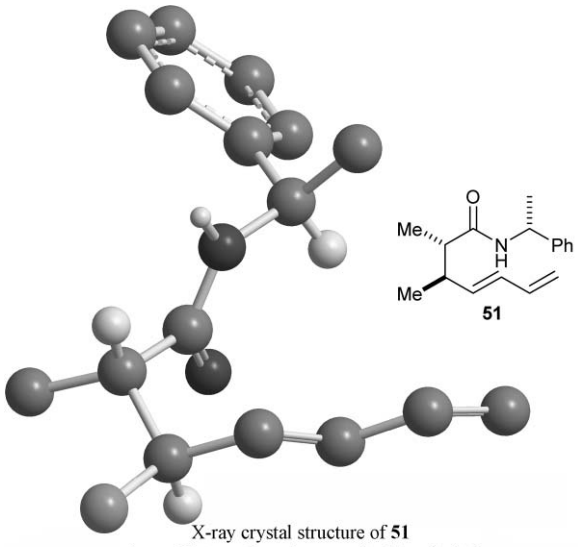
14 Initially, **15** was treated with 1.5 eq of LiHMDS [(i)] to give an approximately 50 : 50 mixture of γ,δ-unsaturated amide **17** and diene **51**. Resubjection of **17** to the reaction conditions was found to give complete conversion to diene **51**; this result is consistent with **17** being formed as the initial product of aza-Claisen rearrangement, with subsequent elimination of benzyl alcohol (under the basic reaction conditions) giving diene **51**. This observation suggested that the use of excess LiHMDS would allow the exclusive preparation of diene **51**. Indeed, treatment of **15** with 3.0 eq of LiHMDS [(ii)] afforded only diene **51** in 88% de. Subsequent purification gave diene **51** in 80% yield and 88% de. The relative configuration within **51** was unambiguously established by single crystal X-ray analysis, with the absolute (2*S*,3*R*,4*E*,α*R*)-configuration being assigned from the known (*R*)-configuration of the α-methylbenzyl stereocentre. In an attempt to prepare aza-Claisen rearrangement product **17** in the absence of diene **51**, *N*-allyl amide **15** was treated with 1.0 eq of LiHMDS. However, analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed that a significant proportion of diene **51** was present, despite the use of a stoichiometric amount of base. Studies were therefore directed towards inducing aza-Claisen rearrangement of the *in situ* formed silylketene aminal derived from *N*-allyl amide **15**.



Reagents and conditions: (i) LiHDMS (1.5 eq), toluene, reflux, 16 h; (ii) LiHDMS (3.0 eq), toluene, reflux, 16 h.



X-ray crystal structure of **51** (some H atoms have been omitted for clarity).

15 Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 190887, see ref. 10.

16 Attempts to assign the double bond configuration for any of the three products were unsuccessful due to the complex nature of the ^{1}H NMR spectrum of this mixture.

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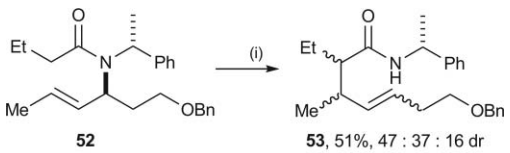
19 Rearrangement of the corresponding "mismatched" (3*S*,4*E*,α*R*)-substrate **52** with 1.5 eq of LiHMDS and 2.0 eq of TMSCl [(i)] proceeded to high conversion to give a 47 : 37 : 16 mixture of diastereoisomers as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Chromatographic purification of the mixture gave an inseparable 47 : 37 : 16 mixture of diastereoisomers in 51% isolated yield.



Reagents and conditions: (i) LiHDMS (1.5 eq), TMSCl (2.0 eq), toluene, reflux, 16 h.

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