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PAPER

Asymmetric α -2-tosylethenylation of N,N-dialkyl-L-amino acid esters *via* the formation of non-racemic ammonium enolates[†]

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Asymmetric α -2-tosylethenylation of (*S*)-2-(pyrrolidin-1-yl)propanoic acid esters was shown to produce good yields with high enantioselectivities. The reaction proceeds *via* the formation of a non-racemic ammonium enolate without an external source of chirality.

Introduction

Ethynyl tolyl sulfone (1) is a highly reactive Michael acceptor and reacts with various nucleophiles to produce 2-tosylethenyl derivatives under mild conditions.¹ Conjugate addition of tertiary amines to 1 generates the corresponding zwitterionic intermediates, which serve as unique synthetic intermediates.² Weston et al. applied this reaction to the synthesis of medium- and large-ring cyclic amines using a 3-aza-Cope rearrangement of the zwitterionic intermediates.3 Recently, we reported the asymmetric α -2-tosylethenylation of N-alkyl-L-proline esters with 1 via the formation of the zwitterionic intermediate (Scheme 1).⁴ Because this method worked for N-alkyl-L-proline esters, we have attempted to extend the reaction protocol to N,N-dialkyl acyclic amino acid esters 2 to obtain the corresponding α -(2-tosylethenyl) derivatives 3 (Scheme 2). The proposed reaction would proceed via the formation of a zwitterionic intermediate A, proton transfer to an ammonium ylide **B**, conjugate addition of **B** to 1, and the elimination of an N-(2-tosylethenyl) substituent from nitrogen.



Scheme 1 Asymmetric α -2-tosylethenylation of N-alkyl-L-proline esters.

Results and discussion

We examined the reaction of (*S*)-cyclohexyl 2-(benzyl(methyl)amino)propanoate (**2a**) with 2.0 equivalents of **1** in DMF at 0 °C for 4 h (Table 1, entry 1). Unreacted **1** was quenched by the addition of methylamine to prevent further reactions. None of the α -adduct **3a** was detected. The reactions of 2-(allyl(benzyl)amino)



Scheme 2 α -2-Tosylethenylation of *N*,*N*-dialkyl acyclic amino acid ester **2** with **1**.

(2b), 2-(dibenzylamino) (2c), and 2-(diallylamino) (2d) derivatives with 1 gave similar results (entries 2-4).⁵ This lack of reactivity could be explained by the steric repulsion of the tertiary amines inhibiting the initial conjugate addition of 2a-d to 1. Thus, we prepared the 2-(dimethylamino) derivative 2e and performed the reaction (entry 5). The α -adduct **3e** was obtained in 26% yield. Unexpectedly, 3e was obtained in an enantio-enriched form (4% ee), even though the expected reaction intermediate is the achiral ammonium ylide B depicted in Scheme 2. Prompted by this unexpected observation, we investigated the reaction using other types of N,N-dialkyl amino acid esters with 1. Next, we prepared the 2-piperidinyl derivatives (2f, 2g) and examined their reactivity (entries 6, 7). The ee values of the corresponding α -adducts 3 were dramatically improved (3f: 17%, 75% ee; 3g: 36%, 77% ee). Surprisingly, when the reactions of the 2-pyrrolidinyl derivatives (2h, 2i) were performed under the same conditions (entries 8, 9), the α -adducts **3h** or **3i** were obtained in reasonable yields with high enantioselectivities (3h: 69%, 92% ee; 3i: 81%, 91% ee). Use of the tert-butyl ester derivatives (2g, 2i) resulted in improved yields of 3. The configuration of **3i** was determined to be S after conversion to 5 by reductive desulfonylation and hydrogenation (Scheme 3). The specific rotation value of 5 was compared to that of an authentic S sample prepared from (S)- α -ethylalanine *tert*-butyl ester $[(S)-6].^{6}$

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- Ts (S)_CO₂^tBu CO₂R³ $O_{2}R^{3}$ **1** (2.0 equiv) R^{2} DMF 0 °C, 0.05 M Ts 4 h Ts 2 3 ee (%) \mathbb{R}^1 \mathbb{R}^2 \mathbb{R}^3 Yield (%)a Entry CH₂Ph ^cHex 0 Me a 2 CH₂Ph CH₂CH=CH₂ ^cHex b 0^{c} 3 CH₂Ph CH₂Ph ^cHex с 0^{c} 4 CH₂CH=CH₂ CH₂CH=CH₂ ^cHex d 0 4 75 77 92 5 ^cHex Me Me 26 e 6 $-(CH_2)_{5}-$ ^cHex f 17 -(CH₂)₅-7 ^tBu 36 g 8 ^cHex 69 -(CH₂)₄h 91 (S) ^tBu 81 -(CH₂)₄i

Table 1 Effects of substituents on the asymmetric α -2-tosylethenylation

of N,N-dialkyl acyclic amino acid esters 2

^{*a*} Isolated yield. ^{*b*} Determined by HPLC analysis. ^{*c*} Recovered **2a–d** in 75– 99% yield. See also ref. 5.



Scheme 3 Determination of the absolute configuration of 3i. *Reagents and conditions*: (i) Mg, THF–MeOH, 50 °C, (ii) H₂, Pd–C, EtOAc, rt, (iii) 1,4-butanediol di-*p*-toluenesulfonate, KHCO₃, MeCN, reflux.

