

**INTRODUCTION OF AN N1 UNIT TO MONOENES OR 1,6-DIENES
USING CHLORAMINE-T-SILVER NITRATE: A NEW ROUTE TO
AZIRIDINES OR BICYCLIC PYRROLIDINES**

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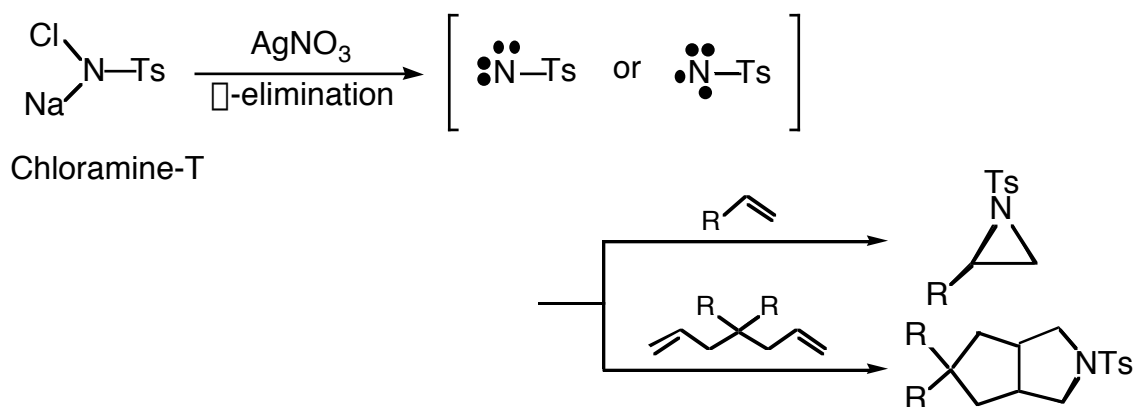
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Abstract - Aziridine derivatives are synthesized from a variety of olefins using commercially available Chloramine-T as a nitrogen source in the presence of AgNO₃. The method is applicable to a tandem cyclization of 1,6-dienes accompanied by an N1 unit incorporation to afford bicyclic pyrrolidine derivatives.

Nitrogen-containing heterocycles, such as aziridines,¹ pyrrolidines,² and related compounds frequently confer potent and diverse biological activities as substructures of natural products. Thus, their syntheses have attracted considerable attention over the years.^{1,3} An N1 unit introduction to organic molecules is one of the effective routes for producing such heterocycles.^{1,3,4} Commercially available Chloramine-T (CT) is known not only as a versatile oxidizing reagent but also as a nitrogen source in organic synthesis.⁵

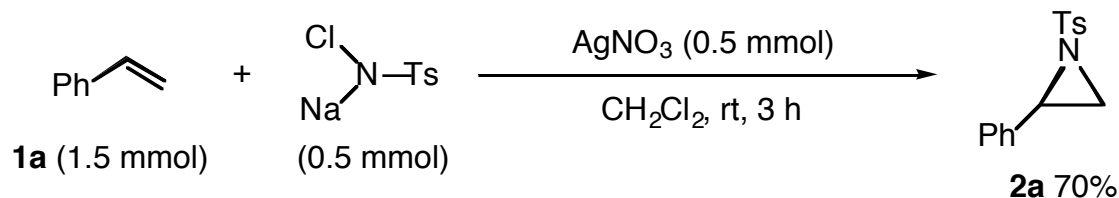
We, and other groups, have previously reported on several methods for the construction of nitrogen-containing heterocycles utilizing CT as an N1 unit.⁶ To further extend this strategy, AgNO₃, a potent reagent for capture of halide ions, was applied to the synthesis of aziridines and bicyclic pyrrolidines involving the generation of a nitrene species from CT. During the course of our studies in this area, Rai *et al.* reported on the aziridination of olefins using CT in the presence of AgNO₃ in THF, in which the substrates were restricted to styrene, acrylonitrile, and ethyl acrylate.⁷ Although we investigated the same reaction, no reproducibility was observed (*vide infra*). Here, we report on the aziridination of olefins utilizing CT as an N1 unit in the presence of AgNO₃, and on the finding that this system is applicable to the synthesis of bicyclic pyrrolidines from 1,6-dienes *via* a tandem cyclization (Scheme 1).



