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A convenient synthetic route to enantiopure *N*-tosylazetidines from α-amino acids

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Abstract—A general and convenient synthetic route to various chiral 2-substituted- and 2,4-disubstituted-*N*-tosylazetidines (ee >99%) is described in good overall yields starting from chiral α-amino acids using very simple chemistry.

Over the years, biologically active nitrogen-containing molecules including a wide variety of natural products have attracted the attention of organic chemists in order to develop novel, synthetically useful and elegant methodologies for the synthesis of such types of compound as targets or designs for new drugs and important intermediates in organic synthesis. Azetidines are an important class of small ring heterocyclic compounds[1] found in many naturally occurring or synthetically important organic molecules which exhibit interesting biological and pharmacological properties.[2,3] Moreover, enantiopure azetidines have been successfully utilized as ligands,[4] catalysts in various asymmetric syntheses[5] and ring opening reactions to prepare many important nitrogen-containing organic compounds.[6] Recently, 2-substituted-*N*-tosylazetidines have been utilized as masked 1,4-dipoles for the construction of nitrogen-containing six-membered heterocycles.[7] In continuation of our research activity in azetidine chemistry, we introduced an alternative method for stereoselective nucleophilic ring opening of 2-aryl-*N*-tosylazetidines.[8] In order to continue our mechanistic investigations on the chemistry of N-activated azetidines, we required a variety of enantiopure *N*-tosylazetidines. Although several methods for the synthesis of chiral azetidines are known in the literature,[9] we report herein, a very simple, practical, and general synthetic route to various chiral 2-substituted- and 2,4-disubstituted-*N*-tosylazetidines (ee >99%), starting from easily available α-amino acids.

The reported method involves homologation of α-amino acids to the corresponding β-amino acids or β-amino aldehydes which are transformed into optically active *N*-tosylazetidines by intramolecular N-heterocyclization of the corresponding γ-amino alcohols in good overall yields (Scheme 1). Our strategy was further extended to the syntheses of enantiopure 2,4-disubstituted-*N*-tosylazetidines including 2-cyano-*N*-tosylazetidines. The latter could be easily transformed into the corresponding azetidine-2-carboxylic acid derivatives[10] and various chiral ligands.[4b]

Although, the Arndt–Eistert method could be used for homologation of enantiopure α-amino acids to β-amino acids,[11] the occurrence of side reactions[12] made this strategy less promising for our purpose. In our approach α-amino acids **1** were reduced to the corresponding β-amino alcohols following a literature procedure[13] (the latter could also be obtained commercially). Tosylation[14] of the β-amino alcohols with 2 equiv of TsCl in excess pyridine at −30 °C followed by treatment with NaCN in DMSO at rt gave *N*-tosyl β-amino nitriles **2** in excellent yields. β-Amino nitriles **2** were hydrolyzed to the corresponding acids **3** by treatment with 40% aq NaOH under refluxing conditions. Subsequently, γ-amino alcohols **4** were obtained by reduction of **3** with $LiAlH_4$ in THF at room temperature. Finally, alcohols **4** were cyclized to the corresponding 2-substituted-*N*-tosylazetidines **5** in excellent yields (>99% ee) by treatment with TsCl and excess KOH in THF under reflux.[15] Alternatively, the nitrile group of **2** was carefully

Keywords: Chiral substituted-*N*-tosylazetidine; 2-Cyano-*N*-tosylazetidine; α-Amino acid; β-Amino acid; β-Amino aldehyde; Chiral cyanohydrin; Enantiopure.
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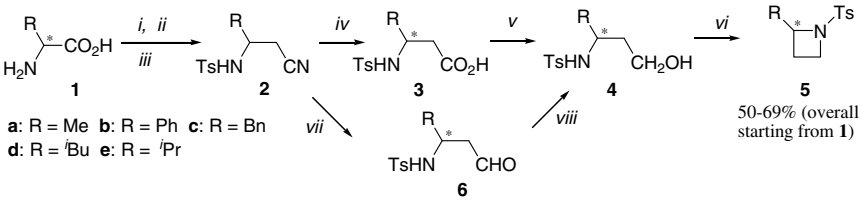