To improve the chemical yield and enantioselectivity of the asymmetric α -2-tosylethenylation, we tested this reaction in various conditions (Table 2). The reaction proceeded with the same levels of enantioselectivity in dichloromethane, toluene, THF, and ethyl acetate (entries 1–4, 88–94% ee). The use of ethyl acetate

Table 2 Asymmetric α -2-tosylethenylation of **2i** in various conditions

<		1 (2.0 equiv) solvent, temp., conc., 4 h		► N CO₂′Bu		
	2i			Ts (S)- 3i		
Entry	Solvent	Temp./°C	Conc./M	Yield (%) ^a	ee (%)	
1	CH ₂ Cl ₂	0	0.05	97	90	
2	Toluene	0	0.05	92	88	
3	THF	0	0.05	91	94	
4	EtOAc	0	0.05	99	90	
5	ⁱ PrOH	0	0.05	92	93	
6	EtOH	0	0.05	85	88	
7	MeOH	0	0.05	81	78	
8	$THF-H_2O(2:1)$	0	0.05	91	93	
9	$MeOH-H_2O(2:1)$	0	0.05	74	83	
10	CF ₃ CH ₂ OH	0	0.05	29	81	
11	EtOAc	rt	0.05	71 ^c	90	
12	EtOAc	-40	0.05	86	96	
13	EtOAc	0	0.01	92	91	
14	EtOAc	0	0.2	77 ^c	93	

^{*a*} Isolated yield. ^{*b*} Determined by HPLC analysis. ^{*c*} Small amount of by-product was obtained (entry 11, 14%; entry 14, 11%). Details: see ref. 7.

afforded **3i** in the quantitative yield. Alcoholic solvents, such as isopropanol or ethanol, could also be used (entries 5, 6), but the use of methanol resulted in a lower ee (entry 7, 78% ee). The addition of water to THF or methanol did not negatively affect the reaction (entries 8, 9). The yield was decreased when a more acidic solvent, such as 2,2,2-trifluoroethanol, was used (entry 10, 29%, 81% ee). Next, we investigated the effects of reaction temperature and concentration. The yield was lowered at room temperature because of the formation of by-product⁷ (entry 11, 71%, 90% ee). The enantioselectivity was improved at lower reaction temperature (-40 °C) (entry 12, 86%, 96% ee). The remarkable effects (entry 13, 92%, 91% ee); however, the yield was lowered under higher concentration (0.2 M) because of formation of the same by-product⁷ described above (entry 14, 77%, 93% ee).

To define the scope and limitation of the present asymmetric α -2-tosylethenylation, we prepared a series of substrates derived from acyclic L-amino acids and examined their reactions with 1 (Table 3). The use of primary esters, such as *n*-butyl (2j) or benzyl (2k) as substrates, resulted in lower yields because of the undesired side reactions⁸ (entry 1, 40%, 88% ee; entry 2, 11%, 90% ee). Other α -amino acid derivatives prepared from phenylalanine (21) or leucine (2m) reacted smoothly with the same levels of enantioselectivity (entry 3, 99%, 81% ee; entry 4, 80%, 92% ee), but the valine derivative 2n was less reactive (entry 5). The corresponding α -adduct **3n** was obtained in only 27% yield with 95% ee. The yield was improved to 54% after 48 h of stirring (entry 6). The reaction of the 2-phenylglycine derivative 20 (85%) ee) gave **30** with a lower enantioselectivity (entry 7, 40% ee). The *N*,*N*-diethylamide derivative **2p** did not react at all (entry 8). It is worth noting that the reaction of the acyclic amino acid derivative **2i** proceeded without adding **1** in excess (entries 9, 10).

Although its exact origin is unclear, the high stereoselectivity might be rationalized as a result of the formation of the non-racemic ammonium enolate (memory of chirality)^{9,10} (Scheme 4). Conjugate addition of **2i** to **1** generates the zwitterionic intermediate **A**. Intermediate **A** is converted to the ammonium ylide **B** by

Table 3 Asymmetric $\alpha\text{-}2\text{-}tosylethenylation of acyclic L-amino acid derivatives 2$

\langle	N R^2 R^1 R^2	EtOAc,	===- Ts Ts Ts EtOAc, 0 °C, 0.05 M, 4 h			0 N R ¹ 3 ^a Ts	
Entry	Equiv. of 1	\mathbf{R}^1	\mathbb{R}^2		Yield (%) ^b	ee (%) ^c	
1	2.0	Me	O ⁿ Bu	j	40	88	
2	2.0	Me	OCH ₂ Ph	k	11	90	
3	2.0	CH_2Ph	O'Bu	1	99	81	
4	2.0	ⁱ Bu	O'Bu	m	80	92	
5	2.0	ⁱ Pr	O'Bu	n	27	95	
6	2.0	ⁱ Pr	O'Bu	n	54 ^d	95	
7	2.0	Ph	O ^c Hex	0	90	40^{e}	
8	2.0	Me	NEt_2	р	0	_	
9	1.5	Me	O'Bu	ī	90	93	
10	1.0	Me	O'Bu	i	86	91	

^{*a*} The absolute configurations of **3j–o** were assigned tentatively by analogy with (*S*)-**3i**. ^{*b*} Isolated yield. ^{*c*} Determined by HPLC analysis. ^{*d*} Stirred for 48 h at 0 °C. ^{*e*} The *enantio*-purity of **2o** was 85% ee.



Scheme 4 Proposed mechanism for the asymmetric α -2-tosylethenylation of **2i**.

intramolecular deprotonation of the more acidic α -proton. Ylide **B** serves as a non-racemic ammonium enolate **B'**, which undergoes conjugate addition with **1** diastereoselectively to afford the (S)-zwitterion **C**. Elimination of the N-2-tosylethenyl substituent from nitrogen by the reaction with a nucleophile such as **2i** affords α -adduct **3i** with high enantioselectively and regenerate the intermediate **A**.

To rule out the effect of the intermediates or products for the asymmetric induction, we examined the reaction of a 1 : 1 mixture of (S)-2i and (rac)-2l with 1 under the same conditions (Scheme 5). The α -adducts 3i and 3l were obtained, respectively; however, no remarkable changes to the product ee were observed (3i: 93% ee, 3l: 0% ee).



Scheme 5 α -2-Tosylethenylation of 1:1 mixture of (S)-2i and (rac)-2l.

Next, we carried out the reaction of non-racemic substrate (S)-2i at different% ee (25% ee, 51% ee, and 75% ee) and obtained the results against the % ee of the product 3i. The non-linear effects were not observed (Scheme 6).

To eliminate the asymmetric [1,2] vinylic Stevens rearrangement^{11,12} of the non-racemic ammonium enolate **B'** as a possible pathway, we examined a base-induced [1,2] Stevens rearrangement of the *N*-benzyl ammonium salt **7** (Scheme 7). The reaction would



Scheme 6 Reaction of non-racemic substrate (S)-2i at different % ee.



