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Asymmetric α-2-tosylvinylation of in situ-generated *N*-2-tosylvinyl proline-derived ammonium ylides

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ABSTRACT

Asymmetric α-2-tosylvinylation of *N*-substituted proline esters using ethynyl tolyl sulfone as an electrophile was shown to proceed in good yield with high enantioselectivities without the addition of any bases. The reaction proceeds via the formation of *N*-2-tosylvinyl ammonium ylides.

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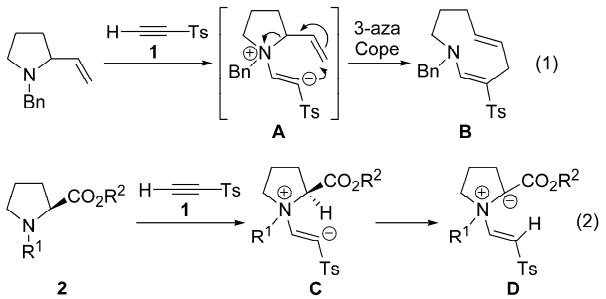
Ethynyl tolyl sulfone (**1**) is a compound of interest in organic synthesis because it works as a powerful Michael acceptor and reacts with various nucleophiles to produce 2-tosylvinyl derivatives.[1] The reactions are applied for ring-expansion of nitrogen-containing heterocycles using cyclic tertiary amines as substrates.[2,3] Weston and Back et al. reported that the conjugate addition of cyclic tertiary amines to **1** afforded *N*-2-tosylvinyl ammonium zwitterion **A** under mild conditions and that **A** rearranged to the ring-expansion product **B** via 3-aza Cope rearrangement (Scheme 1, eq 1).[3] These results suggest that the reaction of *N*-substituted L-proline ester **2** with **1** would give the corresponding zwitterion **C**, which would then be converted into an ammonium ylide **D** via intramolecular hydrogen transfer (eq 2). The ylide **D** might afford α-substituted proline esters by [1,2] Stevens or Sommelet–Hauser rearrangements.[4,5]



Scheme 1. Reactions of *N*-substituted pyrrolidines with ethynyl tolyl sulfone (**1**)

We investigated the reaction of *N*-benzyl-L-proline *tert*-butyl ester (**2a**) with 1.0 equivalent of **1** in dichloromethane at 0 °C for 4 h (Table 1, entry 1). The unreacted **1** was quenched by the addition of methylamine to prevent undesirable reactions. Contrary to our expectations, no detectable amount of the [1,2] Stevens rearrangement products, such as α-benzylproline derivatives, were obtained. However, the α-2-tosylvinyl adduct **3a** was obtained in 52% yield with 34% ee. Assignments of the structure and (*R*)-configuration of **3a** were determined by comparison of the ^{1}H NMR chemical shifts and specific rotation value with the (*R*)-authentic sample.[6] Thus, we decided to expand the scope and limitation of this asymmetric α-2-tosylvinylation, and we examined the reactions in various solvents to improve the yield and stereoselectivity. The use of toluene, THF, ethyl acetate, DMF decreased the chemical yields (17–34%); however, the enantioselectivities were improved to moderate levels (entries 2–5, 69–80% ee). Protic solvents, such as isopropanol, could also be used (entry 6, 50%, 42% ee). The use of excess amount of **1** (1.5–2.0 equivalents) improved the chemical yield without affecting the enantioselectivity (entries 7–10). When the reaction of **2a** was carried out with 2.0 equivalents of **1** in DMF, the adduct **3a** was obtained in 59% yield with 80% ee (entry 10).

With the optimized conditions (Table 1, entry 10) in hand, we prepared a series of *N*-substituted proline esters **2b**–**g** to determine steric effects of the *N*- (R^1) and ester- (R^2) substituents on the yield and enantioselectivity (Table 2). When the reaction of *N*-benzyl proline cyclohexyl ester **2b** was carried out under the

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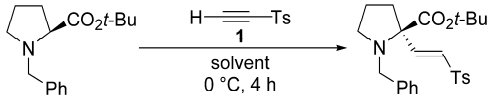
Table 1. Enantioselective α-2-tosylvinylation of **2a** in various solvents

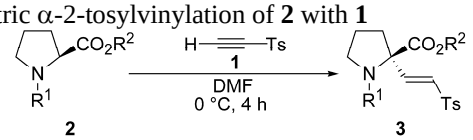


Entry	Solvent	Equiv. of **1**	Yield (%)[a]	Ee (%)[b]
1	CH_2Cl_2	1.0	52	34
2	toluene	1.0	34	69
3	THF	1.0	17	69
4	EtOAc	1.0	22	73
5	DMF	1.0	34	80
6	*i*-PrOH	1.0	50	42
7	CH_2Cl_2	1.5	85	27
8	CH_2Cl_2	2.0	89	25
9	DMF	1.5	44	79
10	DMF	2.0	59	80

[a] Isolated yield. [b] Determined by chiral HPLC analysis.

