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Memory of chirality in intramolecular conjugate addition of enolates: a novel access to nitrogen heterocycles with contiguous quaternary and tertiary stereocenters

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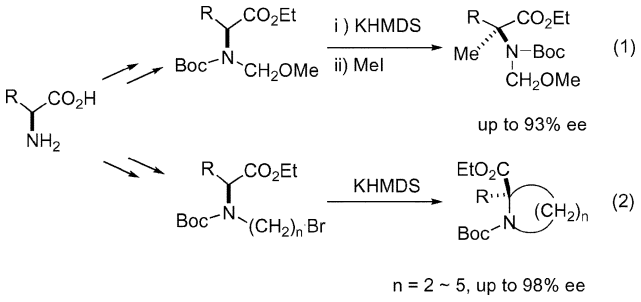
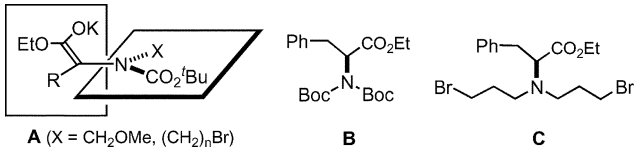
Nitrogen heterocycles with contiguous quaternary and tertiary stereocenters have been prepared in high enantiomeric purity by intramolecular conjugate addition of enolates generated from α-amino acid derivatives *via* memory of chirality.

The stereoselective construction of chiral quaternary stereocenters is one of the most challenging tasks in synthetic organic chemistry.[1] We have developed a direct method for the enantioselective construction of α,α-disubstituted α-amino acids from α-amino acids *via* memory of chirality.[2,3] Under these conditions, α-methylation of *N*-*tert*-butoxycarbonyl(Boc)-*N*-methoxymethyl(MOM)-α-amino acid derivatives takes place in up to 93% ee without the aid of external chiral sources such as chiral auxiliaries or chiral catalysts [Scheme 1 (1)].[4] A chiral non-racemic enolate **A** (R = CH_2Ph, X = CH_2OMe) with a chiral C–N axis has been proposed as the crucial intermediate for this novel asymmetric induction, whose racemization barrier is 16.0 kcal mol^{-1} and the corresponding half-life of racemization is 22 h at −78 °C. We further developed a route for the straightforward synthesis of cyclic amino acids with a quaternary stereocenter from readily available α-amino acids *via* memory of chirality [Scheme 1 (2)].[5] An axially chiral enolate intermediate **A** [X = $(CH_2)_nBr$] was also proposed to be a crucial intermediate. Experimental evidence for the axially chiral enolate intermediates **A** involves the observation that α-alkylation of **B** and **C** gave racemic products, respectively, under the similar conditions to those in Scheme 1 because the enolates generated from these derivatives cannot be axially chiral along the C–N axis.

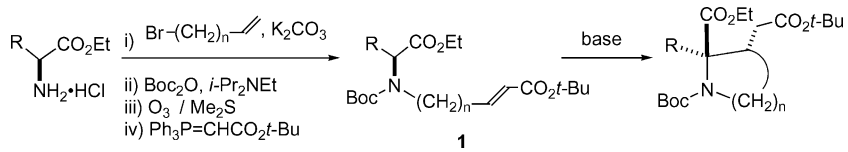


Scheme 1



We report here a new method for the asymmetric construction of highly substituted nitrogen heterocycles *via* the intramolecular conjugate addition of enolates generated from α-amino acid derivatives according to the strategy in Scheme 2. To preserve chirality during enolate formation and the subsequent C–C bond formation, the choice of the protecting group on the nitrogen of the α-amino acids is critical. According to our previous results on the inter- and intra-molecular alkylation of α-amino acid derivatives,[2,4,5] where the Boc group is essential for the generation of a chiral non-racemic enolate intermediate of high enantiomeric purity, the *N*-Boc-α-amino acid derivative with a Michael acceptor **1** was designed as a substrate for the present purpose. Substrate **1** was readily prepared from α-amino acid ethyl esters through *N*-alkylation with an ω-bromo-1-alkene, introduction of a Boc group to the nitrogen, ozonolysis of the double bond, and a Wittig reaction.