Scheme 7 [1,2] Stevens rearrangement of (*S*)-*N*-benzyl-2-(pyrrolidin-1-yl)propanoic acid ester-derived ammonium salt **7**.

proceed *via* the formation of a similar ammonium ylide **B** or enolate **B'**; the rearrangement product **8** was not obtained in an *enantio*-enriched form (69%, 0% ee).

Conclusions

In conclusion, we have reported that the asymmetric α -2-tosylethenylation of (*S*)-2-(pyrrolidin-1-yl)propanoic acid esters **2** using ethynyl tolyl sulfone **1** as an electrophile¹³ produces a good yield with high enantioselectivity without the addition of any bases. The reaction would proceed *via* the formation of a non-racemic ammonium enolate without an external source of chirality (memory of chirality).

Experimental section

General

¹H and ¹³C NMR spectra were measured on a Varian 400 MHz (1H: 400 MHz, 13C: 100 MHz) spectrometer. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Infrared spectra were recorded on a Perkin Elmer Spectrum GX FT-IR spectrometer. Specific rotations were recorded on a JASCO Polarimeter P-1010. Highresolution mass spectra were measured on a Thermofisher Scientific LC/FT-MS spectrometer. Elemental analyses were recorded on a J-Science Lab Micro Corder JM10. HPLC analyses were performed using a JASCO HPLC pump PU-2080 and a UV/VIS detector UV-2075. Reactions were conducted in a round-bottomed flask with a magnetic stirring bar under an argon atmosphere. For thin layer chromatography (TLC) analysis throughout this work, Merck TLC plates (silica gel 60 F254) were used. The products were purified by preparative column chromatography on silica gel (silica gel 60 N, spherical neutral, KANTO Chemical Co., Inc., Japan).

Representative procedure for the asymmetric α -tosylethenylation of $N_{\gamma}N$ -dialkyl L-amino acid ester 2i

A solution of ethynyl tolyl sulfone (1) (72 mg, 0.40 mmol) in ethyl acetate (1.3 mL) was added to a solution of **2i** (40 mg, 0.20 mmol)

in ethyl acetate (2.7 mL) at 0 °C under an argon atmosphere. After stirring for 4 h at the same temperature, the excess amount of 1 was quenched by addition of 40% methylamine solution in methanol (46 μ L, 0.45 mmol). The resulting mixture was stirred for 15 min at 0 °C, diluted with water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. Purification of the residue by chromatography on silica gel (*n*-hexane/ethyl acetate = 2/1 as eluent) gave (*S*,*E*)-*tert*-butyl 2-methyl-2-(pyrrolidin-1-yl)-4-(*p*-toluenesulfonyl)but-3-enoate (**3i**) (75 mg, 99% yield) as a white solid.

(*E*)-Cyclohexyl 2-(*N*,*N*-dimethylamino)-2-methyl-4-(*p*-toluenesulfonyl)but-3-enoate (3e)

Yellow oil (Found: C, 63.0; H, 7.7; N, 3.4. Calc. for C₂₀H₂₉NO₄S: C, 63.3; H, 7.7; N, 3.7%); $[\alpha]_{559}^{24}$ -1.5 (c 1.00 in EtOH); 4% ee [determined by HPLC analysis: Daicel Chiralpak AD-H column, *n*-hexane/ethanol = 92/8 as eluent, flow rate = 0.50 mL min⁻¹, $t_{\rm R}$ = 24.7 min for the major enantiomer and 29.0 min for the minor enantiomer]; v_{max}(film)/cm⁻¹ 3059, 2938, 2861, 2793, 1721, 1634, 1597, 1452, 1403, 1369, 1320, 1235, 1147, 1086, 1037, 1013, 972, 912, 813, 736, 683; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me₄Si) 7.76 (2H, d, J = 8.2 Hz, ArH), 7.33 (2H, d, J = 8.2 Hz, ArH), 7.13 (1H, d, J = 15.2 Hz, TsCH=CH), 6.58 (1H, d, J = 15.2 Hz, TsCH = CH), 4.83 (1H, tt, J = 8.8, 4.0 Hz, OCH), 2.43 (3H, s, ArCH₃), 2.28 (6H,s, N(CH₃)₂), 1.93–1.64 (4H, m, c-Hex), 1.58–1.22 (6H, m, c-Hex), 1.38 (3H, s, 2-CH₃); $\delta_{\rm C}$ (100 MHz, CDCl₃, CHCl₃) 170.7, 146.9, 144.3, 137.4, 131.6, 129.9, 127.7, 73.9, 67.2, 39.7, 31.48, 31.46, 25.2, 23.51, 23.50, 21.6, 20.6; HRMS-ESI (m/z): $[M + H]^+$ calc. for C₂₀H₃₀NO₄S, 380.1890; found, 380.1876.

(*E*)-Cyclohexyl 2-methyl-2-(piperidin-1-yl)-4-(*p*-toluenesulfonyl)but-3-enoate (3f)

Colorless oil (Found: C, 66.0; H, 8.1; N, 3.6. Calc. for C₂₃H₃₃NO₄S: C, 65.8; H, 7.9; N, 3.3%); $[\alpha]_{589}^{25}$ -16.2 (*c* 1.00 in EtOH); 75% ee [determined by HPLC analysis: Daicel Chiralpak AD-H column, *n*-hexane/ethanol = 95/5 as eluent, flow rate = 0.50 mL min⁻¹, $t_{\rm R}$ = 17.0 min for the major enantiomer and 20.8 min for the minor enantiomer]; v_{max}(film)/cm⁻¹ 3058, 2937, 2858, 1723, 1632, 1597, 1452, 1371, 1320, 1240, 1179, 1147, 1120, 1087, 1034, 1013, 961, 908, 864, 835, 812, 737, 704, 685; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me₄Si) 7.76 (2H, d, J = 8.2 Hz, ArH), 7.33 (2H, d, J = 8.2 Hz, ArH), 7.16 (1H, d, J = 15.2 Hz, TsCH=CH), 6.61 (1H, d, J = 15.2 Hz, TsCH = CH), 4.82 (1H, tt, J = 8.6, 3.6 Hz, OCH), 2.48 (4H, t, J = 5.0 Hz, NCH₂), 2.43 (3H, s, ArCH₃), 1.83–1.63 (4H, m, c-Hex), 1.56–1.24 (12H, m, piperidinyl-CH₂ and c-Hex), 1.35 (3H, s, 2-CH₃); $\delta_{\rm C}$ (100 MHz, CDCl₃, CHCl₃) 170.7, 148.3, 144.2, 137.5, 130.9, 129.8, 127.5, 73.5, 67.7, 48.4, 31.5, 31.4, 26.6, 25.2, 24.6, 23.4, 23.3, 22.6, 21.5, 20.7, 14.0; HRMS-ESI (m/z): [M + H]⁺ calc. for C₂₃H₃₄NO₄S, 420.2203; found, 420.2188.

