A new diastereoselective aza-allyl conjugate addition–Michael addition–ring closure reaction sequence and its application in the construction of six contiguous stereogenic centres†

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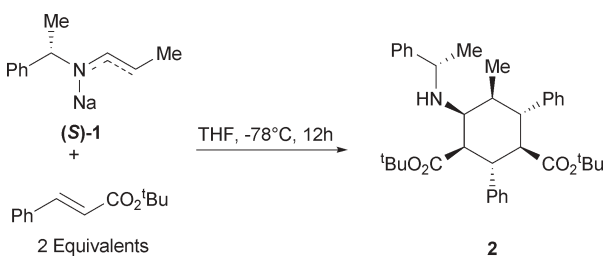
Reaction of the sodium anion of (*S*)-*N*-(α-methylbenzyl)allylamine with two equivalents of *tert*-butyl cinnamate results in a remarkable tandem aza-allyl conjugate addition–Michael addition–ring closure reaction, resulting in a chiral aminocyclohexane containing six new vicinal stereogenic centres with excellent levels of stereocontrol.

The developing fields of asymmetric multi-component reactions and cascade/domino sequences,[1] have the potential to greatly enhance the efficiency of stereoselective procedures.[2] In the specific area of ring annulation, the **MI**chael addition–**MI**chael addition–**R**ing **C**losure (**MIMIRC**) series of reactions allows for the construction of single or multi-cyclic ring systems, bearing multiple contiguous stereogenic centres, in a rapid and expedient manner.[3] The newly formed ring(s) may contain from 3 to 12 atoms, with the number of reacting components ranging from 2 to 4, with between 1–4 new stereocentres being formed. Indeed, the outstanding potential of these reactions has recently been demonstrated in catalytic three component stereoselective ring annulation reactions that afford chiral products containing up to four stereocentres with excellent levels of stereocontrol.[4]

As part of our ongoing studies into the structural chemistry of chiral alkali metal amides, we recently described the impact that changing the counterion from Li to Na has on the structure of the anion derived from (*S*)-*N*-(α-methylbenzyl)allylamine.[5] It was demonstrated that whilst the corresponding Li complex retains its allylic structure,[6] the Na derivative undergoes a facile internal 1,3-sigmatropic rearrangement in the presence of tmeda to quantitatively afford its 1-aza-allyl species, {[(*S*)-α-(PhC(H)MeNC(H)CHCH$_3$)]Na·tmeda}$_2$.[7] Whilst tmeda was initially used to facilitate crystallisation, we now know that this rearrangement occurs readily in THF solution to afford 1-aza-allyl anion **1** without any other donor solvent being present. Related aza-allyl-anions have previously been shown to take part in conjugate additions to α,β-unsaturated esters *via* their soft nucleophilic vinylic carbon centres in a highly stereoselective manner.[8] Consequently, we now report that using sodium 1-aza-allyl anion **1** as a nucleophile results in a highly stereoselective series of tandem aza-allyl conjugate addition–Michael addition–ring closure reactions, resulting in a 'one-pot' asymmetric synthesis of enantiomerically pure aminocyclohexane **2** that contains six *new* vicinal stereogenic centres.[9]

The ring annulation reaction that was carried out is shown in Scheme 1.§ Metallation of (*S*)-*N*-(α-methylbenzyl)allylamine with ^{n}BuNa in hexane at room temperature gave an orange precipitate indicative of the sodium amide {[(*S*)-α-(PhC(H)CH$_3$)(CH$_2$CHCH$_2$)N]Na}$_\infty$. Subsequent removal of the hexane and addition of THF led to a bright red solution that was shown to be the 1-aza-allylic form (*S*)-**1** by NMR studies in d$_8$-THF. This solution was cooled to −78 °C and added slowly to a THF solution containing one equivalent of (*E*)-*tert*-butyl cinnamate *via* a canula at −78 °C. The resultant reaction mixture was allowed to warm slowly to room temperature overnight when the now yellow solution was quenched with 0.1 M HCl and washed with saturated NaHCO$_3$ solution. The crude product was isolated as a viscous yellow oil which solidified on standing. ^{1}H NMR analysis revealed the presence of a single major product in good yield, with any other stereoisomeric products present having been formed in <5% yield.[10] Column chromatography, using a packed silica column and 2.5% ethyl acetate–10% triethylamine–87.5% hexane as eluent gave the major aminocyclohexane product **2** as a white microcrystalline solid which was readily recrystallised from ethanol to give an isolated yield of 26%. Repeating this conjugate addition reaction using the ideal stoichiometric ratio of one equivalent of amide **1** to two equivalents of *tert*-butyl cinnamate resulted in this aminocyclohexane **2** being isolated in an improved 44% yield.

