HETEROCYCLES, Vol. 70, 2006, pp. 57 - 64. © The Japan Institute of Heterocyclic Chemistry
Received, 21st June, 2006, Accepted, 25th July, 2006, Published online, 25th July, 2006. COM-06-S(W)9

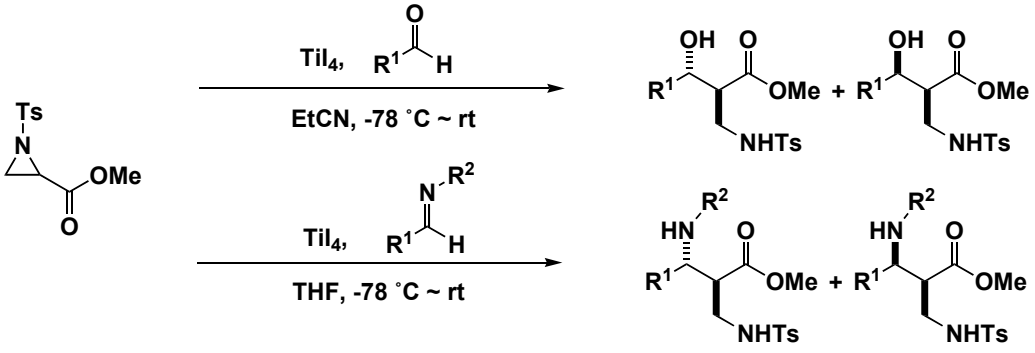
TITANIUM TETRAIODIDE MEDIATED REDUCTIVE OPENING OF AZIRIDINES, LEADING TO THE ALDOL AND MANNICH-TYPE REACTIONS

Makoto Shimizu,* Hiroshi Kurokawa, Shuji Nishiura, and Iwao Hachiya

Department of Chemistry for Materials, Mie University, Tsu, Mie 514-8507, Japan. E-mail: mshimizu@chem.mie-u.ac.jp

Abstract – Reductive ring-opening of *N*-tosylazirindes was readily carried out with titanium tetraiodide to form the titanium enolates, which in turn were subjected to addition reaction with aldehydes or imines to give aldol or Mannich-type products in good yields.

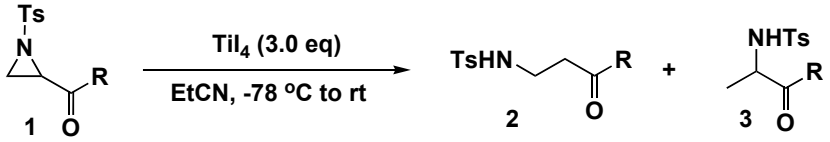
The ability of titanium tetraiodide to reduce various organic molecules has been well documented in our previous investigations.[1] Recent study has revealed that TiI_4 effects the reductive aldol reaction of *N*-tosylimine derived from ethyl glyoxylate with aldehydes to give α-amino-β-hydroxy esters in good yields.[2] In this reaction chemoselective reduction of the imino moiety with titanium tetraiodide was well-controlled to give the titanium enolate of α-amino ester in a highly stereocontrolled manner, which resulted in the stereoselctive formation of *anti*-α-amino-β-hydroxy esters. Aziridine is a three-membered heterocyclic compound containing a nitrogen atom and readily undergoes a ring-opening reaction with nucleophiles,[3] and therefore, it is used extensively as a convenient aminoethyl synthon for the synthesis of a variety of biologically important molecules containing a nitrogen.



Scheme 1.

This paper is dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.

For example, reductive ring-opening reactions of aryl or alkyl aziridinyl ketones has been used recently for the preparation of β-amino-β'-hydroxy ketones.[4] We focused on the reducing ability of titanium tetraiodide coupled with high reactivity of the aziridines and have now found that the aldol and Mannich-type reactions proceed to give adducts in good to excellent yields (Scheme 1). The initial examination was carried out to check the reducing ability of titanium tetraiodide using two types of aziridines (**1a** and **b**).

