Asymmetric Carbonyl Migration of α-Amino Acid Derivatives via Memory of Chirality

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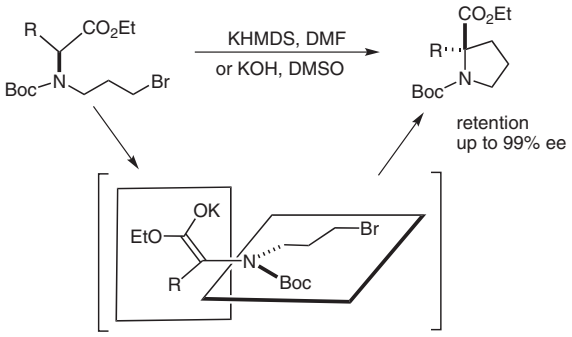
Abstract: *N-tert*-Butoxycarbonylcarbamates of α-amino acid derivatives underwent asymmetric carbonyl migration by treatment with KHMDS in DMF to give α-amino acid derivatives with an additional ester group at the newly formed tetrasubstituted carbon center in up to 99% ee.

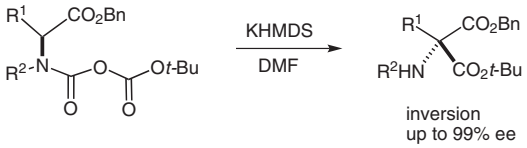
Key words: amino acids, chirality, stereoselectivity, tetrasubstituted carbon, carbonyl migration

We have studied asymmetric alkylation and conjugate addition via memory of chirality.[1–5] This asymmetric transformation was proposed to proceed via axially chiral enolate intermediates without the need of external chiral sources such as chiral auxiliaries or chiral catalysts. For the generation of the axially chiral enolates, the choice of the nitrogen substituents is critically important. For example, treatment of *N-tert*-butoxycarbonyl-*N*-ω-bromoalkyl α-amino acid derivatives (*tert*-butoxycarbonyl = Boc) with bases generates axially chiral enolates, which undergo intramolecular alkylation to give amino acid derivatives with a tetrasubstituted carbon center in up to 99% ee (Scheme 1).[2] In the course of our studies on chemistry of axially chiral enolates, we found that *N-tert*-butoxycarbonylcarbamates of α-amino acid derivatives underwent asymmetric carbonyl migration to give α-amino acid derivatives with an additional ester group at the newly formed tetrasubstituted carbon in up to 99% ee (Scheme 2). Here, we describe the preliminary aspects of the present asymmetric transformation and its stereochemical course.

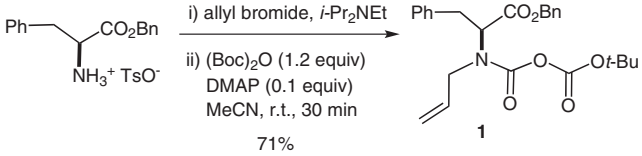
Basel and Hassner reported that *N-tert*-butoxycarbonylcarbamates are the labile intermeditaes for the formation of *N*-Boc derivatives, however, they could be isolated by tretament of amines with $(Boc)_2O$ and 4-dimethylaminopyridine (DMAP) in MeCN at 0 °C for one to five minutes.[6] According to this procedure, *N*-allyl-*N-tert*-butoxycarbonylcarbamate derivative **1** was prepared from phenylalanine benzyl ester in 71% yield (Scheme 3). Compound **1** is stable after six months at –18 °C (in a freezer), while the corresponding ethyl ester was labile and suffered from some decomposition to give the corresponding Boc derivative within a week even at –18 °C.