Initial characterisation of aminocyclohexane **2** was carried out using ^{1}H and ^{13}C NMR spectroscopy, elemental analysis and



Scheme 1 Formation of aminocyclohexane derivative **2** containing six new stereocentres.

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† Electronic supplementary information (ESI) available: NMR spectra of **2** and **5**. See DOI: 10.1039/b707707f
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electrospray mass spectrometry. The ring structure of the molecule and the relative stereochemistry of the vicinal substituents around the cyclohexyl ring was revealed from analysis of the cyclohexyl ^{1}H–^{1}H coupling constants, and further confirmed from COSY and NOESY spectra (see ESI†). However, whilst this data provided information on the relative stereochemistry of the cyclohexyl ring substituents, it did not indicate their stereochemical relationship to the stereogenic centre of its (*S*)-α-methylbenzylamine fragment. Attempts to assign the absolute configuration of aminocyclohexane **2** by X-ray-crystallography were initially frustrated by the fact that its crystals grew as very fine hairs. However, one sample of aminocyclohexane **2** that crystallised slowly from ethanol over several weeks produced crystals of sufficient bulk for X-ray data to be collected.¶ The resultant crystal structure of **2** is presented in Fig. 1 and shows, as anticipated from NMR analysis, that five of the six ring protons adopt axial positions, with the α-methylbenzylamine substituent adopting an axial conformation.

A detailed mechanistic understanding of this transformation has yet to be established, however, a reasonable mechanism that explains the outcome of this addition–cyclisation reaction is shown in Scheme 2. Firstly, *syn*-selective conjugate addition of the (*E*)-1-aza-allyl species (*S*)-**1** to the s-*cis* conformer of (*E*)-*tert*-butyl cinnamate occurs *via* a cyclic eight-membered transition state **TS-1** with complete stereocontrol.[11] The stereochemistry of this initial conjugate addition reaction is controlled by the configuration of the α-stereocentre of (*S*)-**1**, with steric interactions in **TS-1** being minimised *via* presentation of the sterically undemanding α-proton of (*S*)-**1** towards the α-alkene proton of (*E*)-*tert*-butyl cinnamate. This type of transition state has been invoked previously to rationalise the 1,4-addition of (*E*)-lithium enolates to other types of (*E*)-α,β-unsaturated acceptors.[12] The resultant (*Z*)-*tert*-butyl ester enolate **3** (which is formed in favour of its (*E*)-enolate due to the steric demand of its *tert*-butyl ester fragment) then undergoes *syn*-selective Michael addition onto a second *tert*-butyl cinnamate acceptor, *via* cyclic eight-membered transition state **TS-2**, to give a second ester enolate (*Z*)-**4** containing a further two new stereogenic centres.[13] It is proposed that **TS-2** occurs preferentially to minimise interactions between the *tert*-butoxy ester substituents of enolate (*Z*)-**3** and *tert*-butyl cinnamate, with facial selectivity being controlled by the sterically demanding phenyl substituent of (*Z*)-**3** being directed away from (*E*)-*tert*-butyl cinnamate. Finally,