same conditions, the enantioselectivity was slightly improved (entry 1, **3b**: 45%, 89% ee). Reactions of primary esters such as *n*-butyl (**2c**) or benzyl (**2d**) afforded **3c** or **3d** in excellent enantioselectivities; however, the yields were lower (entry 2, **3c**: 39%, 96% ee; entry 3, **3d**: 39%, >99% ee). Sterically hindered *N*-diphenylmethyl derivative **1e** did not react at all (entry 4). The initial formation of the zwitterion **C** might have been inhibited in this case. In contrast, the reaction of sterically less-demanding *N*-methyl (**2f**) or *N*-allyl (**2g**) derivatives proceeded smoothly to afford **3f** or **3g** in moderate yields with good enantioselectivities (entry 5, 78%, 93% ee; entry 6, 70%, 95% ee). The reactions of **2f** and **2g** with 1.0 equivalent of **1** resulted in lower yields (entry 7, 57%; entry 8, 57%). We found that 2.0 equivalents of **1** should be used to obtain **3** in acceptable yield. It is worth noting that the reaction of the *N*-allyl substrate **2g** gave **3g** in moderate yield with excellent enantioselectivity (entry 6) without formation of [2,3] Stevens[7] or 3-aza Cope rearrangement[8] products.

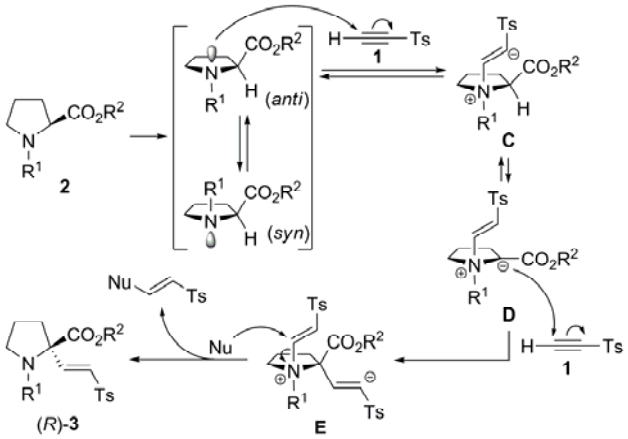
Table 2. Effects of the substituent on the nitrogen in asymmetric α-2-tosylvinylation of **2** with **1**



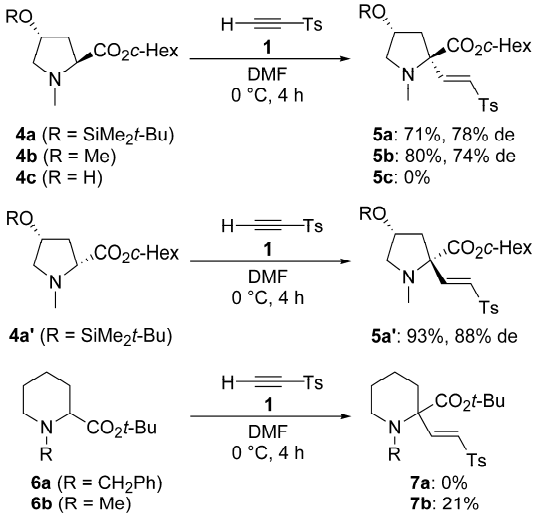
Entry	R^1	R^2		Equiv. of **1**	Yield (%)[a]	Ee (%)[b,c]
1	CH_2Ph	*c*-Hex	**b**	2.0	45	89
2	CH_2Ph	*n*-Bu	**c**	2.0	39	96
3	CH_2Ph	CH_2Ph	**d**	2.0	39	>99
4	$CHPh_2$	*c*-Hex	**e**	2.0	0	–
5	Me	*c*-Hex	**f**	2.0	78	93
6	allyl	*c*-Hex	**g**	2.0	70	95
7	Me	*c*-Hex	**f**	1.0	57	93
8	allyl	*c*-Hex	**g**	1.0	57	96

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] The absolute configurations of **3b**–**g** were determined by analogy with **3a**.

The high stereoselectivity, although its exact origin is unclear at present, might be rationalized as the result of the stereoselective formation of *N*-(2-tosylvinyl)proline-derived ammonium ylide **D** and diastereoselective addition of **D** to **1** to form zwitterion **E** (Scheme 2). *N*-Substituted-L-proline ester **2** is in equilibrium between the *syn*- and *anti*-conformational isomers. The *anti*-isomer of **2** would be desirable for conjugate addition to **1** and affords zwitterion **C**.[9] The zwitterion **C** deprotonates more the acidic proton at α-position of the ester-carbonyl to form ammonium ylide **D**. Conjugate addition of **D** to reactive electrophile **1** would give zwitterion **E** diastereoselectively because of the steric repulsion of the *N*-2-tosylvinyl substituent. Finally, the *N*-2-tosylvinyl substituent is eliminated by reaction with nucleophiles to form α-adduct (*R*)-**3**. The reaction proceeds via formation of a mixture of diastereomeric intermediates. Decomposition of undesirable intermediates which leads to (*S*)-**3** might proceed in DMF and (*R*)-**3** was obtained with high enantioselectivities. Use of dichloromethane or isopropanol might minimize the decomposition and (*R*)-**3** was obtained with low enantioselectivities.