Scheme 1. Generation of a nitrene species from Chloramine-T and its application to the synthesis of aziridines and pyrrolidines

When styrene (1.5 mmol) was treated with CT (0.5 mmol) and AgNO₃ (0.5 mmol) in CH₂Cl₂ (2.0 mL) at room temperature for 3 h, *N*-(*p*-toluenesulfonyl)-2-phenylaziridine (**2a**) was obtained in 70% yield (Scheme 2).⁸ Since a similar aziridination was reported by Rai's group,⁹ as mentioned above, during the course of our research, we reinvestigated the aziridination of styrene using their method. However, the corresponding aziridine was not produced at all. The result well agreed with our preliminary experiment showing that the aziridination did not proceed when THF was used as a solvent, instead of CH₂Cl₂ or

benzene.



Scheme 2. Aziridination of styrene using CT and AgNO_3

The aziridination of a variety of olefins other than styrene was also successful using the CT- AgNO_3 system (Table 1). *trans*- α -Methylstyrene was converted to the corresponding aziridine in 59% yield under the same conditions as were used for the reaction of styrene (method A; run 1). When the reaction was carried out with two equivalents of both CT and AgNO_3 in benzene at 60 °C for 3 h (method B), the

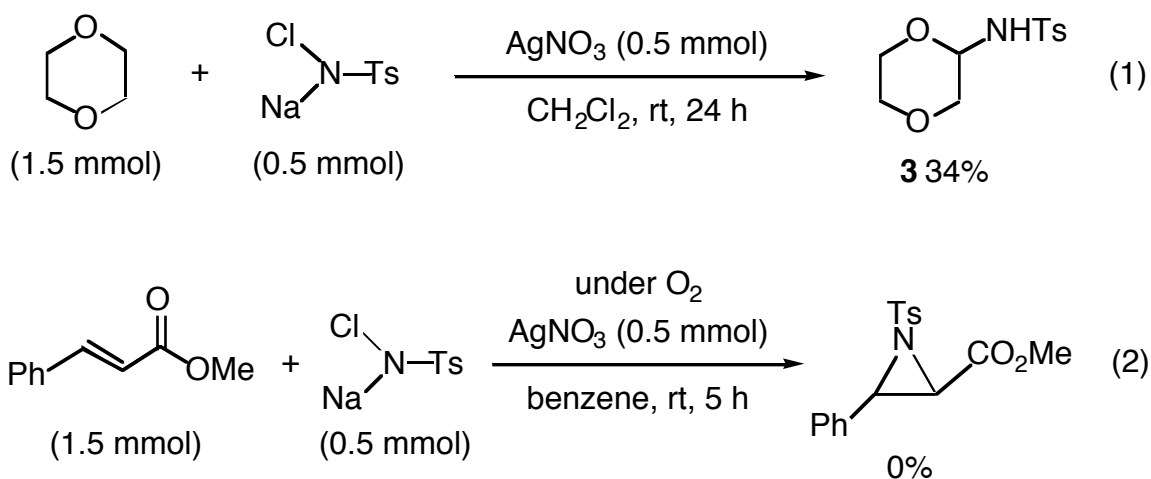
Table 1. Aziridination of olefins using Chloramine-T and AgNO_3

run	substrate	method ^a	time (h)	yield (%) (<i>cis/trans</i>)
1	1b	A	3	59 (14 / 86)
2	1b	B	3	92 (6 / 94)
3	1c	B	3	89 (7 / 93)
4	1d	B	8	53
5	1e	B	14	43 (38 / 62)
6	1f	B	14	53 (43 / 57)
7	1g	A ^b	6	54 (0 / 100)
8	1h	A	5	47 (0 / 100)

^a Method A: olefin (1.5 mmol), CT (0.5 mmol), AgNO_3 (0.5 mmol), CH_2Cl_2 (2.0 mL), rt, under Ar. Method B: olefin (0.5 mmol), CT (1.0 mmol), AgNO_3 (1.0 mmol), benzene (5.0 mL), 60 °C, under Ar. ^b Solvent: benzene (2.0 mL).