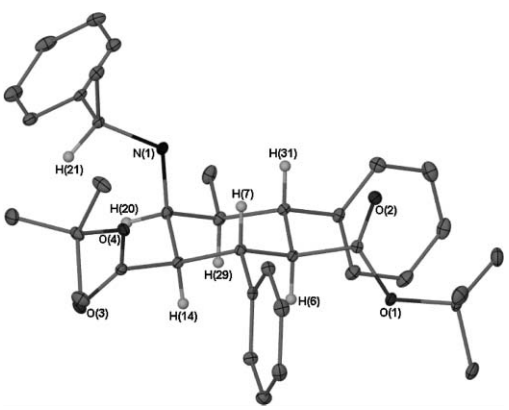
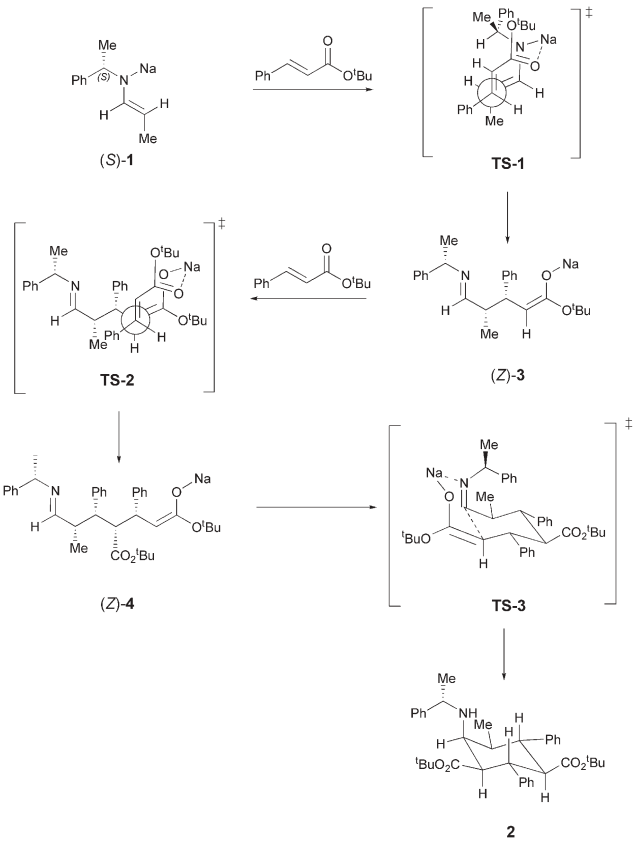


Fig. 1 Crystal structure of aminocyclohexane **2**. Thermal ellipsoids are shown at 30%, with only those hydrogens located on stereogenic carbon atoms shown.



Scheme 2 Proposed mechanism for the formation of aminocyclohexane **2**.

intramolecular 6-*exo*-trig cyclisation of the enolate fragment of (*Z*)-**4** onto its imino functionality occurs *via* six-membered transition state **TS-3**, resulting in formation of the final two new stereocentres of cyclohexane **2** with complete stereocontrol. It is proposed that diastereocontrol is achieved in this final cyclisation reaction *via* coordination of the nitrogen atom of (*Z*)-**4** to the sodium counterion of its enolate fragment, which positions the imino-functionality in a pseudo-axial environment.[14] It should be noted that the initial aza-allyl conjugate addition of (*S*)-**1** appears to be the rate limiting step in this reaction cascade, since no acyclic products derived from either (*Z*)-**3** or (*Z*)-**4** could be isolated, even when the stoichiometry of the reactants in this addition–cyclisation reaction were modified in an attempt to favour their isolation.

In conclusion, we have demonstrated a remarkable tandem aza-allyl conjugate addition–Michael addition–ring closure reaction that affords aminocyclohexane **2** containing six new stereogenic centres in 44% yield. It is particularly noteworthy that all six new stereogenic centres formed in this cascade reaction are ultimately fixed by the original stereocentre of the (*S*)-α-methylbenzylamine fragment. Currently, we are undertaking investigations to establish the scope and generality of this reaction, and the role other vinyl, amide and ester substituents may have on the degree of stereoselectivity.

