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Double diastereoselective [3,3]-sigmatropic aza-Claisen rearrangements

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Asymmetric [3,3]-sigmatropic aza-Claisen rearrangement of the (*Z*)-*N*-allyl-*N*,*O*-silylketene aminal of (3*S*,4*E*,α*R*)-1-benzyloxy-3-(*N*-propionyl-*N*-α-methylbenzylamino)hex-4-ene furnishes (2*S*,3*R*,4*E*,α*R*)-*N*-α-methylbenzyl-2,3-dimethyl-7-benzyloxyhept-4-enamide in > 92% d.e.; rearrangement of the diastereomeric (3*R*,4*E*,α*R*)-(*Z*)-*N*,*O*-silylketene aminal proceeds with low diastereoselectivity.

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 an asymmetric *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]-rearrangement of the (*Z*)-lithium enolate **2**, gives the *syn*-amide product **3** in 78% d.e. and 85% yield (Fig. 1).[8] Although the aza-Claisen rearrangement of *N*-allyl amide enolate **2** proceeds with good levels of stereocontrol (78% d.e.), it was envisaged that the diastereoselectivity of this type of rearrangement process should be improved by synergistic combination of two stereodirecting components within the rearranging substrate structure. The preliminary findings of investigations concerning the double diastereoselective [3,3] sigmatropic aza-Claisen rearrangement of diastereomeric benzyl ethers such as **4** and **5** (Fig. 2), containing both an *N*-α-methylbenzyl group and an adjacent C(3) stereogenic centre, are described herein.

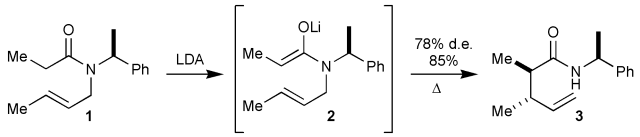


Fig. 1

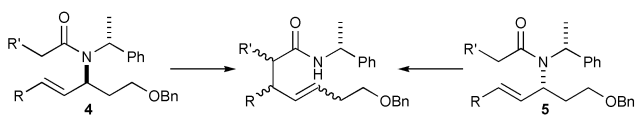
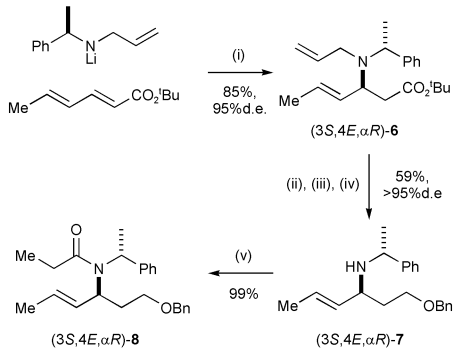


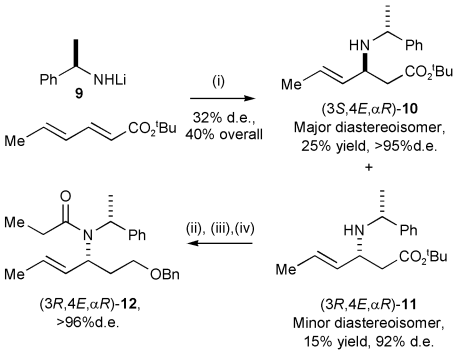
Fig. 2

Rearrangement precursor (3*S*,4*E*,α*R*)-1-benzyloxy-3-(*N*-propionyl-*N*-α-methylbenzylamino)hex-4-ene **8** was prepared stereoselectively *via* a simple five step synthetic sequence. Conjugate addition of homochiral (*R*)-*N*-allyl-*N*-α-methylbenzylamide to (*E*,*E*)-*tert*-butyl hex-2,4-dienoate gave the known tertiary β-amino ester (3*S*,4*E*,α*R*)-**6** in 85% yield and > 95% d.e.,[9] with subsequent ester reduction, *O*-benzylation and *N*-deallylation giving benzyl ether (3*S*,4*E*,α*R*)-**7** in 59% yield over three steps and in > 96% d.e. Subsequent *N*-acylation with propionyl chloride furnished the required rearrangement substrate (3*S*,4*E*,α*R*)-**8** (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) lithium (*R*)-*N*-allyl-*N*-α-methylbenzylamide, THF, −78 °C; (ii) $LiAlH_4$, THF, 0 °C to rt; (iii) BnBr, 15-crown-5, NaH, Δ; (iv) $RhCl(PPh_3)_3$, MeCN : H_2O, Δ; (v) CH_3CH_2COCl, NEt_3, DMAP, DCM, rt.