Scheme 2. Proposed mechanism for the asymmetric α-2-tosylvinylation of **2**

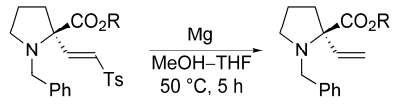


Scheme 3. Reactions of cyclic amino acid esters with **1**

In order to define the scope and limitations of this reaction, we applied our reaction to other types of cyclic amino acid esters (Scheme 3). Reactions of *trans*-4-*tert*-butyldimethylsilyloxy- (**4a**) and 4-methoxy- (**4b**) L-proline derivatives with **1** under optimized reaction conditions (DMF, 0 °C, 4 h) gave corresponding adducts **5a** or **5b** with lower stereoselectivities (**5a**: 71%, 78% de; **5b**: 80%, 74% de) than the 4-non-substituted analogue **3f** (Table 2, entry 5, 93% ee).[10] However, a reaction of *cis*-stereoisomer **4a'** under the same conditions afforded the corresponding diastereomer **5a'** with higher stereoselectivity (**5a'**: 93%, 88% de). These results would support our proposed mechanism depicted in Scheme 2. The 4-substituent, which is located on the same face as the *N*-alkyl (R^1) of ylide **D** would

inhibit the stereoselective conjugated addition of **D** to **1** due to steric repulsion. A reaction of the 4-hydroxy (**4c**) derivative did not afford the expected product. The α,*O*-bis(2-tosylvinyl) derivative (R = *trans*-TsCH=CH) was obtained in 26% yield with a complex mixture of unidentified products. Next, we attempted reactions of *N*-substituted pipecolinic acid *tert*-butyl esters **6** with **1**. However, the attempts were unsuccessful because of the lower nucleophilicity of the piperidinyl tertiary amine. The reaction of *N*-benzyl derivative **6a** did not give the product with the recovery of the substrate. The sterically less-demanding *N*-methyl derivative **6b** reacted with **1** to afford **7b** in only 21% yield.

Finally, we examined the reductive desulfonylation of **3a** and **3b** by treatment with magnesium metal in THF–methanol at 50 °C (Scheme 4). The corresponding α-vinyl prolines **8a** or **8b** were obtained in moderate yields (**8a**: 65%, **8b**: 54%).



3a (R = *t*-Bu) **8a**: 65%
3b (R = *c*-Hex) **8b**: 54%

Scheme 4. Reductive desulfonylation of **3a** and **3b** with Mg

In conclusion, we have reported the asymmetric α-2-tosylvinylation of *N*-substituted proline esters using ethynyl tolyl sulfone (**1**) as an electrophile.[11] This reaction was shown to proceed in good yield with high enantioselectivities without addition of any bases. The reaction proceeds via the formation of *N*-2-tosylvinyl ammonium ylides.

Acknowledgments

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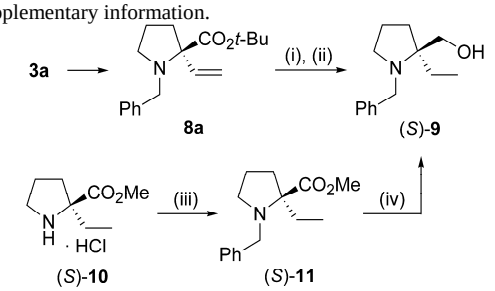
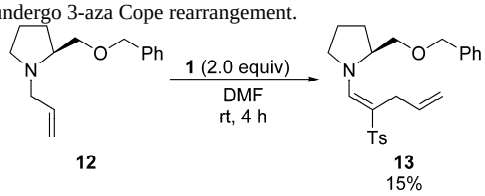
6. The assignments were carried out after conversion of **3a** to amino alcohol **9**. The (*R*)-authentic sample of **9** was prepared from (*S*)-α-ethylproline methyl ester hydrochloride [(*S*)-**10**]. Conditions: (i) $LiAlH_4$, THF, 0 °C to rt. (ii) H_2, Pd-C, EtOAc, rt. (iii) $PhCH_2Br$, $KHCO_3$, MeCN, reflux. (iv) $LiAlH_4$, THF, reflux. Details: see Supplementary information.



7. Even if the reaction was carried out at –55 °C for 24 h, the corresponding [2,3] Stevens rearrangement product (α-allyl proline derivative) was not obtained.
8. We attempted a reaction of **12** with **1** to examine the extent to which *N*-allyl pyrrolidine derivatives undergo 3-aza Cope rearrangement (rt, DMF, 4 h). The corresponding rearrangement product **13** was obtained in only 15% yield. Compound **2g** might not undergo 3-aza Cope rearrangement.



12 **13** 15%

9. *N*-Quaternization of *N*-substituted L-proline esters by treatment with electrophiles such as alkyl halides proceeds from the same face with the ester substituents preferably at 2-position. See ref. 5.
10. The stereochemistries of **5a** and **5b** were assigned by ^1H NMR. Details: see Supplementary information.
11. We attempted reactions using other types of electron-deficient terminal acetylenes, such as ethyl propiolate or 1-phenylprop-2-yn-1-one. However, the corresponding α-adducts were not obtained.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at XXX.