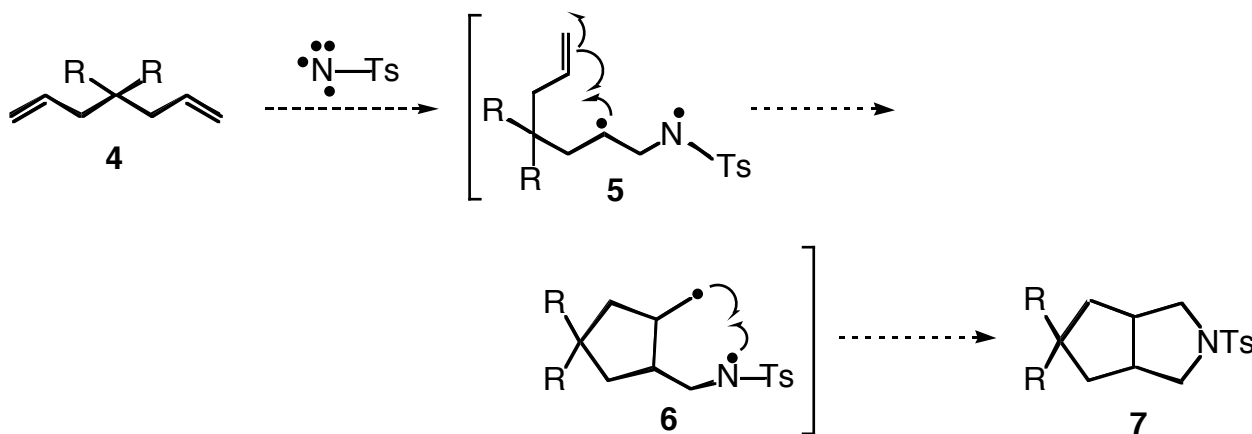
yield was improved to 92% with high diastereoselectivity (*cis/trans* = 6/94) (run 2).¹⁰ *cis*-1-Methylstyrene was also aziridinated in excellent yield to afford the predominantly *trans*-isomer (run 3).¹⁰ 1,2-Dihydronaphthalene and aliphatic olefins, such as *trans*- and *cis*-2-octenes, could be converted to the corresponding aziridines in moderate yields (runs 4–6).¹⁰ Although our alternative methods of aziridination catalyzed by CuCl^{6a} or I₂^{6b} are not suitable for the synthesis of aziridines from electron-deficient olefins, the present system permits the aziridination of methyl cinnamate and *trans*-chalcone with the conservation of the stereochemistry of the starting olefins (runs 7 and 8).

In order to clarify the most likely reaction pathway for this reaction, the following experiments were carried out (Scheme 3). When three equivalents of 1,4-dioxane were treated with CT and AgNO₃ in CH₂Cl₂ at room temperature for 24 h, C-H insertion of an NTs unit to the oxygen of 1,4-dioxane proceeded to provide **3** in 34% yield.¹¹ The aziridination of methyl cinnamate did not take place when the argon atmosphere was changed to oxygen.¹² In addition, from the results of stereochemistry of the reactions as shown Table 1 (runs 1–3, 5, and 6), it is likely that the reactions proceed *via* a stepwise cyclization. These experimental facts suggest that the present reaction might involve a nitrogen radical species (a triplet state nitrene).