While the conjugate addition of homochiral secondary lithium amide (*R*)-*N*-allyl-*N*-α-methylbenzylamide enables the selective preparation of (3*S*,4*E*,α*R*)-**8**, synthesis of diastereomeric (3*R*,4*E*,α*R*)-**13** required the unselective conjugate addition of lithium (*R*)-*N*-α-methylbenzylamide **9** to (*E*,*E*)-*tert*-butyl hex-2,4-dienoate, giving (3*S*,4*E*,α*R*)-**10** and (3*R*,4*E*,α*R*)-**11** in 32% d.e. Column chromatography enabled separation of the diastereoisomers, affording (3*S*,4*E*,α*R*)-**10** as the major diastereoisomer in 25% overall yield and > 95% d.e., and the required (3*R*,4*E*,α*R*)-**11** as the minor diastereoisomer in 15% yield and 92% d.e. Subsequent manipulation of (3*R*,4*E*,α*R*)-**11** gave (3*R*,4*E*,α*R*)-**12** (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) (*R*)-*N*-α-methylbenzylamide, THF, −78 °C; (ii) $LiAlH_4$, THF, 0 °C to rt; (iii) BnBr, 15-crown-5, NaH, Δ; (iv) CH_3CH_2COCl, NEt_3, DMAP, DCM, rt.

The aza-Claisen rearrangements of the diastereomeric precursors (3*S*,4*E*,α*R*)-**8** and (3*R*,4*E*,α*R*)-**12** were then investigated. Treatment of (3*S*,4*E*,α*R*)-**8** (> 96% d.e.) with LHMDS and TMSCl on toluene at reflux afforded γ,δ-unsaturated amide (2*S*,3*R*,4*E*,α*R*)-*N*-α-methylbenzyl 2,3-dimethyl-7-benzyloxyhept-4-enamide **13** with high diastereoselectivity (> 92% d.e.), and in 90% yield as a single diastereoisomer after purification by column chromatography and recrystallisation (Scheme 3). The relative configuration within **13** was established by single crystal X-ray diffraction (Fig. 3),† with the absolute

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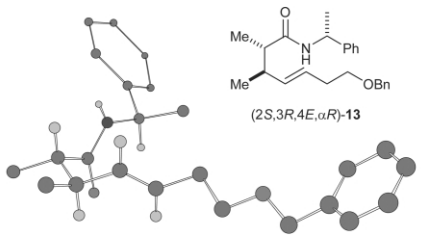
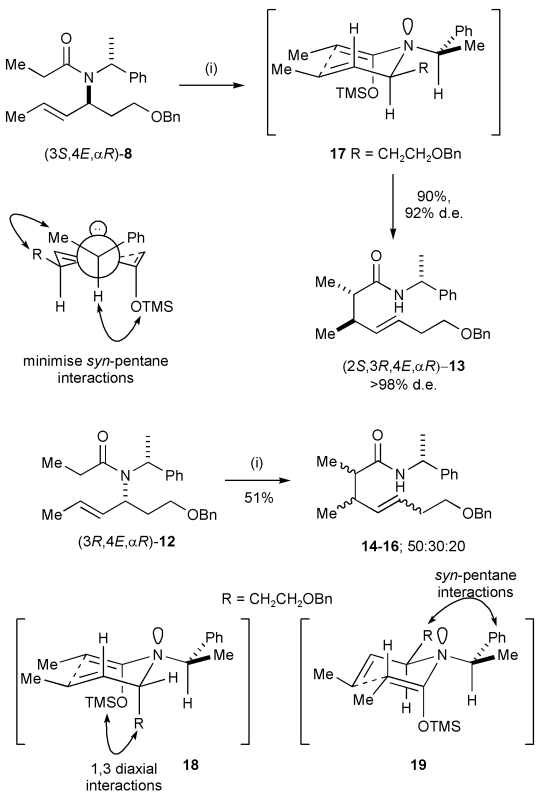


Fig. 3 Chem 3D representation of the X-ray crystal structure of (2*S*,3*R*,4*E*,α*R*)-**13** (some H removed for clarity).