Scheme 1 Our previous work on asymmetric alkylation via an axially chiral enolate intermediate



Scheme 2 Present work on asymmetric carbonyl migration via memory of chirality



Scheme 3 Preparation of *N-tert*-butoxycarbonylcarbamate derivative **1**

With stable *N-tert*-butoxycarbonylcarbamate **1** in hand, asymmetric carbonyl migration of **1** was examined (Table 1). The reaction took place by treatment of **1** with potassium hexamethyldisilazide (KHMDS) in various solvents at 20 °C (entries 1–5). The extent of asymmetric induction was strongly depended on the solvent polarity. The highest ee (65% ee) was obtained in the reaction in the most polar solvent, DMSO (entry 5). We then examined the reactions at lower temperatures (entries 6–8). The reactions in toluene and THF were sluggish, and gave **2a** in low yields (26–33%) but in high ee (86–88% ee; entries 6 and 7). The best result was obtained in the reaction in DMF. Treatment of **1** with 1.2 equivalents of KHMDS in DMF for two hours at –60 °C gave the desired product **2a** in 99% ee and in 49% yield (entry 8). Use of excess

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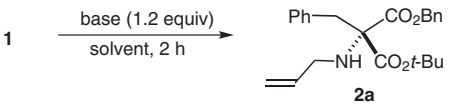
amount (2.4 equiv) of KHMDS did not improve the yield of **2a** (41% yield, 97% ee, entry 9). Use of other bases such as NaHMDS, LiHMDS, or LiTMP diminished both of the yield of carbonyl migration (5–31% yield) and enantioselectivity (85–87% ee; entries 10–12). The major side path was the formation of the corresponding Boc derivative of **1** resulting from decarboxylation. The product **2a** obtained in these reactions had an *R*-configuration at the newly formed stereogenic center (vide infra), which indicates that the migration took place with inversion of the configuration in each case.

Table 1 Optimization of the Conditions for Asymmetric Carbonyl Migration

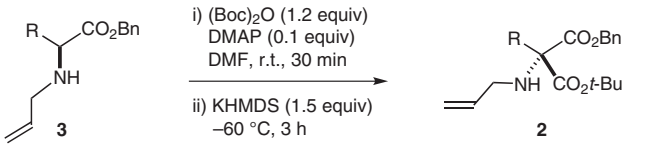


Entry	Base	Solvent	Temp (°C)	Yield (%)	ee (%)
1	KHMDS[a]	toluene	20	64	10
2	KHMDS[a]	Et_2O	20	49	18
3	KHMDS[a]	THF	20	50	26
4	KHMDS[a]	DMF	20	73	38
5	KHMDS[a]	DMSO	20	68	65
6[b]	KHMDS[a]	toluene	–78	26	88
7[b]	KHMDS[a]	THF	–78	33	86
8	KHMDS[a]	DMF	–60	49	99
9[c]	KHMDS[a]	DMF	–60	41	97
10	NaHMDS[d]	DMF	–60	30	87
11	LiHMDS[e]	DMF	–60	31	85
12	LiTMP[f]	DMF	–60	5	87

[a] KHMDS = potassium hexamethyldisilazide.
[b] The reaction was run for 24 h.
[c] 2.4 equiv of KHMDS was used.
[d] NaHMDS = sodium hexamethyldisilazide.
[e] LiHMDS = lithium hexamethyldisilazide.
[f] LiTMP = lithium 2,2,6,6-tetramethylpiperidide.

We then examined a one-step procedure for **2a** and the analogues in order to improve the overall yield of the carbonyl migration and to avoid handling the labile *N*-*tert*-butoxycarbonylcarbamate derivatives (Table 2). Since the asymmetric migration proceeded in a stereospecific manner in DMF at low temperature, preparation of the *N*-*tert*-butoxycarbonylcarbamates was performed in DMF. Quantitative formation of **1** was observed when *N*-allyl amine **3a** (R = Bn) was treated with $(Boc)_2O$ and DMAP in DMF at room temperature for 15 minutes. Based on this observation, a one-step procedure for **2** was successfully developed using DMF as a common solvent both for the formation of *N*-*tert*-butoxycarbonylcarbamates and for carbonyl migration of the resulting *N*-*tert*-butoxycarbonylcarbamates (Table 2). Allyl amine **3a** (R = Bn) was treated with 1.2 equivalents of $(Boc)_2O$ and 0.1 equivalent of DMAP in DMF at room temperature for 30 minutes. After cooling to –60 °C, the reaction mixture was treated with 1.5 equivalents of KHMDS at –60 °C for two hours to give **2a** in 53% yield and 98% ee (entry 1). On the same treatment, allyl amine derivative **3b** (R = *i*-Pr) derived from L-valine gave **2b** (R = *i*-Pr) in 49% yield and 98% ee (entry 2). Similarly, **2c** (R = Me) was obtained in 64% yield and 97% ee from **3c** (R = Me) derived from L-alanine (entry 3).