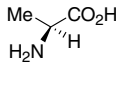
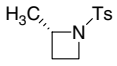
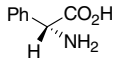
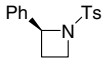
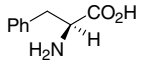
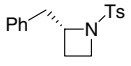
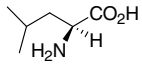
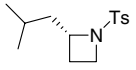
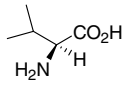
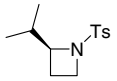
Scheme 1. Synthesis of enantiopure 2-substituted-*N*-tosylazetidines from α-amino acids. Reagents and conditions: (i) $NaBH_4$–I_2, THF, 0 °C to reflux, 18 h, 80–94%; (ii) TsCl, Py, 0 °C to −30 °C overnight, 90–95%; (iii) NaCN, DMSO, rt, 2 h, 90–95%; (iv) 40% NaOH, 110 °C, 12–15 h, 50% H_2SO_4, 80–85%; (v) LAH, THF, 0 °C–rt, 1 h, 98%; (vi) TsCl/KOH, THF, reflux, 30 min, 98%; (vii) DIBAL-H, THF, −65 °C, 30 min, 85%; (viii) $NaBH_4$, MeOH, 0 °C–rt, 2 h, 90%.

reduced using DIBAL-H at −65 °C in THF to give the corresponding β-amino aldehyde **6**, which was further reduced with $NaBH_4$ in MeOH to the same γ-amino alcohol **4** (Scheme 1). The generalization of this strategy for the synthesis of several chiral 2-substituted-*N*-tosylazetidines (**5a**–**e**) starting from various α-amino acids is shown in Table 1.

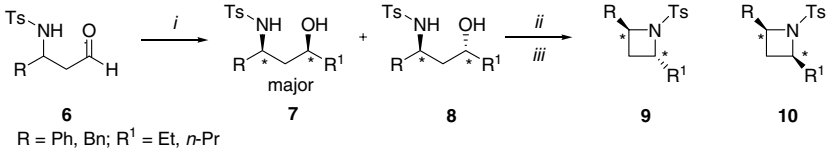
Next, structural diversity in the azetidine nucleus was introduced by exploiting *N*-tosyl-β-amino aldehyde **6**. We envisioned that addition of a variety of nucleophiles to aldehyde **6** obtained from β-amino nitriles **2**, would lead to diastereomeric mixtures of secondary γ-amino alcohols. Separation of the diastereomers followed by stereoselective N-heterocyclization, would lead to enantiopure 2,4-disubstituted-*N*-tosylazetidines. The proposed strategy was realized as delineated in Scheme 2. Grignard reaction to aldehyde **6** produced a diastereomeric mixture of γ-amino alcohols **7** and **8** favoring the *syn* diastereomer. The diastereomers were separated through column chromatography leading to enantiopure **7** and **8**. Intramolecular N-heterocyclization of **7** and **8** separately, using Mitsunobu's protocol,[16] afforded the enantiopure 2,4-disubstituted-*N*-tosylazetidines[17] **9** and **10**, respectively, in excellent yields (Table 2).

We anticipated that cyanohydrin formation from aldehyde **6** followed by cyclization would be a straightforward route to the corresponding cyano azetidines. These cyanohydrins could then be utilized as precursors in organic synthesis. When aldehyde **6** was treated with NaCN and sodium metabisulfite in water for 10 min,[18] cyanohydrins **11** and **12** were obtained as a diastereomeric mixture in excellent yield. After column chro-

Table 1. Synthesis of enantiopure 2-substituted *N*-tosylazetidines from α-amino acids

Entry	Amino acid[a]	Azetidine[b]	Overall yield[c] (%)	$[\alpha]_D^{25}$	Mp (°C)
1		 **5a**	50	+66.6	66
2		 **5b**	61	−310.7	133
3		 **5c**	55	+126	86–88
4		 **5d**	58	+130.2	49
5		 **5e**	69	+105	53–55

[a] ee of amino acids were >99%.
[b] ee's >99% determined by chiral HPLC.
[c] Overall yield starting from **1**, after column chromatographic purification.