(2*S*,3*R*,4*E*,α*R*) configuration following from the known (*R*)-configuration of *N*-α-methylbenzylamine.

To determine whether this highly diastereoselective rearrangement represented the matched or mismatched reaction manifold, diastereomeric benzyl ether (3*R*,4*E*,α*R*)-**12** was subjected to rearrangement under identical conditions. Although the reaction proceeded to high conversion by ^{1}H NMR spectroscopy, a complex inseparable mixture of three of the possible eight diastereomeric γ,δ-unsaturated amide products **14–16** were produced in a 50 : 30 : 20 ratio. The relative configurations contained within the diastereomeric products **14–16** were not unambiguously identified, but the mixture was isolated in 51% yield after purification by chromatography (Scheme 3).



Scheme 3 *Reagents and Conditions*: (i) LHMDS (1.5 eq), TMSCl (2 eq), toluene, Δ.

These experiments clearly indicate that rearrangement of (3*S*,4*E*,α*R*)-**8** represents the synergistically matched reaction, while rearrangement of the corresponding (3*R*,4*E*,α*R*)-**12** the mismatched case. The high levels of diastereoselectivity observed upon rearrangement of (3*S*,4*E*,α*R*)-**8** may be rationalised by the reaction proceeding *via* the (*Z*)-*N*,*O*-silyl ketene aminal through the chair transition state **17** in which all alkyl substitutents occupy pseudo-equatorial sites, which gives rise to the observed (2*S*,3*R*,4*E*,α*R*)-configuration of γ,δ-unsaturated amide **13**. The double diastereoselectivity observed in the rearrangement of the diastereomeric (*Z*)-*N*,*O*-silyl ketene aminals derived from (3*S*,4*E*,α*R*)-**8** and (3*R*,4*E*,α*R*)-**12** may be rationalised by conformational minimisation of both *syn*-pentane[10] and 1,3-diaxial interactions in the chair transition state. In this model, the nitrogen lone pair is assumed to occupy preferably a position between the largest C(α)Ph and C(α)Me substituents, *anti* to C(α)H, minimising the dominant *syn*-pentane interaction with the trimethylsilyloxy group of the ketene aminal. For rearrangement of the (*Z*)-*N*,*O*-silyl ketene aminal from (3*S*,4*E*,α*R*)-**8**, this conformation enables the largest C(α)Ph substituent to occupy a position *anti* to the *N*-allyl fragment, with the C(α)Me group eclipsing the C(3)R substituent.[11]

Application of this transition state model to the mismatched rearrangement indicates that the expected chair transition states **18** and **19** would be destabilised by 1,3 diaxial interactions between the C(3)R group and the trimethylsilyloxy group in **18**, or *syn*-pentane interactions with the C(α)Ph substituent in **19**. The difference in energy between these and any alternative transition states for the rearrangement is therefore diminished, resulting in the observed low levels of diastereoselectivity upon rearrangement.

In conclusion, the matched rearrangement configuration for the substrates is readily achievable *via* the diastereoselective conjugate addition of lithium (*R*)-*N*-allyl-*N*-α-methylbenzylamide to α,β,γ,δ-unsaturated esters and its application to total synthesis is being investigated further within our laboratory.[12]

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Notes and references

† Crystal data for **13**, $C_{24}H_{31}NO_2$, M = 365.52, orthorhombic, space group $P2_12_12_1$, a = 4.9041(8), b = 14.4817(15), c = 31.335(7) Å, U = 2225.4 Å^3, Z = 4, μ = 0.532 mm. 2766 unique reflections ($23 < \theta < 43$); 2107 reflections used. wR_2 = 0.0747; R_1 = 0.0595 [$I > 3\sigma(I)$]. CCDC 190887. See http://www.rsc.org/suppdata/cc/b3/b306323m/ for crystallographic data in CIF or other electronic format.

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12 One of the referees required further proof that the *N*-α-methylbenzyl group has a beneficial effect upon the matched rearrangement diastereoselectivity. The d.e.s obtained upon rearrangement of the *N*-benzyl and *N*-isopropyl amide analogues were 84% and 75% d.e. respectively and, as expected, fall in between those for the matched and mismatched cases described herein.