Table 2 One-Pot Procedure for **2**[a]



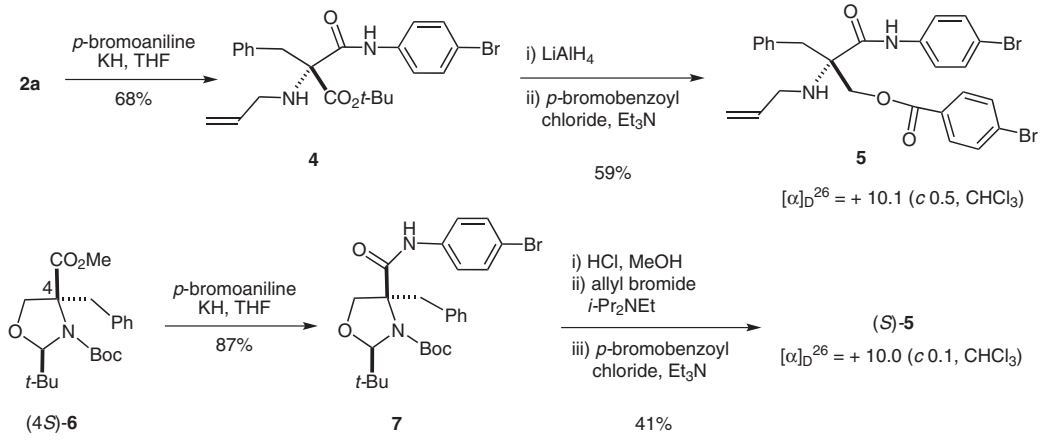
Entry	R	Yield (%)	ee (%)
1	Bn	53	98
2	*i*-Pr	49	98
3	Me	64	97

[a] The absolute configuration of **2b** (R = *i*-Pr) and **2c** (R = Me) was tentatively assigned to be *R* according to the analogy to **2a** (R = Bn).

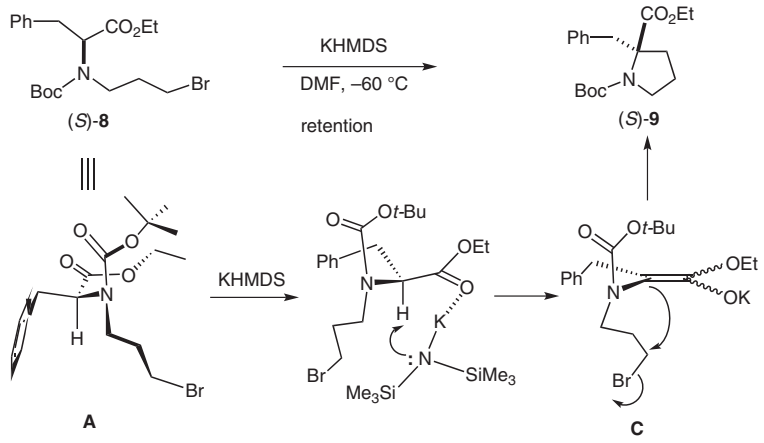
The absolute configuration of **2a** was determined to be *R* by its transformation into **5** (Scheme 4). The benzyl ester of **2a** was selectively transformed to its *p*-bromoanilide **4** by treatment with *p*-bromoaniline and potassium hydride in 68% yield. Reduction of **4** with lithium aluminum hydride followed by *p*-bromobenzoylation gave **5**, which showed $[\alpha]_D$ +10.1 (c = 0.5, $CHCl_3$). On the other hand, known serine derivative (4*S*)-**6** was prepared according to the literature.[7] (4*S*)-**6** was transformed into (*S*)-**5** according to the procedure in Scheme 4, which showed an optical rotation identical to that obtained from **2a**. Accordingly, the absolute configuration of **2a** obtained by the carbonyl migration of **1** was determined to be *R*. This indicates that the carbonyl migration of **1** proceeded with inversion of configuration.