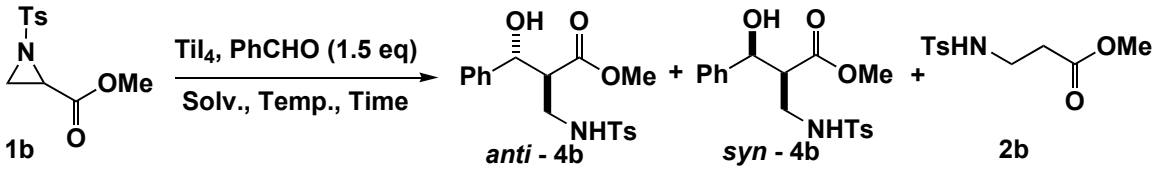


1a: R = Me 14.2 h 44% 22%
1b: R = OMe 15.3 h 73% 0%

Scheme 2.

As can be seen from Scheme 2, although both the methyl ketone (**1a**) and the ester (**1b**) gave reduction products in good yields, the reduction of the ketone (**1a**) was not regioselective, giving two isomeric ketones (**2a** and **3a**) in 44 and 22% yields, respectively. This may be due to a subtle difference of the electron-withdrawing abilities of ketone and esters, and therefore, in terms of regioselectivity ester derivatives were used for further aldol and Mannich-type reactions. The TiI_4-mediated aldol reaction of 2-methoxycarbonylaziridine with benzaldehyde under various conditions was examined, and Table 1 summarizes the results.

Table 1. Reductive Ring-Opening Aldol Reaction of **1b** with Benzaldehyde under Various Conditions[a]

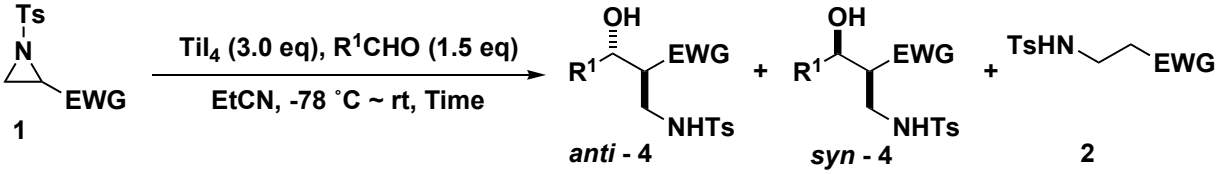


Entry	Solvent	TiI_4 /equiv.	Temp. / °C	Time/h	**4b**/%[b]	*anti* : *syn*[c]	**2b**/%[b]
1	EtCN	1.5	-78 to rt	14.5	61	70 : 30	11
2	EtCN	2.0	-78 to rt	15.0	53	70 : 30	11
3	EtCN	2.5	-78 to rt	14.5	55	73 : 27	17
4	EtCN	3.0	-78 to rt	14.5	69	67 : 33	0
5	EtCN	3.5	-78 to rt	14.0	65	75 : 25	trace
6	MeCN	3.0	-45 to rt	13.5	59	70 : 30	8
7	THF	3.0	-78 to rt	14.0	26	65 : 35	0
8	DME	3.0	-55 to rt	13.5	23	61 : 39	48
9	CH_2Cl_2	3.0	-78 to rt	14.5	37	46 : 54	0

[a]Reaction was carried out according to the typical procedure (Ref. 6). [b]Isolated yield. [c]Based on isolated isomers. Determination of the relative stereochemistry, see Ref. 5.

Among the solvents screened MeCN and EtCN gave the aldol adduct in good yields (Entries 1-6), whereas in THF, DME, and dichloromethane much decreased amounts of the desired product were formed (Entries 7-9). Regarding the amount of TiI_4, the reaction in the presence of 3.0 eq of the iodide gave the best result (Entry 4). Under the optimum conditions, use of a variety of aziridines and aldehydes was examined, and the results are shown in Table 2.[6]