The conditions for the intramolecular conjugate addition of the enolate generated from **1a** were examined (Table 1). Treatment of **1a** with potassium hexamethyldisilazide (KHMDS) in THF at −78 °C for 30 min gave **2** as a sole detectable diastereomer in 51% ee and in 65% yield (entry 1). The relatively low ee of **2** was thought to be the result of the equilibrium between the enolate and the Michael adduct; however, this seems unlikely because shorter (5 min) and longer (60 min) reaction times did not significantly alter the ee of **2**: 50% ee after 5 min, 51% ee after 30 min, and 47% ee after 60 min (entries 1–3). Use of a 4 : 1 mixture of toluene–THF as a solvent, which is the best solvent for the intermolecular asymmetric alkylation,[3g,4] is not suitable for the present purpose in terms of the low ee of the product (19% ee, entry 4). The reaction in DMF gave a 1 : 1 mixture of **2** (84% ee) and **3** (83% ee) in a combined yield of 68% (entry 5). Use of a 1 : 1 mixture of DMF and THF gave the best result. Treatment of **1a** with KHMDS in DMF–THF (1 : 1) gave a 4 : 1 mixture of **2** (91% ee) and **3** (94% ee) in a combined yield of 81% (entry 6).[6] Use of lithium amide bases did not give any of the cyclization products (entries 7 and 8). The relative and absolute configurations of the major product **2** were determined to be (2*R*,3*S*) by an X-ray crystallographic analysis of its derivative **4** which was prepared through selective deprotection of the *N*-Boc group of **2** with 1 M HCl in ethyl acetate, *N*-benzoylation, deprotection of the *tert*-butyl ester with 4 M HCl in ethyl acetate, followed by condensation with (*R*)-1-(1-naphthyl)ethylamine (Fig. 1).[7] Thus, the intramolecular conjugate addition of **1a** took



Scheme 2

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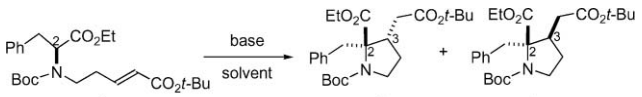
Table 1 Asymmetric intramolecular conjugate addition of **1a**



1a 2 3

Entry	Base[a]	Solvent	Temp/°C, time/min	Yield (%)[b] **2** (% ee)[c]	**3** (% ee)[c]
1	KHMDS[d]	THF	−78, 30	65 (51)	[e]
2	KHMDS[d]	THF	−78, 5	61 (50)	[e]
3	KHMDS[d]	THF	−78, 60	61 (47)	[e]
4	KHMDS[d]	Toluene–THF (4 : 1)	−78, 30	56 (19)	[e]
5	KHMDS[d]	DMF	−60, 30	34 (84)	34 (83)
6	KHMDS[d]	DMF–THF (1 : 1)	−78, 30	65 (91)	16 (94)
7	LHMDS[f]	DMF–THF (1 : 1)	−78, 30	[e, g]	[e, g]
8	LTMP[h]	DMF–THF (1 : 1)	−78, 30	[e, i]	[e, i]

[a] 1.1 Equiv. of base was used. [b] Isolated yield. [c] Ee was determined with the corresponding *N*-benzoyl derivative by HPLC analysis. [d] Potassium hexamethyldisilazide. [e] Not detected. [f] Lithium hexamethyldisilazide. [g] Several unidentified products. [h] Lithium 2,2,6,6-tetramethylpiperidide. [i] Recovery of starting material.

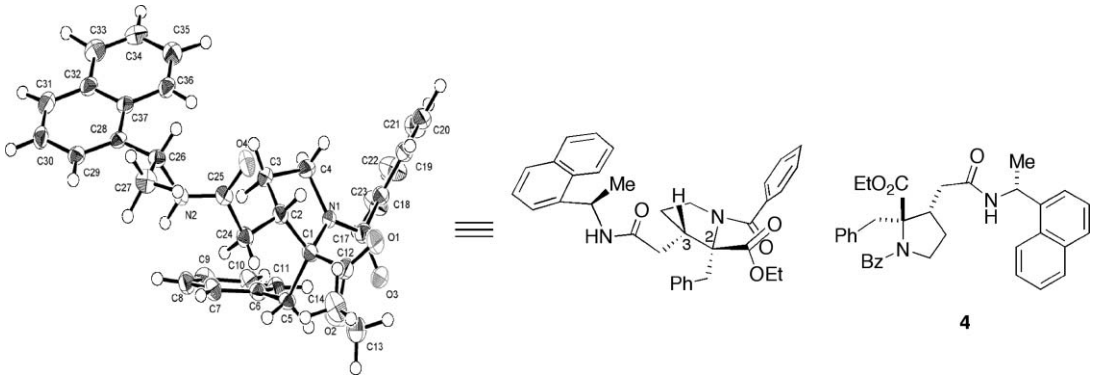
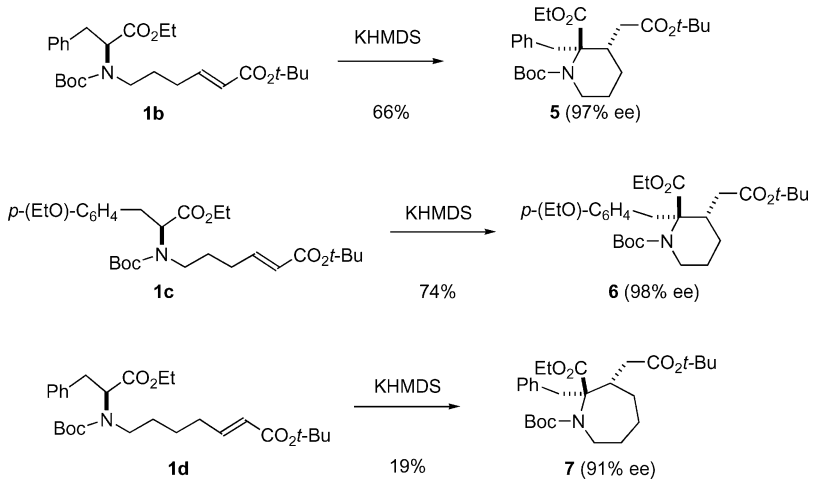


Fig. 1 X-Ray structure of **4**.