(*E*)-*tert*-Butyl 2-methyl-2-(piperidin-1-yl)-4-(*p*-toluenesulfonyl)but-3-enoate (3g)

Colorless oil (Found: C, 63.9; H, 8.0; N, 3.8. Calc. for $C_{21}H_{31}NO_4S$: C, 64.1; H, 7.9; N, 3.6%); $[\alpha]_{589}^{24}$ –21.1 (*c* 1.00 in EtOH); 77% ee [determined by HPLC analysis: Daicel Chiralcel OJ-H column, *n*-hexane/ethanol = 99/1 as eluent, flow rate = 0.50 mL min⁻¹, $t_{\rm R}$ = 34.1 min for the minor enantiomer and 37.8 min for the major enantiomer]; $v_{\rm max}$ (film)/cm⁻¹ 2975, 2935, 2854, 2816, 1723, 1628, 1597, 1455, 1393, 1369, 1319, 1286, 1253, 1148, 1123, 1087, 1049, 961, 885, 840, 812, 770, 675; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me₄Si) 7.76 (2H, d, *J* = 8.2 Hz, ArH), 7.32 (2H, d, *J* = 8.2 Hz, ArH), 7.14 (1H, d, *J* = 15.4 Hz, TsCH=CH), 6.59 (1H, d, *J* = 15.4 Hz, TsCH=CH), 6.59 (1H, d, *J* = 15.4 Hz, TsCH=CH), 1.54 (1H, d, *J* = 4.8 Hz, NCH₂), 2.43 (3H, s, ArCH₃), 1.54–1.38 (6H, m, piperidinyl-CH₂), 1.44 (9H, s, *t*-Bu), 1.31 (3H, s, 2-CH₃); $\delta_{\rm C}$ (100 MHz, CDCl₃, CHCl₃) 170.5, 148.8, 144.2, 137.6, 130.6, 129.8, 127.6, 82.1, 68.1, 48.5, 28.1, 26.7, 24.7, 21.6, 20.8; HRMS-ESI (*m*/*z*): [M + H]⁺ calc. for C₂₁H₃₂NO₄S, 394.2047; found, 394.2032.

(*S*,*E*)-Cyclohexyl 2-methyl-2-(pyrrolidin-1-yl)-4-(*p*-toluene-sulfonyl)but-3-enoate (3h)

Yellow oil (Found: C, 64.9; H, 7.7; N, 3.6. Calc. for C₂₂H₃₁NO₄S: C, 65.15; H, 7.7; N, 3.45%); [α]²⁵₅₈₉ -27.2 (*c* 1.00 in EtOH); 92% ee [determined by HPLC analysis: Daicel Chiralpak AD-H column, *n*-hexane/ethanol = 95/5 as eluent, flow rate = 0.50 mL min⁻¹, $t_{\rm R}$ = 21.5 min for (S)-**3h** and 25.5 min for (R)-**3h**]; $v_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3059, 2938, 2860, 1722, 1631, 1597, 1452, 1370, 1320, 1302, 1289, 1250, 1193, 1147, 1085, 1035, 1013, 973, 912, 835, 812, 736, 706; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me₄Si) 7.76 (2H, d, J = 8.2 Hz, ArH), 7.33 (2H, d, J = 8.2 Hz, ArH), 7.18 (1H, d, J = 15.4 Hz, TsCH=CH), 6.56 (1H, d, J = 15.4 Hz, TsCH = CH), 4.83 (1H, tt, J = 8.6, 3.8 Hz)OCH), 2.82-2.74 (2H, m, NCH2), 2.71-2.62 (2H, m, NCH2), 2.44 (3H, s, ArCH₃), 1.84–1.63 (8H, m, NCH₂CH₂ and c-Hex), 1.56– 1.24 (6H, m, c-Hex), 1.45 (3H, s, 2-CH₃); $\delta_{\rm C}$ (100 MHz, CDCl₃, CHCl₃) 171.0, 146.6, 144.2, 137.4, 131.1, 129.8, 127.6, 73.6, 65.4, 47.3, 31.4, 25.2, 24.1, 23.4, 23.1, 21.5; HRMS-ESI (*m*/*z*): [M + H]⁺ calc. for C₂₂H₃₂NO₄S, 406.2047; found, 406.2033.