Scheme 2. Synthesis of enantiopure 2,4-di-substituted *N*-tosylazetidines from α-amino acids. Reagents and conditions: (i) R^1MgBr, THF, 0 °C–rt, 2 h; (ii) chromatographic separation of both diastereomers; (iii) PPh_3, DIAD, THF, 0 °C–rt, 2 h. *Relative stereochemistry is shown.

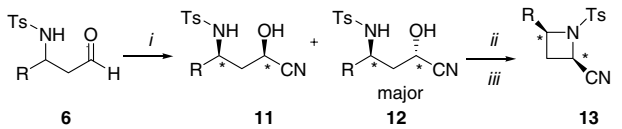
Table 2. Synthesis of enantiopure 2,4-di-substituted *N*-tosylazetidines from α-amino acids

Amino acid[a]	7 and 8	7:8[b] (% yield)[c]	Azetidine[d,e] (% yield)[c]	$[\alpha]_D^{25}$	Mp (°C)
Ph, CO_2H, H, NH_2	**7a**	1.36:1.00 (88)	**9a** (88)	−125	61
	8a		**10a** (95)	−144	110
	7b	1.67:1.00 (72)	**9b** (83)	−130	45
	8b		**10b** (87)	−157	112–114
Ph, CO_2H, H_2N, H	**7c**	1.51:1.00 (85)	**9c**[f] (89)	+79	—
	8c		**10c** (96)	+47	102–104

[a] ee of amino acids were >99%.
[b] Ratio determined by chiral HPLC and ^1H NMR of the crude reaction mixture.
[c] Yield after column chromatographic purification.
[d] Stereochemistry determined by NOE.
[e] ee's >99% determined by chiral HPLC.
[f] Liquid at room temperature.

matographic separation, the major *anti* diastereomer **12** was subjected to Mitsunobu conditions to afford cyano azetidine **13** in 38–40% yield (Scheme 3). In all cases, the cis/trans relationships of the substituents were confirmed by NOE experiments (Fig. 1).

The stereochemical outcome in both nucleophilic addition reactions with aldehyde **6** (Schemes 2 and 3) is rationalized in Scheme 4. During Grignard addition to

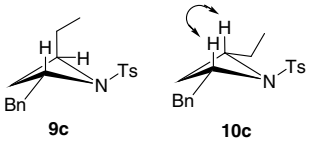


6 **11** **12** **13**

R = Ph, **11a** : **12a** = 1 : 1.27, Yield of (**11a**+**12a**) = 98%, Yield of **13a** = 40%

R = Bn, **11b** : **12b** = 1 : 1.33, Yield of (**11b**+**12b**) = 98%, Yield of **13b** = 38%

Scheme 3. Synthesis of enantiopure substituted *N*-tosyl-cyanoazetidines from α-amino acids. (i) NaCN, $Na_2S_2O_5$, 0 °C–rt, 10 min; (ii) separation of major diastereomer **12**; (iii) **12** was subjected to PPh_3, DIAD, THF, 0 °C–rt, 2 h. *Relative stereochemistry is shown, stereochemistry of **13** was confirmed by NOE.