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Notes and references

§ Asymmetric synthesis of cyclohexane **2**. (*S*)-*N*-(α-methylbenzyl)allylamine (0.81 g, 5 mmol) **1** was added dropwise to a suspension of ^{n}BuNa (0.40 g, 5 mmol) in hexane (15 cm^3) at room temperature and allowed to stir for 30 minutes. Addition of THF (0.41 cm^3, 5 mmol) resulted in the dissolution of the precipitate. All solvent was evaporated *in vacuo* yielding an orange oil. This oil was solubilised in THF (20 cm^3) and added dropwise to two equivalents of *tert*-butyl cinnamate (2.04 g, 10 mmol) in THF (20 cm^3) at −78 °C and stirred under a nitrogen atmosphere for 12 h. The solution was quenched with 0.1 M HCl (30 cm^3) and the pH adjusted to 8 using saturated $NaHCO_3$ solution. The resulting mixture was extracted with diethyl ether (3 × 50 cm^3). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure, yielding a highly viscous yellow oil, which was purified by column chromatography on silica using ethyl acetate–triethylamine–hexane (2.5 : 10 : 87.5) as eluent to give aminocyclohexane **2** as a white microcrystalline solid that was recrystallised from ethanol; (1.25 g, 44%). mp: 235–236 °C; ^{1}H-NMR (400 MHz, $CDCl_3$, 30 °C): δ = 7.24–7.31 (15 H, m, Ph*H*), 3.71 (1 H, q, $J_{(7,CH_3)}$ = 6.5 Hz, H7), 3.40 (1 H, t, $J_{(2,3)}$ = 11.5 Hz, $J_{(3,4)}$ = 11.5 Hz, H3), 3.21 (1 H, t, $J_{(1,2)}$ = 3.2 Hz, $J_{(1,6)}$ = 3.2 Hz, H1), 3.02 (1 H, dd, $J_{(1,2)}$ = 3.2 Hz, $J_{(2,3)}$ = 11.5 Hz, H2), 2.82 (1 H, t, $J_{(4,5)}$ = 11.6 Hz, $J_{(5,6)}$ = 11.6 Hz, H5), 2.51 (1 H, t, $J_{(3,4)}$ = 11.5, $J_{(4,5)}$ = 11.5 Hz, H4), 1.82–1.73 (1 H, m, H6), 1.56 (1 H, m, N*H*), 1.39 (3 H, d, $J_{(CH_3,7)}$ = 6.5 Hz, C7CH_3), 1.18 (9 H, s, *t*Bu), 0.72 (9 H, s, *t*Bu), 0.28 (3 H, d, $J_{(CH_3,6)}$ = 6.5 Hz, C6CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$, 30 °C): δ = 172.9 ($CO_2{}^{t}$Bu), 172.8 ($CO_2{}^{t}$Bu), 146.3 (*ipso*-C), 141.8 (*ipso*-C), 141.6 (*ipso*-C), 128.9 (*C*H), 128.7 (*C*H), 128.2 (*C*H), 127.2 (*C*H), 127.3 (*C*H), 126.9 (*C*H), 126.7 (*C*H), 81.3 ($C(CH_3)_3$), 79.9($C(CH_3)_3$), 59.0 (*C*H), 58.6 (*C*H), 58.4 (*C*H), 54.8 (*C*H), 48.1 (*C*H), 43.8 (*C*H), 42.4 (*C*H), 27.9 ($C(CH_3)_3$), 27.6 ($C(CH_3)_3$), 24.4 (CH_3), 17.3 (CH_3). Elemental analysis: found: C, 77.7; H, 8.4; N, 2.4. Calc. for $C_{37}H_{47}NO_4$: C, 78.0; H, 8.3; N, 2.5%. MS: *m*/*z* 570.3 (MH^+, 100%), 514.2 ([MH − ^{t}Bu], 3%).

¶ Crystallographic data: $C_{37}H_{47}NO_4$, *M* = 569.76, colourless needle, 0.32 × 0.04 × 0.03 mm^3, orthorhombic, space group $P2_12_12_1$(#19), *a* = 5.8650(2), *b* = 19.1247(7), *c* = 29.4680(11) Å, *V* = 3305.3(2) $Å^3$, *Z* = 4, D_c = 1.145 g cm^{-3}, Bruker-Nonius FR591 Kappa ApexII, MoKα radiation, λ = 0.71073 Å, *T* = 150(2) K, $2\theta_{max}$ = 54.94°, 20 518 reflections collected, 4289 unique (R_{int} = 0.0377). Final GooF = 1.028, *R*1 = 0.0363 (for 3515 reflections with $I > 2\sigma(I)$), w*R*2 = 0.0820 (all data), refinement on F^2, 393 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.073 mm^{-1}. CCDC 648199. For crystallographic data in CIF or other electronic format, see DOI: 10.1039/b707707f

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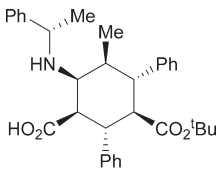

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