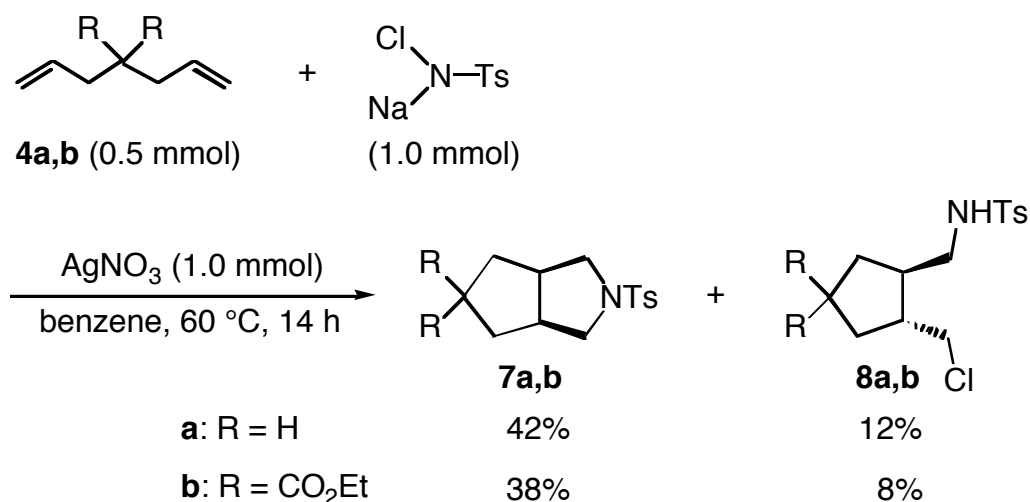
Scheme 3. Experiments designed to identify the reaction intermediates

This prediction prompted us to propose the following radical reaction (Scheme 4). If 1,6-diene (**4**) is employed in the present system, a tandem cyclization would occur *via* biradical intermediates (**5** and **6**) to afford the bicyclic pyrrolidine derivative (**7**).



Scheme 4. Reaction scheme for a tandem cyclization of 1,6-diene with a triplet state *N*-tosyl nitrene

In fact, when 1,6-heptadiene (**4a**) was treated with CT and AgNO₃ under the conditions used in method B for 14 h, the anticipated bicyclic pyrrolidine derivative (**7a**) was obtained in 42% yield along with *trans*-substituted cyclopentane derivative (**8a**) (Scheme 5).¹³ The substituted bicyclic pyrrolidine derivative (**7b**) was also formed from **4b**. Evidence of the formation of by-product (**8**) would confirm the generation of intermediate (**6**) shown in Scheme 4. Although 5-*exo*-cyclization in a *cis*-fashion from **5** to **6** would readily provide bicyclic products (**7**) *via* the second cyclization, the recombination of the biradical of the resulting *trans*-isomer would be rather difficult and, as a result, compounds (**8**) were formed. In general, the 5-*exo*-cyclization of the 1-methyl-5-hexenyl radical at 60 °C gives a mixture of *cis*- and *trans*-diastereomers of (2-methylcyclopentyl)methyl radical (*cis/trans* = 3.2/1),¹⁴ the ratio of which is in good agreement with that of **7**:**8**. This provides support for the present reaction proceeding *via* a tandem radical cyclization.



Scheme 5. Tandem cyclization of 1,6-dienes using CT and AgNO₃

In summary, we reported that the CT–AgNO₃ system is applicable to the synthesis of not only aziridines from monoenes including electron-deficient olefins but also bicyclic pyrrolidines from 1,6-dienes. The finding herein suggests that a nitrogen radical species (a triplet state nitrene) is involved, when the reaction is conducted using CT and AgNO₃. Further applications of the method to the synthesis of other heterocycles are currently in progress.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. a) J. A. Deyrup, In *The Chemistry of Heterocyclic Compounds*, Vol. 42, ed. by A. Hassner, Wiley, New York, 1983, pp. 1-214; b) A. Padwa and A. D. Woolhouse, In *Comprehensive Heterocyclic*