(*S*,*E*)-*tert*-Butyl 2-methyl-2-(pyrrolidin-1-yl)-4-(*p*-toluenesul-fonyl)but-3-enoate (3i)

White solid (Found: C, 63.4; H, 7.9; N, 3.6. Calc. for C₂₀H₂₉NO₄S: C, 63.3; H, 7.7; N, 3.7%); $[\alpha]_{589}^{25}$ -30.5 (c 1.00 in EtOH); 91% ee [determined by HPLC analysis: Daicel Chiralpak AS-H column, *n*-hexane/isopropanol = 90/10 as eluent, flow rate = 0.50 mL min⁻¹, $t_{\rm R} = 23.1$ min for (*R*)-3i and 31.6 min for (*S*)-**3i**]; $v_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3062, 2972, 2875, 2828, 1729, 1596, 1475, 1456, 1392, 1368, 1303, 1269, 1146, 1088, 1039, 990, 930, 877, 844, 815, 740, 699; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me₄Si) 7.76 (2H, d, J = 8.0 Hz, ArH), 7.33 (2H, d, J = 8.0 Hz, ArH), 7.16 (1H, d, J = 15.2 Hz, TsCH=CH), 6.53 (1H, d, J = 15.2 Hz, TsCH = CH), 2.81–2.73 (2H, m, NCH₂), 2.71–2.63 (2H, m, NCH₂), 2.43 (3H, s, ArCH₃), 1.76–1.68 (4H, m, NCH₂CH₂), 1.45 (9H, s, t-Bu), 1.42 (3H, s, 2-CH₃); $\delta_{\rm C}$ (100 MHz, CDCl₃, CHCl₃) 170.8, 147.0, 144.2, 137.5, 130.8, 129.8, 127.5, 82.1, 65.6, 47.2, 28.0, 24.1, 23.1, 21.5; HRMS-ESI (m/z): $[M + H]^+$ calc. for C₂₀H₃₀NO₄S, 380.1890; found, 380.1878.

(*S*,*E*)-*n*-Butyl 2-methyl-2-(pyrrolidin-1-yl)-4-(*p*-toluenesulfonyl)but-3-enoate (3j)

Yellow oil (Found: C, 63.1; H, 7.9; N, 3.9. Calc. for $C_{20}H_{29}NO_4S$: C, 63.3; H, 7.7; N, 3.7%); $[\alpha]_{589}^{22}$ –26.0 (*c* 1.00 in EtOH); 88% ee [determined by HPLC analysis: Daicel Chiralpak AS-H column, *n*-hexane/isopropanol = 90/10 as eluent, flow

rate = 0.50 mL min⁻¹, $t_{\rm R}$ = 30.9 min for (*R*)-3i and 36.9 min for (*S*)-**3j**]; $v_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3058, 2962, 2873, 1727, 1630, 1597, 1459, 1378, 1321, 1302, 1289, 1246, 1196, 1147, 1085, 1018, 968, 836, 812, 708; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me₄Si) 7.76 (2H, d, J = 8.2 Hz, ArH), 7.33 (2H, d, J = 8.2 Hz, ArH), 7.18 (1H, d, J = 15.2 Hz, TsCH=CH), 6.56 (1H, d, J = 15.2 Hz, TsCH = CH), 4.15 (1H, dt, J = 12.4, 6.8 Hz, $OCH_2CH_2CH_2CH_3$), 4.12 (1H, dt, J = 12.4, 6.8 Hz, OCH₂CH₂CH₂CH₃), 2.81–2.70 (2H, m, NCH₂), 2.69–2.59 (2H, m, NCH₂), 2.44 (3H, s, ArCH₃), 1.78–1.69 (4H, m, NCH₂CH₂), 1.61 (2H, tt, J = 7.4, 6.8 Hz, OCH₂CH₂CH₂CH₃), 1.46 (3H, s, 2-CH₃), 1.35 (2H, tq, J = 7.4, 7.4 Hz, OCH₂CH₂CH₂CH₃), 0.93 (3H, t, J = 7.4 Hz, OCH₂CH₂CH₂CH₃); $\delta_{\rm C}$ (100 MHz, CDCl₃, CHCl₃) 171.7, 146.3, 144.3, 137.4, 131.2, 129.9, 127.7, 65.5, 65.0, 47.4, 30.6, 24.1, 23.1, 21.6, 19.1, 13.6; HRMS-ESI (m/z): $[M + H]^+$ calc. for C₂₀H₃₀NO₄S, 380.1890; found, 380.1872.

(*S*,*E*)-Benzyl 2-methyl-2-(pyrrolidin-1-yl)-4-(*p*-toluenesulfonyl)but-3-enoate (3k)

Yellow oil (Found: C, 66.6; H, 6.6; N, 3.6. Calc. for C₂₃H₂₇NO₄S: C, 66.8; H, 6.6; N, 3.4%); $[\alpha]_{559}^{25}$ -19.1 (c 1.00 in EtOH); 90% ee [determined by HPLC analysis: Daicel Chiralpak AS-H column, *n*-hexane/isopropanol = 90/10 as eluent, flow rate = 0.50 mL \min^{-1} , $t_{\rm R} = 22.0$ min for (S)-3k and 30.5 min for (R)-3k]; $v_{\rm max}$ (film)/cm⁻¹ 3059, 3034, 2964, 2872, 1728, 1630, 1596, 1495, 1455, 1376, 1320, 1300, 1289, 1186, 1146, 1084, 1017, 968, 911, 812, 752, 699; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me₄Si) 7.72 (2H, d, J = 8.0 Hz, ArH), 7.39-7.26 (7H, m, ArH), 7.18 (1H, d, J = 15.2 Hz, TsCH=CH), 6.53 (1H, d, J = 15.2 Hz, TsCH = CH), 5.18 $(1H, d, J = 12.4 \text{ Hz}, CH_2\text{Ph}), 5.15 (1H, d, J = 12.4 \text{ Hz}, CH_2\text{Ph}),$ 2.78–2.68 (2H, m, NCH₂), 2.67–2.58 (2H, m, NCH₂), 2.43 (3H, s, ArCH₃), 1.74–1.63 (4H, m, NCH₂CH₂), 1.47 (3H, s, 2-CH₃); $\delta_{\rm C}$ (100 MHz, CDCl₃, CHCl₃) 171.4, 146.0, 144.3, 137.2, 135.3, 131.4, 129.8, 128.5, 128.4, 128.2, 127.6, 66.8, 65.5, 47.3, 24.0, 23.0, 21.6; HRMS-ESI (m/z): $[M + H]^+$ calc. for C₂₃H₂₈NO₄S, 414.1734; found, 414.1725.