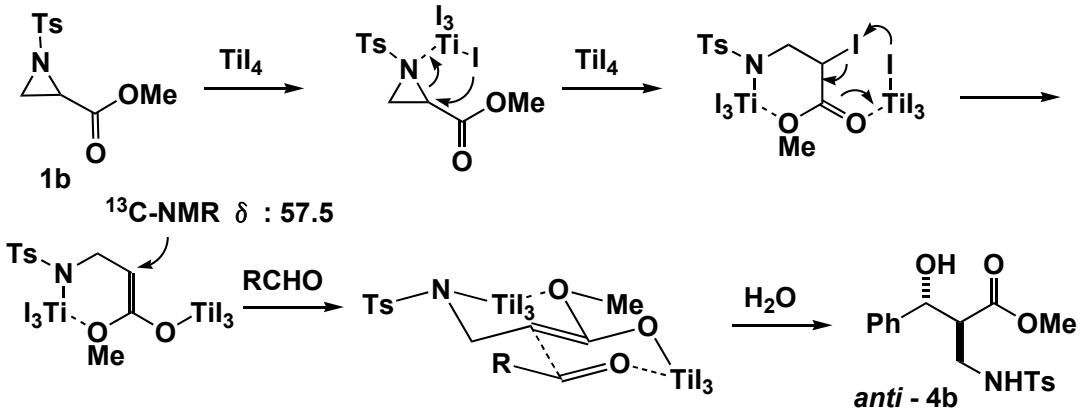
Table 2. Reductive Ring-Opening Aldol Reaction of **1** with Various Aldehydes[a]



Entry	EWG	R^1	Time/h	**4**/%[b]	*anti* : *syn*[c]	**2**/%[b]
1	COMe	Ph	14.5	37	38 : 62	11
2	COOMe	Ph	14.5	69	67 : 33	0
3	COOEt	Ph	16.5	64	74 : 26	0
4	COO^{t}Bu	Ph	13.5	0	-	0
5	CN	Ph	14.0	0	-	69
6	COOMe	4-ClC_6H_4	14.0	71	70 : 30	0
7	COOMe	4-$MeOC_6H_4$	14.0	69	91 : 9	0
8	COOMe	1-Naphthyl	15.0	35	59 : 41	0
9	COOMe	^{n}Pent	17.0	29	72 : 28	24
10	COOMe	^{i}Pr	14.0	trace	-	64
11	COOMe	CCl_3	14.5	0	-	71

[a]Reaction was carried out according to the typical procedure (Ref. 6). [b]Isolated yield. [c]Based on isolated diastereomers.

First, the effects of the electron-withdrawing group at the C2 of the aziridine were examined (Entries 1-5). Use of the aziridine having a ketone gave the adduct in low yield, whereas yields and selectivity were improved using the methyl and the ethyl ester derivatives (Entries 1-3). The reductive ring-opening reaction of aziridine appeared to be sensitive to the steric bulk of the ester group, and the *tert*-butyl ester gave neither the adduct (**4**) nor the ring-opening product (**2**) (Entry 4). In the case of cyano derivative, only the ring-opening product (**2**) was obtained in moderate yield (Entry 5). Using the methyl ester (**1b**), the reaction proceeded to give the adducts (**4**) in good yields with moderate diastereoselectivity when aromatic aldehydes were utilized. In the case with 4-methoxybenzaldehyde, the reaction gave the adduct (**4**) in excellent diastereoselectivity (Entry 7). However, when 1-naphthyl and aliphatic aldehydes were used, the reaction gave the adducts in low yields (Entries 8-11). Regarding the reaction mechanism, Scheme 3 shows a possible pathway.

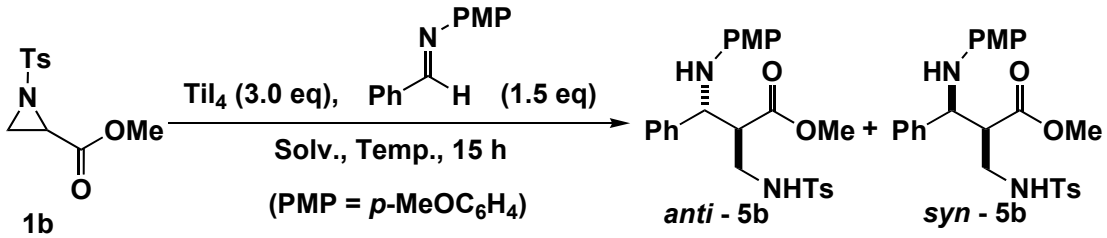


Scheme 3.

The present reaction appears to involve a selective nucleophilic attack of the iodide anion at the C2 of the aziridine, and the subsequent reaction with another iodide anion effects the formation of the enolate species, where the titanium on the nitrogen coordinates with the oxygen of the ester. A six-membered metalla-cycle is in turn formed, and therefore, the (*E*)-enolate may be selectively produced. This (*E*)-enolate then reacts with aldehyde to give the *anti*-aldol adduct selectively via a bicyclic transition state. The formation of the titanium enolate was confirmed by the spectral method.[7]

We next examined the Mannich-type reaction using aldimines, and Table 3 summarizes the examination of reaction conditions.