- Chemistry*, Vol. 7, ed. by W. Lwowski, Pergamon, Oxford, 1984, pp. 47-93; c) W. H. Pearson, B. W. Lian, and S. C. Bergmeier, In *Comprehensive Heterocyclic Chemistry II*, Vol. 1A, ed. by A. Padwa, Pergamon, Oxford, 1996, pp. 1-60; d) R. S. Atkinson, *Tetrahedron*, 1999, **55**, 1519; e) J. B. Sweeney, *Chem. Soc. Rev.*, 2002, **31**, 247.
- For example, see: D. O'Hagen, *Nat. Prod. Rep.*, 2000, **17**, 435.
 - a) R. J. Sundberg, In *Comprehensive Heterocyclic Chemistry II*, Vol. 2, ed. by C. W. Bird, Pergamon, Oxford, 1996, pp. 119-206; b) A. Nadin, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3493; c) A. Nadin and A. Mitchinson, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2553; d) A. Nadin and A. Mitchinson, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2862; e) G. W. Gribble and T. L. Gilchrist, *Progress in Heterocyclic Chemistry*, Vol. 13, Pergamon, Oxford, 2001.
 - a) W. Lwowski, *Nitrenes*, Wiley, New York, 1970; b) T. Kametani, F. F. Ebetino, T. Yamanaka, and K. Nyu, *Heterocycles*, 1974, **2**, 209; c) O. Meth-Cohn, *Heterocycles*, 1980, **14**, 1497; d) B. C. G. Soderberg, *Curr. Org. Chem.*, 2000, **4**, 727.
 - a) M. M. Campbell and G. Johnson, *Chem. Rev.*, 1976, **78**, 65; b) K. B. Sharpless, A. O. Chong, and K. Oshima, *J. Org. Chem.*, 1976, **41**, 177; c) E. Herranz and K. B. Sharpless, *J. Org. Chem.*, 1978, **43**, 2544; d) D. H. Bremner, In *Synthetic Reagents*, Vol. 6, ed. by J. S. Pizey, Wiley, New York, 1985, pp. 9-59; e) M. C. Agrawal and S. K. Upadhyay, *J. Sci. Ind. Res.*, 1990, **49**, 13; f) G. Li, H.-T. Chang, and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 451; g) A. E. Rubin and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2637; h) W. Pringle and K. B. Sharpless, *Tetrahedron Lett.*, 1999, **40**, 5151; i) V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 3455; j) M. A. Andersson, R. Epple, V. V. Fokin, and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 472.
 - a) T. Ando, S. Minakata, I. Ryu, and M. Komatsu, *Tetrahedron Lett.*, 1998, **39**, 309; b) T. Ando, D. Kano, S. Minakata, I. Ryu, and M. Komatsu, *Tetrahedron*, 1998, **54**, 13485; c) J. U. Jeong, B. Tao, I. Sagasser, H. Henniges, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1998, **120**, 6844; d) D. P. Albane, P.

S. Aujla, P. C. Taylor, S. Challenger, and A. M. Derrick, *J. Org. Chem.*, 1998, **63**, 9569; e) S. L. Ali, M. D. Nikalje, and A. Sudalai, *Org. Lett.*, 1999, **1**, 705; f) L. Simkhovich and Z. Gross, *Tetrahedron Lett.*, 2001, **42**, 8089; g) D. Kano, S. Minakata, and M. Komatsu, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3186; h) S. Minakata, D. Kano, Y. Oderaotoshi, and M. Komatsu, *Org. Lett.*, 2002, **4**, 2097.

7. K. A. Kumar, K. M. L. Rai, and K. B. Umesha, *Tetrahedron*, 2001, **57**, 6993.

8. **General procedure for the synthesis of aziridines using CT and AgNO₃**

Method A: Olefins (1.5 mmol) were added to a suspension of Chloramine-T (141 mg, 0.5 mmol) and AgNO₃ (85 mg, 0.5 mmol) in distilled CH₂Cl₂ (2.0 mL). The mixture was stirred at room temperature for the times indicated in Table 1 under an atmosphere of argon. After the addition of Et₂O (10 mL), the mixture was passed through a short silica gel column using Et₂O (80 mL) as an eluent. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc).

Method B: Olefins (0.5 mmol) were added to a suspension of Chloramine-T (282 mg, 1.0 mmol) and AgNO₃ (170 mg, 1.0 mmol) in distilled benzene (5.0 mL). The mixture was stirred at 60 °C for the times indicated under an atmosphere of argon. After the addition of Et₂O (10 mL), the mixture was passed through a short silica gel column using Et₂O (80 mL) as an eluent. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc).