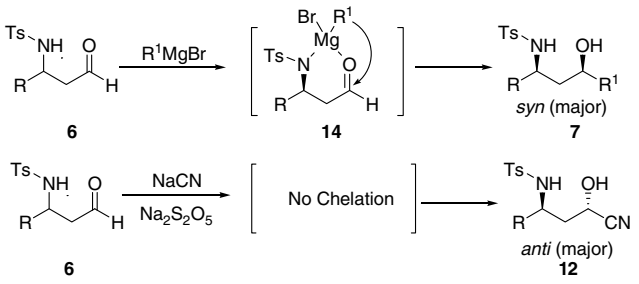


9c **10c**

Figure 1. Determination of the stereochemistry of **9c** and **10c** by NOE.

aldehyde **6**, the major *syn* diastereomer **7** resulted probably due to the formation of six-membered chelate **14**. The poor diastereoselectivity in the Grignard addition reaction can be explained by considering the reduced electron availability of the sulfonamide nitrogen of **6**. In contrast, cyanohydrin formation from aldehyde **6**, is sterically controlled by the β-chiral center, leading to the major *anti* diastereomer **12**.

In conclusion, we have developed a promising and concise route toward enantiopure substituted *N*-tosylazetidines, starting from easily available α-amino acids. Numerous activated azetidines could be synthesized in enantiomerically pure form starting from the appropriate



Scheme 4. Rationale for the diastereoselectivity in the addition of nucleophiles to chiral β-amino aldehyde **6**.

amino acid precursors. The advantages of our method include the use of inexpensive reagents, very simple work-up conditions and excellent yields in each step. Further applications of this methodology to construct poly-functionalized N-activated azetidines and other nitrogen-containing heterocyles are under investigation in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.033.