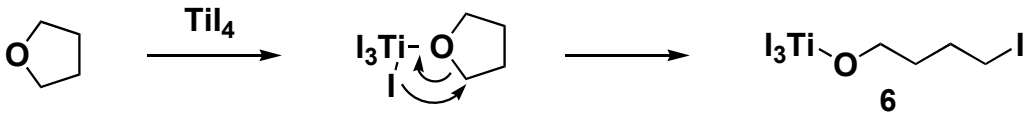
Table 3. Reductive Ring-Opening Mannich-Type Reaction of **1b** with Imine[a]



Entry	Solvent	Temp. / °C	**5b**/%[b]	*syn* : *anti*[c]
1	EtCN	-78 to rt	54	52 : 48
2	MeCN	-45 to rt	58	51 : 49
3	THF	-78 to rt	71	65 : 35
4	DME	-55 to rt	18	56 : 44
5	CH_2Cl_2	-78 to rt	0	-
6	PhMe	-78 to rt	0	-
7	THF[d]	-78 to rt	86	64 : 36

[a]Reaction was carried out similarly to the aldol cases (Ref. 6). [b]Isolated yield. [c]Ratio determined by ^{1}H NMR. [d]TiI_4 was first treated with THF at 0 °C for 0.5 h, and to it was added **1b** and the imine successively at -78 °C, and the mixture was allowed to warm to rt during 15 h (Ref. 9).

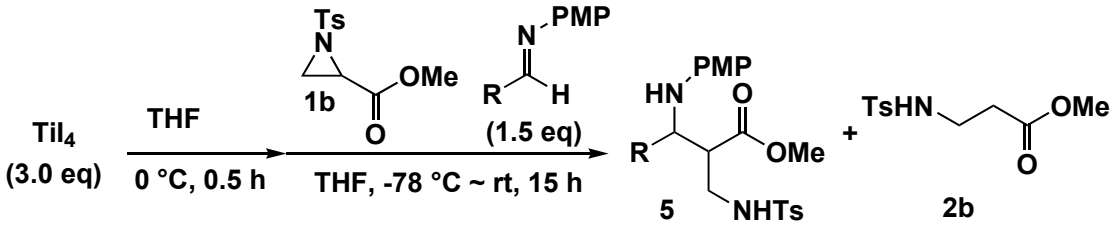
In contrast to the aldol reaction, use of EtCN or MeCN as solvent proved to be insufficient in terms of the product yields (Entries 1 and 2). This may be due to the high coordination ability of the imino moiety to titanium species to form a relatively stable complex as compared with the carbonyl counterpart, resulting in the decrease in the reactivity of the titanium enolate. On the other hand, the use of THF gave better result (Entry 3). Close examination of the reaction mixture in THF revealed the formation of the alkoxytitanium species (**6**) derived from the ring-opening iodination of THF with TiI_4.[8] This alkoxy titanium (**6**) was thought to be responsible for the improvement of the Mannich-type adduct formation presumably due to the modified Lewis acidity of the titanium species. Further optimization of the reaction conditions; *i. e.*, pre-treatment of TiI_4 with THF, improved the product yield (Entry 7).[9]



Scheme 4.

The Mannich-type reaction was carried out under the optimum conditions (Table 3, Entry 7) using various imines, and Table 4 summarizes the results.

Table 4. Reductive Ring-Opening Mannich-Type Reaction of **1b** with Various Imines[a]



Entry	R	**5**/%[b]	*syn* : *anti*[c]	**2b**/%[b]
1	Ph	86	64 : 36	-
2	1-Naphthyl	68	72 : 28	-
3	2-Naphthyl	84	66 : 34	-
4	4-$MeOC_6H_4$	61	66 : 34	-
5	2-$MeOC_6H_4$	62	55 : 45	-
6	4-ClC_6H_4	85	65 : 35	-
7	EtO_2C	25	53 : 47	52
8	[c]Hex	29	68 : 32	28
9	*trans*-PhCH=CH	10	61 : 39	33
10	PhC≡C	5	64 : 36	68