(*S*,*E*)-*tert*-Butyl 2-benzyl-2-(pyrrolidin-1-yl)-4-(*p*-toluene-sulfonyl)but-3-enoate (31)

Colorless oil (Found: C, 68.4; H, 7.5; N, 3.0. Calc. for C₂₆H₃₃NO₄S: C, 68.5; H, 7.3; N, 3.1%); $[\alpha]_{589}^{27}$ +15.8 (c 1.00 in EtOH); 81% ee [determined by HPLC analysis: Daicel Chiralpak AS-H column, *n*-hexane/isopropanol = 90/10 as eluent, flow rate = 0.50 mL min⁻¹, $t_{\rm R} = 22.5$ min for (*R*)-31 and 27.8 min for (*S*)-31]; $v_{\rm max}$ (film)/cm⁻¹ 3062, 3032, 2974, 2934, 2873, 1718, 1597, 1495, 1454, 1393, 1369, 1319, 1302, 1264, 1147, 1086, 1021, 973, 841, 813, 737, 702; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me₄Si) 7.70 (2H, d, J = 8.4Hz, ArH), 7.32 (2H, d, J = 8.4 Hz, ArH), 7.21–7.14 (3H, m, Ph), 7.01–6.94 (2H, m, Ph), 6.79 (1H, d, J = 15.2 Hz, TsCH=CH), 6.62 (1H, d, J = 15.2 Hz, TsCH = CH), 3.49 (1H, d, J = 13.0Hz, CH₂Ph), 2.95–2.86 (2H, m, NCH₂), 2.80 (1H, d, J = 13.0 Hz, CH₂Ph), 2.73–2.64 (2H, m, NCH₂), 2.44 (3H, s, ArCH₃), 1.79–1.67 (4H, m, NCH₂CH₂), 1.43 (9H, s, t-Bu); $\delta_{\rm C}$ (100 MHz, CDCl₃, CHCl₃) 169.5, 147.2, 144.1, 137.6, 135.0, 131.4, 130.4, 129.7, 128.1, 127.7, 127.0, 82.6, 69.6, 47.1, 44.8, 28.2, 23.7, 21.5; HRMS-ESI (m/z): $[M + H]^+$ calc. for C₂₆H₃₄NO₄S, 456.2203; found, 456.2186.

(*S*,*E*)-*tert*-Butyl 4-methyl-2-(pyrrolidin-1-yl)-2-(2'-*p*-tosylvinyl)pentanoate (3m)

Yellow solid (Found: C, 65.4; H, 8.4; N, 3.4. Calc. for C₂₃H₃₅NO₄S: C, 65.5; H, 8.4; N, 3.3%); $[\alpha]_{589}^{25}$ -39.9 (c 1.00 in EtOH); 92% ee [determined by HPLC analysis: Daicel Chiralpak AS-H column, *n*-hexane/isopropanol = 95/5 as eluent, flow rate = 0.50 mL min⁻¹, $t_{\rm R} = 24.8 \text{ min for } (R)$ -3m and 33.2 min for (S)-3m]; $v_{\rm max}$ (film)/cm⁻¹ 3059, 2964, 2872, 1717, 1628, 1597, 1457, 1392, 1368, 1320, 1300, 1241, 1146, 1087, 1039, 1017, 977, 921, 841, 811, 707, 686; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me₄Si) 7.77 (2H, d, J = 8.0 Hz, ArH), 7.32 (2H, d, J = 8.0 Hz, ArH), 7.20 (1H, d, J = 15.2 Hz, TsCH=CH), 6.65 (1H, d, J = 15.2 Hz, TsCH = CH), 2.80–2.71 (2H, m, NCH₂), 2.61–2.52 (2H, m, NCH₂), 2.43 (3H, s, ArCH₃), 2.00– 1.91 (1H, m, CH₂CH(CH₃)₂), 1.71–1.56 (6H, m, CH₂CH(CH₃)₂ and NCH₂CH₂), 1.47 (9H, s, t-Bu), 0.853 (3H, d, J = 6.4 Hz, $CH_2CH(CH_3)_2$, 0.850 (3H, d, J = 6.4 Hz, $CH_2CH(CH_3)_2$); δ_C (100 MHz, CDCl₃, CHCl₃) 170.3, 147.2, 144.1, 137.8, 131.0, 129.8, 127.6, 82.2, 68.6, 47.4, 46.8, 28.2, 24.5, 24.3, 23.7, 23.5, 21.6; HRMS-ESI (m/z): $[M + H]^+$ calc. for C₂₃H₃₆NO₄S, 422.2360; found, 422.2344.

(*S*,*E*)-*tert*-Butyl 2-isopropyl-2-(pyrrolidin-1-yl)-4-(*p*-toluenesul-fonyl)but-3-enoate (3n)

White solid (Found: C, 64.65; H, 8.2; N, 3.6. Calc. for C₂₂H₃₃NO₄S: C, 64.8; H, 8.2; N, 3.4%); $[\alpha]_{559}^{26}$ -51.5 (c 1.00 in EtOH); 95% ee [determined by HPLC analysis: Daicel Chiralpak AS-H column, *n*-hexane/isopropanol = 97/3 as eluent, flow rate = 0.50 mL min⁻¹, $t_{\rm R} = 42.3 \text{ min for } (R)$ -3n and 48.3 min for (S)-3n]; $v_{\rm max}({\rm film})/{\rm cm}^{-1}$ 3059, 2971, 2930, 2875, 1716, 1633, 1597, 1456, 1392, 1369, 1320, 1297, 1289, 1252, 1147, 1087, 1017, 976, 928, 878, 841, 815, 734, 709; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me₄Si) 7.78 (2H, d, J = 8.2 Hz, ArH), 7.32 (2H, d, J = 8.2 Hz, ArH), 7.07 (1H, d, J = 15.2 Hz, TsCH=CH), 6.58 (1H, d, J = 15.2 Hz, TsCH = CH), 2.84–2.73 (2H, m, NCH₂), 2.53–2.45 (2H, m, NCH₂), 2.43 (3H, s, ArCH₃), 2.37 (1H, qq, J = 6.8, 6.8 Hz, $CH(CH_3)_2$), 1.70–1.57 (4H, m, NCH_2CH_2 , 1.48 (9H, s, t-Bu), 0.84 (3H, d, J = 6.8 Hz, $CH(CH_3)_2$), $0.74 (3H, d, J = 6.8 Hz, CH(CH_3)_2); \delta_C (100 MHz, CDCl_3, CHCl_3)$ 170.4, 144.1, 144.0, 138.0, 132.9, 129.8, 127.6, 82.1, 72.5, 46.7, 33.5, 28.3, 23.6, 21.6, 18.5, 16.4; HRMS-ESI (m/z): [M + H]⁺ calc. for C₂₂H₃₄NO₄S, 408.2203; found, 408.2189.