The characteristics of all the aziridines reported here (aziridines from olefins (**1a-d** and **1g**,¹⁵ **1e** and **1f**,^{6b} and **1h**¹⁶)) were found to be identical to those published previously.

9. ¹H NMR spectral data of aziridines reported by Rai's group are not identical with those published by Evans'¹⁵ and Sharpless'^{6c} groups which were also confirmed by us.^{6a}

10. The stereochemistry of the olefins recovered was investigated. When *trans*- and *cis*-octenes and *trans*-□-methylstyrene were employed in the present reaction, isomerizations of the olefins were not

observed at all in the reaction mixture. In the case of *cis*- \square -methylstyrene, the *trans*-olefin was detected in the reaction mixture (*cis* / *trans* = 91 / 9).

11. D. Carr, T. P. Seden, and R. W. Turner, *Tetrahedron Lett.*, 1969, 477.
12. Methyl cinnamate (100%) and *p*-toluenesulfonamide (17%) derived from CT were detected in an ethereal extract from the reaction mixture. Although iodometry on an aqueous extract showed oxidizing activity (71% based on CT employed in the reaction), the structure(s) of the oxidizing species is uncertain at the present stage.
13. Similar to the procedure of Method B given in ref. 8.

3-(*p*-Toluenesulfonyl)-3-azabicyclo[3.3.0]octane (7a). white solid; mp 75-77 °C; TLC R_f 0.43 (hexane/EtOAc, 7:3); IR (KBr) 1342, 1163 cm^{-1} ; ^1H NMR (CDCl_3 , 270 MHz) \square 1.34-1.77 (m, 6H, (CH_2)₃), 2.43 (s, 3H, Ar- CH_3), 2.51-2.58 (m, 2H, CH), 2.88 (dd, 2H, $J = 3.5, 9.9$ Hz, CHCHH), 3.11 (dd, 2H, $J = 7.8, 9.9$ Hz, CHCHH), 7.33 (d, 2H, $J = 8.1$ Hz, Ar- H), 7.68 (d, 2H, $J = 8.1$ Hz, Ar- H); ^{13}C NMR (CDCl_3 , 68 MHz) \square 21.6, 23.2, 32.8, 42.6, 54.6, 127.9, 129.4, 132.2, 143.3; MS (EI): m/z (%) = 265 (5) $[\text{M}]^+$, 155 (5), 110 (45), 91 (24), 42 (100); Anal. Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_2\text{S}$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.19; H, 7.13; N, 5.13.

***trans*-1-Chloromethyl-2-(*p*-toluenesulfonylaminomethyl)cyclopentane (8a).** yellow oil; TLC R_f 0.35 (hexane/EtOAc, 7:3); IR (neat) 3278, 1329, 1161 cm^{-1} ; ^1H NMR (CDCl_3 , 270 MHz) \square 1.23-1.97 (m, 6H, (CH_2)₃), 2.43-2.48 (m, 5H, CH and Ar- CH_3), 2.83-2.90 (m, 1H, CHHNHTs), 2.95-3.02 (m, 1H, CHHNHTs), 3.48 (d, 2H, $J = 5.9$ Hz, $-\text{CH}_2\text{Cl}$), 4.43 (br t, 1H, $J = 3.1$ Hz, NHTs), 7.32 (d, 2H, $J = 7.3$ Hz, Ar- H), 7.74 (d, 2H, $J = 7.3$ Hz, Ar- H); ^{13}C NMR (CDCl_3 , 68 MHz) \square 21.6, 24.2, 30.7, 42.9, 45.2, 47.2, 48.7, 126.9, 129.6, 136.6, 143.3; MS (CI, isobutane): m/z (%) = 302 (100) $[\text{M}+1]^+$, 155 (30), 110 (26); HRMS (CI, methane): m/z Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_2\text{ClS}$ $[(\text{M} + \text{H})^+]$: 302.0982. Found: 302.0984.