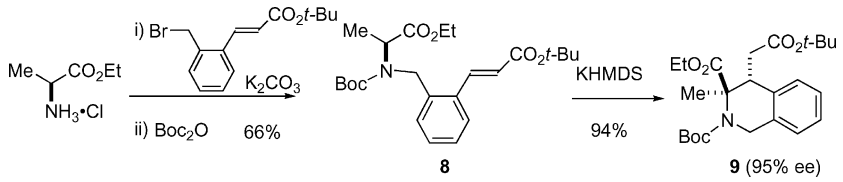
place with a retention of configuration at C(2) and a relative *trans*-stereochemistry between the two ester groups.

Six-membered ring cyclization by intramolecular conjugate addition took place with almost complete stereoselectivity (Scheme 3). Treatment of **1b** with KHMDS in DMF–THF (1 : 1) at −78 °C for 30 min gave **5** (97% ee) as a single detectable diastereomer in 66% yield. While the absolute configuration of **5** has not yet been determined, the relative stereochemistry was confirmed from the NOESY spectrum. Similarly, tyrosine derivative **1c** gave **6** in 98% ee and in 74% yield. In these reactions, 2,2,3-trisubstituted piperidines were obtained in high enantioselectivity simply by the base-treatment of the precursors derived from α-amino acids. Seven-membered ring cyclization from **1d** proceeded to give **7** in 91% ee, albeit in only 19% yield. Compounds **2**, **3**, and **5**–**7** are regarded as precursors for conformationally constrained L-glutamate analogues.[8]

The present protocol was applied to the synthesis of a multi-substituted tetrahydroisoquinoline derivative. A precursor for cyclization, **8**, was prepared in 66% overall yield by coupling of an alanine ethyl ester and (*E*)-*tert*-butyl 3-(2-bromomethylphenyl)acrylate followed by the introduction of a Boc group. Treatment of **8** with KHMDS in THF–DMF (1 : 1)



Scheme 3



Scheme 4

at −78 °C for 30 min gave **9** in 95% ee and in 94% yield as a single diastereomer (Scheme 4). Thus, a highly stereoselective and concise route to 3,3,4-trisubstituted tetrahydroisoquinoline has been developed.

In summary, pyrrolidine-, piperidine-, and tetrahydroisoquinoline-derivatives with contiguous quaternary and tertiary stereocenters were prepared in high enantiomeric purity simply by base-treatment of the acyclic precursor derived from α-amino acids in the absence of external chiral sources. This provides a straightforward route to multi-substituted nitrogen heterocycles, which are potentially useful as pharmacophores for drug discovery[9] and also as possible intermediates for natural product synthesis.[10]

Acknowledgements

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6 Typical procedure for the intramolecular conjugate addition of enolates: a KHMDS solution in THF (0.56 M in THF, 0.98 mL, 0.55 mmol) was diluted with THF–DMF (1 : 1, 3.0 mL) and cooled down to −78 °C. A solution of starting compound **1a** (0.5 mmol) in THF–DMF (1 : 1, 1.5 mL) was added to the KHMDS solution over 5 min. After 30 min, the mixture was quenched by saturated aqueous NH_4Cl (5 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by preparative TLC (ethyl acetate–hexane 15 : 85) to **2** (65%, 91% ee) and **3** (16%, 94% ee). The ee values were determined by HPLC analysis of the corresponding *N*-benzoyl derivatives: for the benzoate of **2**, Chiralpak AD, flow 1.75 mL min^{-1}, 10% *i*-PrOH/hexane, t_R = 11.7 (2*R*,3*S*), 17.8 (2*S*,3*R*) min; for the benzoate of **3**, Chiralpak AD, flow 1.5 mL min^{-1}, 6% *i*-PrOH/hexane, t_R = 10.9 (2*R*,3*R*), 13.4 (2*S*,3*S*) min.

7 Crystal data for **4**: $C_{35}H_{36}N_2O_4$, M = 548.66, monoclinic, a = 10.197(5), b = 16.139(8), c = 10.043(5) Å, β = 114.160(6)°, V = 1508.0(13) $Å^3$, space group $P2_1$, Z = 2, D = 1.208 g cm^{-1}, Mo-Kα (λ = 0.71070 Å, T = 93 K), measured reflections = 10 224. Structure solution by SIR-97, refinement by full-matrix least-squares using all reflections (SHELXL-97), $R = 0.062$ [$|F_o| > 2\sigma(F_o)$], R_w = 0.136 (all reflections), GOF = 1.10. CCDC reference number 253569. See http://www.rsc.org/suppdata/ob/b4/b416535g/ for crystallographic data in CIF or other electronic format.

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