The stereochemical course of the carbonyl migration of (*S*)-**1** into (*R*)-**2a** is shown in Scheme 6 based on our rationale for asymmetric cyclization of (*S*)-**8** into (*S*)-**9**, which proceeds with retention of configuration (Scheme 5).[2]

A conformation search of (*S*)-**8** gives the most stable conformer **A**. Deprotonation of the C(α)–H bond, which is oriented *anti* to the N–C(Boc) bond, is proposed to preferentially occur to give enantiomerically enriched enolate **C** with a chiral C–N axis, which undergoes intramolecular alkylation to give (*S*)-**9** with a total retention of configuration.[2] The stereochemical course was shown to be highly dependent on the base and the solvent employed.[2] Among bases and solvents, a combination of KHMDS and DMF gave cyclization products with retention of configuration in the highest selectivity.[2] By analogy, a possible rationale

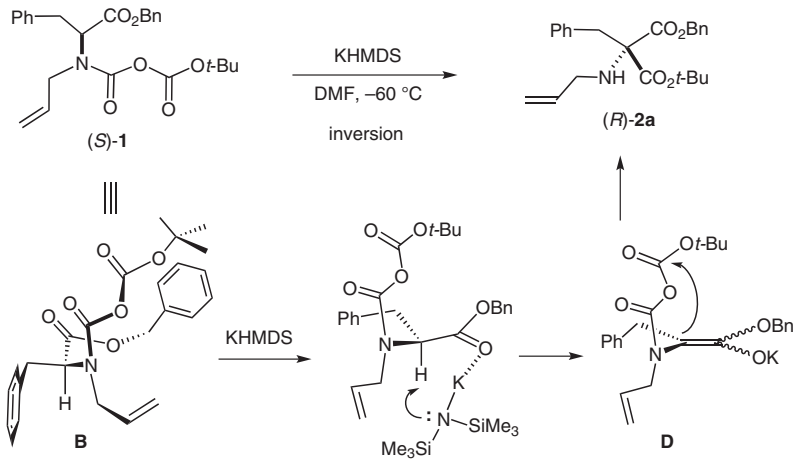


Scheme 4 Selective transformation of the benzyl ester of **2a** to an amide and the determination of the absolute configuration of **2a**



Scheme 5 A rationale for the stereochemical course of our previous work on asymmetric alkylation via an axially chiral enolate intermediate

for the stereochemical course for the transformation of (*S*)-**1** into (*R*)-**2a** is shown in Scheme 6. Conformational search of **1** gives the most stable conformer **B**.[8] Deprotonation of the C(α)–H bond, which is oriented *anti* to the N–C(*N*-*tert*-butoxycarbonylcarbamate) bond, with KHMDS would give enantiomerically enriched enolate **D** with a chiral C–N axis, which undergoes carbonyl migration to give (*R*)-**2a** with a total inversion of configuration. While this is merely an explanation without experimental proof, the tendency of the solvent effects on the stereochemical course of asymmetric migration of **1** (Table 1) was parallel to that of asymmetric cyclization of (*S*)-**8**.[2] The stereochemical result for the transformation of (*S*)-**8** into (*S*)-**9** (retention) seems opposite to that of (*S*)-**1** into (*R*)-**2a** (inversion), however, the stereochemical course of the deprotonation process with KHMDS is essentially