(*R*,*E*)-Cyclohexyl 2-phenyl-2-(pyrrolidin-1-yl)-4-(*p*-toluenesulfonyl)but-3-enoate (30)

Colorless oil (Found: C, 69.4; H, 7.4; N, 3.1. Calc. for $C_{27}H_{33}NO_4S$: C, 69.35; H, 7.1; N, 3.0%); $[\alpha]_{589}^{22}$ +15.3 (*c* 1.00 in EtOH); 40% ee [determined by HPLC analysis: Daicel Chiralpak AS-H column, *n*-hexane/isopropanol = 92/8 as eluent, flow rate = 0.50 mL min⁻¹, t_R = 42.6 min for (*R*)-**30** and 50.6 min for (*S*)-**30**]; v_{max} (film)/cm⁻¹ 3061, 2937, 2860, 1722, 1625, 1597, 1492, 1449, 1400, 1319, 1232, 1196, 1145, 1086, 1033, 1010, 987, 907, 835, 813, 761, 736, 700; δ_H (400 MHz, CDCl₃, Me₄Si) 7.70 (2H, d, *J* = 8.4 Hz, ArH), 7.33– 7.22 (8H, m, ArH and TsCH=CH), 6.61 (1H, d, *J* = 15.2 Hz, TsCH = CH), 4.96 (1H, tt, *J* = 8.6, 4.0 Hz, OCH), 2.87–2.78 (2H, m, NCH₂), 2.58–2.49 (2H, m, NCH₂), 2.44 (3H, s, ArCH₃), 1.90– 1.77 (2H, m, *c*-Hex), 1.77–1.60 (6H, m, NCH₂CH₂ and *c*-Hex), 1.60–1.21 (6H, m, *c*-Hex); δ_C (100 MHz, CDCl₃, CHCl₃) 170.1, 145.5, 144.2, 138.0, 137.6, 131.0, 129.8, 128.3, 128.1, 127.9, 127.6, 74.1, 73.8, 48.3, 31.51, 31.48, 25.2, 24.5, 23.4, 21.6; HRMS-ESI (*m*/*z*): [M + H]⁺ calc. for C₂₇H₃₄NO₄S, 468.2203; found, 468.2183.

(*S*,*E*)-Cyclohexyl 2-[allyl(2'-tosylpenta-1',4'-dienyl)amino]propanoate (9)⁵

Colorless oil (Found: C, 66.6; H, 7.8; N, 3.15. Calc. for $C_{24}H_{33}NO_4S$: C, 66.8; H, 7.7; N, 3.25%); $[\alpha]_{589}^{26}$ –90.1 (*c* 1.00 in EtOH); v_{max} (film)/cm⁻¹ 3081, 2938, 2860, 1732, 1622, 1494, 1451, 1419, 1281, 1198, 1170, 1138, 1085, 1031, 1015, 917, 814, 761, 707; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me₄Si) 7.69 (2H, d, *J* = 8.2 Hz, ArH), 7.63 (1H, s, 1'-H), 7.24 (2H, d, *J* = 8.2 Hz, ArH), 5.84–5.65 (2H, m, CH₂CH = CH₂), 5.24–5.13 (2H, m, CH₂CH=CH₂), 4.97–4.85 (2H, m, CH₂CH=CH₂), 4.81 (1H, tt, *J* = 8.8, 3.2 Hz, OCH), 4.09 (1H, q, *J* = 7.2 Hz, NCHCO), 3.91–3.77 (2H, m, CH₂CH=CH₂), 3.09–2.94 (2H, m, CH₂CH=CH₂), 2.39 (3H, s, ArCH₃), 1.93–1.60 (4H, m, *c*-Hex), 1.60–1.20 (6H, m, *c*-Hex), 1.49 (3H, d, *J* = 7.2 Hz, 2-CH₃); $\delta_{\rm C}$ (100 MHz, CDCl₃, CHCl₃) 171.1, 145.5, 142.3, 139.7, 136.7, 134.4, 129.3, 127.4, 117.0, 115.6, 103.0, 73.9, 61.2, 51.6, 31.4, 29.1, 25.2, 23.5, 21.4, 16.7; HRMS-ESI (*m*/*z*): [M + H]⁺ calc. for C₂₄H₃₄NO₄S, 432.2203; found, 432.2182.

(*S*,3*E*,5*E*)-*tert*-Butyl 2-methyl-2-(pyrrolidin-1-yl)-4,6-ditosylhexa-3,5-dienoate (10)⁷

Yellow solid (Found: C, 62.2; H, 6.9; N, 2.4. Calc. for $C_{29}H_{37}NO_6S_2$: C, 62.2; H, 6.7; N, 2.5%); $[\alpha]_{589}^{28}$ +96.0 (*c* 1.00 in EtOH); v_{max} (film)/cm⁻¹ 3056, 2974, 2927, 2874, 1724, 1628, 1597, 1455, 1370, 1322, 1240, 1149, 1085, 1041, 993, 837, 812, 764, 708; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me₄Si) 7.75 (2H, d, *J* = 8.4 Hz, ArH), 7.70 (2H, d, *J* = 8.4 Hz, ArH), 7.36 (2H, d, *J* = 8.4 Hz, ArH), 7.33 (2H, d, *J* = 8.4 Hz, ArH), 7.10 (1H, d, *J* = 15.8 Hz, 5-H), 6.81 (1H, s, 3-H), 6.41 (1H, d, *J* = 15.8 Hz, 6-H), 2.57–2.35 (4H, m, NCH₂), 2.46 (3H, s, ArCH₃), 2.45 (3H, s, ArCH₃), 1.67–1.54 (4H, m, NCH₂CH₂), 1.41 (9H, s, *t*-Bu), 1.40 (3H, s, 2-CH₃); $\delta_{\rm C}$ (100 MHz, CDCl₃, CHCl₃) 161.1, 145.7, 144.72, 144.66, 144.3, 137.1, 136.4, 131.5, 130.1, 129.9, 129.7, 128.4, 127.7, 83.8, 60.7, 46.5, 27.7, 23.4, 21.7, 21.6, 19.9; HRMS-ESI (*m*/*z*): [M + H]⁺ calc. for $C_{29}H_{38}NO_6S_2$, 560.2135; found, 560.2119.