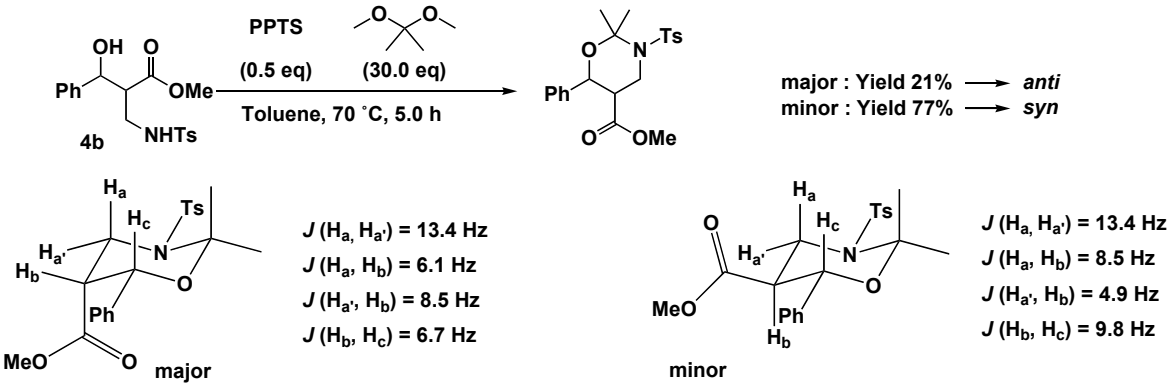
[a]Reaction was carried out according to the typical procedure (Ref. 9). [b]Isolated yield. [c]Ratio determined by ^{1}H NMR. The relative stereochemistry was determined on the 1-naphthyl derivative (Entry 2) in a similar manner to the aldol cases. All other adducts were tentatively assigned on the basis of this result.

Aromatic imines gave the adducts in good to excellent yields (Entries 1-6), whereas use of the aliphatic and ethoxycarbonyl counterparts recorded decreased product yields with concomitant formation of the ring-opening product (**2b**) (Entries 7 and 8), in which moderate diastereoselectivities were observed. The desired adducts were obtained in poor yields with unsaturated analogues (Entries 9 and 10).

In conclusion, we have found that TiI_4 promotes the reductive ring-opening aldol and Mannich-type reactions of 2-alkoxycarbonyl aziridines with aldehydes and aldimines in good to excellent yields, where the reductive formation of the Ti enolate without the use of low valent metal species is noteworthy. Since TiI_4 is commercially available and inexpensive, this procedure offers a convenient method for the reductive formation of the β-amino ester enolate that is a useful synthon for the preparation of β-amino acid derivatives.

REFERENCES AND NOTES

1. (a) M. Shimizu, K. Inayoshi, and T. Sahara, *Org. Biomol. Chem.*, 2005, **3**, 2237. (b) M. Shimizu and T. Toyoda, *Org. Biomol. Chem.*, 2004, **2**, 2891. (c) M. Shimizu, and T. Sahara, *Chem. Lett.*, 2002, **31**, 888. (d) M. Shimizu, F. Kobayashi, and R. Hayakawa, *Tetrahedron*, 2001, **57**, 9591. (e) R. Hayakawa and M. Shimizu, *Org. Lett.*, 2000, **2**, 4079.
2. M. Shimizu, Y. Takeuchi, and T. Sahara, *Chem. Lett.*, 2001, **30**, 1196.
3. (a) C. H. Ding, L. X. Dai, and X. L. Hou, *Synlett*, 2004, 1691. (b) J. F. Hayes, M. Shipman, A. M. Z. Slawin, and H. Twin, *Heterocycles*, 2002, **58**, 243. (c) J. F. Hayes, M. Shipman, and H. Twin, *Chem. Commun.*, 2000, 1791. (d) F. A. Davis, G. V. Reddy, and C. H. Liang, *Tetrahedron Lett.*, 1997, **38**, 5139. (e) J. E. Baldwin, C. N. Farthing, A. T. Russell, C. J. Schofield, and A. C. Spivey, *Tetrahedron Lett.*, 1996, **37**, 3761. (f) K. Sato and A. P. Kozikowski, *Tetrahedron Lett.*, 1989, **30**, 4073. (g) J. E. Baldwin, R. M. Adlington, I. A. O'Neil, C. J. Schofield, A. C. Spivey, and J. B. Sweeney, *Chem. Commun.*, 1989, 1852.
4. T. Mukaiyama, Y. Ogawa, and K. Kuroda, *Chem. Lett.*, 2004, **33**, 1472.
5. The relative stereochemistry of the aldol adducts was determined using the following chemical transformation: Treatment of the major or the minor adduct with 2,2-dimethoxypropane in the presence of PPTs in toluene at 70 ºC afforded the acetal. Examination of the coupling constants of ^{1}H-NMR established the relative stereochemistry.