Scheme 6 A possible stereochemical course for the transformation of (*S*)-**1** into (*R*)-**2a**

same for both cases in terms of the enantioselectivity of the formation of the axially chiral enolates [i.e. the absolute configuration (axial chirality) of **C** is same as that of **D**].[9]

In conclusion, we have developed asymmetric carbonyl migration of the *N-tert*-butoxycarbonylcarbamates of α-amino acid derivatives. This process provides α-amino acid derivatives with an additional ester group at the newly formed tetrasubstituted stereogenic center in a highly enantioselective manner. Compounds with similar structural characteristics have been reported to be prepared by catalytic C-acylation of lactone enolates[10] or asymmetric Sommelet–Hauser rearrangement.[11] The present method provides a unique and new entry to this class of amino acid derivatives from readily available usual amino acids.[12]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

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(8) The most stable conformer **B** was generated by a molecular modeling search (MCMM 50,000 steps) with OPLS 2005 force field and GB/SA solvation model for chloroform using MacroModel (V. 9.0); see Supporting Information.

(9) The possibility that the present asymmetric migration proceeds without the intervention of an axially chiral enolate cannot be excluded. Alternative route may involve a concerted S_Ei process. This route was excluded by the experimental results in the case of asymmetric cyclization shown in Scheme 5 (refs. 2a and 2c). By analogy, we assume that the present asymmetric carbonyl migration would proceed through an axially chiral enolate intermediate.

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(12) **One-Pot Procedure for 2a (Table 2)**: A solution of Boc_2O (105 mg, 0.48 mmol) in DMF (1.0 mL) was added to a solution of **3** (R = Bn; 120 mg, 0.40 mmol) and DMAP (5.0 mg, 0.04 mmol) in DMF (4.1 mL) at r.t. After being stirred for 30 min, the mixture was cooled to –60 °C, KHMDS (0.47 M in THF solution, 1.3 mL, 0.60 mmol) was added dropwise to the mixture. The reaction mixture was stirred at –60 °C for 3 h and then poured into sat. aq NH_4Cl and extracted with EtOAc. The combined organic layers were washed with sat. aq $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by preparative TLC (SiO_2, hexane–EtOAc = 9:1) to give (*R*)-**2a** (82 mg, 53%, 98% ee) as a colorless oil.
HPLC conditions: Daicel Chiralpak OJ-H; hexane–*i*-PrOH, 9:1; flow 0.5 mL/min; t_R = 8.4 (*R*), t_R = 9.9 (*S*); $[\alpha]_D^{25}$ +2.6 (*c* = 2.1, $CDCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.33–7.38 (m, 5 H), 7.17–7.24 (m, 5 H), 5.91 (ddt, *J* = 15.1, 9.6, 5.5 Hz, 1 H), 5.20 (d, *J* = 15.1 Hz, 1 H), 5.16 (ABq, J_{AB} = 12.3 Hz, Δν = 10.6 Hz, 2 H), 5.08 (d, *J* = 9.6 Hz, 1 H), 3.22–3.29 (m, 1 H), 3.26 (ABq, J_{AB} = 14.4 Hz, Δν = 18.4 Hz, 2 H), 3.19 (dd, *J* = 13.1, 5.5 Hz, 1 H), 1.29 (s, 9 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1, 168.5, 135.9, 135.7, 135.2, 130.3, 128.9, 128.53, 128.49, 127.9, 126.8, 116.1, 82.6, 70.8, 67.1, 45.9, 36.8, 27.7. IR ($CDCl_3$): 1728, 1456, 1369, 1190, 1151 cm^{-1}. ESI–MS (+): *m/z* = 418 [M + Na], 340, 278, 204. HRMS: *m/z* calcd for $C_{24}H_{29}NO_4Na$: 418.1994; found: 418.1953.