3-(*p*-Toluenesulfonyl)-7,7-bis(ethoxycarbonyl)-3-azabicyclo[3.3.0]octane (7b). white solid; mp

105 °C; TLC R_f 0.20 (hexane/EtOAc, 7:3); IR (KBr) 1726, 1344, 1168 cm^{-1} ; ^1H NMR (CDCl_3 , 270 MHz) \square 1.19-1.27 (m, 6H, CH_2CH_3), 1.95 (dd, 2H, $J = 7.0, 13.5$ Hz, $(\text{EtOCO})_2\text{CCHH}$), 2.44 (s, 3H, Ar- CH_3), 2.52 (dd, 2H, $J = 8.1, 13.5$ Hz, $(\text{EtOCO})_2\text{CCHH}$), 2.67 (dddd, 2H, $J = 1.4, 7.0, 7.0, 13.5$ Hz, CH), 2.85 (dd, 2H, $J = 7.0, 9.6$ Hz, CHHNTs), 3.16 (dd, 2H, $J = 1.4, 9.6$ Hz, CHHNTs), 4.11-4.20 (m, 4H, CH_2CH_3), 7.33 (d, 2H, $J = 8.4$ Hz, Ar- H), 7.76 (d, 2H, $J = 8.4$ Hz, Ar- H); ^{13}C NMR (CDCl_3 , 68 MHz) \square 14.0, 14.0, 39.6, 41.7, 53.5, 61.5, 62.2, 127.8, 129.4, 131.7, 143.5, 170.5, 171.4; MS (CI, isobutane): m/z (%) = 410 (100) $[\text{M}+1]^+$, 254 (21); Anal. Calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_6\text{S}$: C, 58.66; H, 6.65; N, 3.42. Found: C, 58.43; H, 6.61; N, 3.36.

***trans*-1-Chloromethyl-2-(*p*-toluenesulfonylaminomethyl)-4,4-bis(ethoxycarbonyl)cyclopentane**

(8b). yellow oil; TLC R_f 0.21 (hexane/EtOAc, 7:3); IR (neat) 3288, 1726, 1367, 1163 cm^{-1} ; ^1H NMR (CDCl_3 , 270 MHz) \square 1.21-1.27 (m, 6H, CH_2CH_3), 2.06-2.18 (m, 2H, $(\text{EtOCO})_2\text{CCHH}$), 2.38-2.53 (m, 7H, $(\text{EtOCO})_2\text{CCHH}$, CH, and Ar- CH_3), 2.88-2.97 (m, 1H, CHHNHTs), 3.00-3.09 (m, 1H, CHHNHTs), 3.46-3.58 (m, 2H, CH_2Cl), 4.12-4.23 (m, 4H, CH_2CH_3), 4.69 (br t, 1H, $J = 6.2$ Hz, NHTs), 7.31 (d, 2H, $J = 8.0$ Hz, Ar- H), 7.73 (d, 2H, $J = 8.0$ Hz, Ar- H); ^{13}C NMR (CDCl_3 , 68 MHz) \square 14.1, 21.6, 37.6, 38.0, 41.7, 43.9, 45.6, 46.8, 58.4, 61.7, 61.9, 126.9, 129.7, 136.6, 143.4, 171.4, 171.9; MS (CI, isobutane): m/z (%) = 446 (100) $[\text{M}+1]^+$, 290 (10), 155 (4); HRMS (CI, methane): m/z Calcd for $\text{C}_{20}\text{H}_{29}\text{NO}_6\text{ClS}$ $[(\text{M} + \text{H})^+]$: 446.1404. Found: 446.1400.

14. J. Luszyk, B. Maillard, S. Deycard, D. A. Lindsay, and K. U. Ingold, *J. Org. Chem.*, 1987, **52**, 3509.
15. D. A. Evans, M. M. Faul, and M. T. Bilodeau, *J. Am. Chem. Soc.*, 1994, **116**, 2742.
16. J.-P. Mahy, G. Bedi, P. Battioni, and D. Mansuy, *Tetrahedron Lett.*, 1988, **29**, 1927.