Preparation of *tert*-butyl 2-methyl-2-(pyrrolidin-1-yl)butanoate (5) from 3i

(Step 1) A solution of 3i (296 mg, 0.780 mmol) in THF (7.8 mL) was added to a suspention of magnesium powder (193 mg, 7.94 mmol) in dry methanol (7.8 mL) at 50 °C. The mixture was stirred for 2 h at the same temperature and quenched with saturated aqueous ammonium chlolride at 0 °C. Extractive workup and purification by chromatography on silica gel (nhexane/ethyl acetate = 2/1 as eluent) gave *tert*-butyl 2-methyl-2-(pyrrolidin-1-yl)but-3-enoate (4) (73 mg, 42% yield) as a colorless oil. (Step 2) A mixture of 4 (63 mg, 0.28 mmol) and palladium on carbon (loading: 10 wt%, 5 mg) in ethyl acetate (2.8 mL) was stirred for 1 h under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by chromatography on silica gel (dichloromethane/methanol = 10/1 as eluent) to give 5 (52 mg, 82% yield). Colorless oil (Found: C, 68.4; H, 11.1; N, 6.1. Calc. for $C_{13}H_{25}NO_2$: C, 68.7; H, 11.1; N, 6.2%); $[\alpha]_{589}^{24}$ +8.0 (c 1.00 in CHCl₃); v_{max}(film)/cm⁻¹ 2973, 2876, 1719, 1457, 1391,

1367, 1300, 1248, 1173, 1134, 1121, 1075, 1045, 1026, 1002, 984, 908, 848, 809, 749; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me₄Si) 2.90–2.82 (2H, m, NCH₂), 2.76–2.68 (2H, m, NCH₂), 1.84 (1H, dq, *J* = 13.6, 7.6 Hz, CH₂CH₃), 1.77–1.70 (4H, m, NCH₂CH₂), 1.63 (1H, dq, *J* = 13.6, 7.6 Hz, CH₂CH₃), 1.46 (9H, s, *t*-Bu), 1.24 (3H, s, 2-CH₃), 0.88 (3H, t, *J* = 7.6 Hz, CH₂CH₃); $\delta_{\rm C}$ (100 MHz, CDCl₃, CHCl₃) 173.8, 80.3, 64.9, 46.7, 30.7, 28.3, 24.2, 20.1, 8.6; HRMS-ESI (*m*/*z*): [M + H]⁺ calc. for C₁₃H₂₆NO₂, 228.1958; found, 228.1947.

Preparation of the authentic sample (S)-5

A mixture of (*S*)-**6**⁶ (68 mg, 0.39 mmol, 98% ee), 1,4-butanediol di-*p*-toluenesulfonate¹⁴ (163 mg, 0.41 mmol), and potassium hydrogen carbonate (0.12 g, 1.2 mmol) in acetonitrile (2 mL) was refluxed for 6 h. The resulting mixture was cooled to room temperature and concentrated. The residue was purified twice by chromatography on silica gel (1st: dichloromethane/methanol = 20/1 to 10/1 as eluent; 2nd: *n*-hexane/ethyl acetate = 3/1 to 1.5/1 as eluent) to obtain (*S*)-**5** (26 mg, 29% yield). Colorless oil; $[\alpha]_{589}^{23}$ +8.7 (*c* 1.00 in CHCl₃).

[1,2] Stevens rearrangement of (*S*)-*N*-benzyl-2-(pyrrolidin-1-yl)propanoic acid ester-derived ammonium salt 7

A solution of 7 (73 mg, 0.19 mmol) in THF (4 mL) was treated with potassium tert-butoxide (26 mg, 0.23 mmol) at 0 °C and stirred for 4 h. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (*n*-hexane/ethyl acetate = 2/1as eluent) to afford tert-butyl 2-methyl-3-phenyl-2-(pyrrolidin-1yl)propanoate (8) (38 mg, 69% yield). Colorless oil (Found: C, 74.4; H, 9.3; N, 4.7. Calc. for C₁₈H₂₇NO₂: C, 74.7; H, 9.4; N, 4.8%). 0% ee [determined by HPLC analysis: Daicel Chiralcel OD-H column, *n*-hexane/ethanol/diethylamine = 99.5/0.5/0.05 as eluent, flow rate = 0.50 mL min⁻¹, $t_{\rm R}$ = 8.2 and 9.3 min]; $v_{\rm max}$ (film)/cm⁻¹ 3063, 2972, 2873, 1715, 1604, 1495, 1455, 1391, 1368, 1251, 1163, 1098, 1033, 1011, 964, 939, 912, 849, 737, 701; $\delta_{\rm H}$ (400 MHz, CDCl₃, Me_4Si 7.27–7.17 (5H, m, Ph), 3.32 (1H, d, J = 13.0 Hz, CH_2Ph), 2.97-2.89 (2H, m, NCH2), 2.88-2.80 (2H, m, NCH2), 2.82 (1H, d, J = 13.0 Hz, CH_2 Ph), 1.83–1.74 (4H, m, NCH₂CH₂), 1.46 (9H, s, *t*-Bu), 1.16 (3H, s, 2-CH₃); $\delta_{\rm C}$ (100 MHz, CDCl₃, CHCl₃) 172.6, 137.8, 130.6, 127.8, 126.2, 80.9, 65.3, 46.9, 43.4, 28.3, 24.0, 21.0; HRMS-ESI (m/z): $[M + H]^+$ calc. for C₁₈H₂₈NO₂, 290.2115; found, 290.2103.

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