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15. Representative procedure for the synthesis of substituted *N*-tosylazetidine **5** from **4**: To a suspension of powdered KOH (21.3 mmol, 3 equiv) in 10.0 mL dry THF, a solution of **4** (7.1 mmol, 1.0 equiv) in 25.0 mL dry THF was added. Then TsCl (7.8 mmol, 1.1 equiv) was added portionwise at room temperature and the reaction mixture was refluxed for 30 min. After completion of the reaction, cold water was added and the reaction mixture was extracted with ethyl acetate twice. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude azetidine was purified by column chromatography on silica gel using ethyl acetate and petroleum ether as the eluent.
(*S*)-2-Phenyl-1-tosylazetidine (**5b**): White solid; mp 133 °C; R_f 0.28 (EtOAc:petroleum ether, 1:4), ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08–2.18 (m, 1H), 2.20–2.28 (m, 1H), 2.36 (s, 3H); 3.64–3.75 (m, 2H), 4.80 (t, $J = 8.3$ Hz, 1H), 7.19–7.35 (m, 7H), 7.61 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 25.8, 47.2, 65.6, 126.3, 127.9, 128.4, 128.5, 129.6, 132.1, 140.5, 143.9; ESI-MS $m/z = 288$ (M^++1). Anal. Calcd (%) for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found (%): C, 66.64; H, 5.98; N, 5.09. $[\alpha]_D^{25}$ −310.7 (*c* 0.204 g/100 mL, $CHCl_3$), with >99% ee.
(*S*)-2-Isobutyl-1-tosylazetidine (**5d**): White solid; mp 49 °C; R_f 0.39 (EtOAc:petroleum ether, 1:4), ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, $J = 6.4$ Hz, 3H), 0.81 (d, $J = 6.4$ Hz, 3H), 1.49–1.57 (m, 2H), 1.75–1.92 (m, 3H), 2.39 (s, 3H), 3.43 (q, $J = 8.8$ Hz, 1H), 3.58–3.63 (m, 1H), 3.77–3.84 (m, 1H), 7.30 (d, $J = 8.3$ Hz, 2H), 7.64 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 22.4, 22.9, 23.5, 24.6, 45.4, 47.7, 63.2, 128.3, 129.6, 131.8, 143.8; Anal. Calcd (%) for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24. Found (%): C, 62.75; H, 7.76; N, 5.41. $[\alpha]_D^{25}$ 130.2 (*c* 0.205 g/100 mL, $CHCl_3$), with >99% ee.
16. (a) Mitsunobu, O. *Synthesis* **1981**, 1–28; (b) Cyclization with TsCl/KOH was also found to be equally efficient in all cases except for **13a** and **13b**.
17. Representative procedure for the synthesis of **9** and **10**: In a typical procedure, 2.0 mmol of bromoethane was dissolved in 2.0 mL of dry THF and a quarter of this solution was added dropwise to 2.0 mmol of Mg turnings (suspended in 1.0 mL of THF in the presence of a crystal of iodine) at ice-cold temperature. After disappearance of the yellow color, the rest of the bromoethane solution was added dropwise. Stirring was continued until all the Mg had been consumed. Next, 0.5 mmol of aldehyde **6**, dissolved in 1.0 ml of THF, was added dropwise at 0 °C and the reaction was continued for another 1.5 h at rt. The reaction was quenched by dropwise addition of saturated aq NH_4Cl solution at 0 °C. The crude reaction mixture was extracted with ethyl acetate, the organic layer washed with brine, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. After column chromatographic purification, both diastereomers were obtained in the yields reported in Table 2. Both diastereomers **7** and **8** were cyclized separately under Mitsunobu conditions (1.5 equiv DIAD, 1.5 equiv PPh_3, THF, 2 h) to afford **9** and **10**, respectively, in the yields reported.
(2*R*,4*R*)-2-Benzyl-4-ethyl-1-tosylazetidine (**9c**): Liquid; R_f 0.39 (20% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.66 (t, $J = 7.6$ Hz, 3H), 1.35–1.43 (m, 1H), 1.66–1.73 (m, 1H); 1.86–1.97 (m, 2H), 2.37 (s, 3H), 2.70 (dd, $J = 13.4$, 10.5 Hz, 1H), 3.29 (dd, $J = 13.4$, 3.9 Hz, 1H), 4.04–4.08 (m, 1H), 4.29–4.33 (m, 1H), 7.06–7.25 (m, 7H), 7.69 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 8.3, 21.5, 26.4, 27.2, 40.2, 62.7, 63.6, 126.6, 127.4, 128.5, 129.3, 129.6, 136.7, 137.9, 143.2; IR (cm^{-1}, neat) 3060, 3028, 2963, 2928, 2877, 1599, 1495, 1455, 1337, 1154, 1095, 1022, 816, 736, 704, 672, 633, 606, 549, 499; Anal. Calcd (%) for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04; N, 4.25. Found (%): C, 69.31; H, 7.15; N, 4.32. $[\alpha]_D^{25}$ +79 (*c* 0.41 g/100 mL, $CHCl_3$), with >99% ee.
(2*R*,4*S*)-2-Benzyl-4-ethyl-1-tosylazetidine (**10c**): White solid; mp 102–104 °C; R_f 0.43 (20% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.70 (t, $J = 7.3$ Hz, 3H), 1.41–1.55 (m, 2H), 1.62–1.69 (m, 1H); 1.81–1.88 (m, 1H), 2.38 (s, 3H), 2.89 (dd, $J = 13.7$, 9.0 Hz, 1H), 3.06 (dd, $J = 13.7$, 3.6 Hz, 1H), 3.45–3.52 (m, 1H), 3.73–3.80 (m, 1H), 7.09–7.31 (m, 7H), 7.67 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 8.3, 21.6, 27.3, 28.6, 42.0, 60.4, 61.6, 126.5, 128.2, 128.3, 129.5, 129.7, 132.4, 136.6, 143.8; IR (cm^{-1}, neat) 3057, 3029, 2960, 2899, 2871, 1599, 1496, 1454, 1385, 1340, 1259, 1223, 1153, 1091, 1049, 1022, 941, 807, 766, 740, 699, 665, 602, 549, 500; Anal. Calcd (%) for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04; N, 4.25. Found (%): C, 69.33; H, 7.28; N, 4.33. $[\alpha]_D^{25}$ +47 (*c* 0.42 g/100 mL, $CHCl_3$) with >99% ee.
18. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Revised by Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. Longman Group, UK Ltd., 1989; pp 729–730.