6. To a solution of TiI_4 (250 mg, 0.45 mmol) in EtCN (0.6 mL) was added a solution of benzaldehyde (23.9 mg, 0.225 mmol) in EtCN (0.7 ml) at –78 °C under an argon atmosphere. To the resulting solution was added a EtCN (0.7 mL) solution of *N*-*p*-tosyl-2-alkoxycarbonyl aziridine (**1b**) (38.3 mg, 0.15 mmol) at –78 °C. The mixture was allowed to warm to ambient temperature with stirring for 14.5 h. The reaction was quenched with sat. $NaHCO_3$ aq, and AcOEt and 10% $NaHSO_3$ aq were added successively. The mixture was filtered through a Celite® pad and extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification on preparative silica gel TLC (*n*-hexane-AcOEt = 3 : 2 as an eluent) gave methyl 3-hydroxy-3-phenyl-2-((*p*-tosylamino)methyl)propionate (**4b**) (37.8 mg, 69%). *Anti* adduct: white solid; mp 122-124 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 2.97-3.13 (m, 4H), 3.63 (s, 3H), 4.94 (t, *J* = 5.9 Hz, 1H), 5.14-5.16 (m, 1H), 7.21-7.34 (m, 7H), 7.63-7.67 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ : 21.5, 41.9, 52.2, 73.0, 126.0, 127.1, 128.3, 128.6, 129.7, 136.6, 140.5, 143.5, 173.1. *Syn* adduct: colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.43 (s, 3H), 2.86 (dd, *J* = 5.9 10.2 Hz, 1H), 2.95 (d, *J* = 3.6 Hz, 1H), 3.15-3.33 (m, 2H), 3.59 (s, 3H), 5.15-5.19 (m, 1H), 5.28-5.33 (m, 1H), 7.21-7.34 (m, 7H), 7.63-7.66 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 21.5, 40.8, 52.2, 73.0, 125.7, 127.1, 127.2, 128.0, 128.6, 129.7, 136.6, 140.5, 143.5, 172.9.
7. The ^{13}C NMR signal (δ 57.5) indicated the formation of a single isomer which was tentatively assigned to be the (*E*)-enolate. We have not succeeded in the preparation of the other isomer, yet. The NMR spectra of the titanium enolates; see, for example, (a) D. B. Kimball, R. Michalczyk, E. Moody, M. Ollivault-Shiflett, K. D. Jesus, and L. A. Pete Silks III, *J. Am. Chem. Soc.*, 2003, **125**, 14666. (b) P. Veya, P. G. Cozzi, and C. Eloriani, *Organometallics*, 1995, **14**, 4101. (c) A. Bernardi, M. Cavicchioli, C. Marchionni, D. Potenza, and C. Scolastico, *J. Org. Chem.*, 1994, **59**, 3690.
8. (a) C. C. B. Breen, M. T. Bautista, C. K. Shauer, and P. S. White, *J. Am. Chem. Soc.*, 2000, **122**, 3952. (b) P. Dufour, M. Dartiguenave, Y. Dartiguenave, M. Simard, and A. L. Beauchamp, *J. Organomet. Chem.*, 1998, **563**, 53.
9. A solution of TiI_4 (250 mg, 0.45 mmol) in THF (0.6 mL) was stirred for 30 min at 0 °C under an

argon atmosphere. Then the mixture was cooled to –78 ºC, and to it were added successively solutions of *N*-benzylidene-4-methoxyphenylamine (47.5 mg, 0.225 mmol) in THF (0.7 mL) and *N*-*p*-tosyl-2-alkoxycarbonyl aziridine (**1b**) (38.3 mg, 0.15 mmol) in THF (0.7 mL). The mixture was allowed to warm to ambient temperature with stirring for 15.0 h. The reaction was quenched with sat. $NaHCO_3$ aq, and AcOEt and 10% $NaHSO_3$ aq were added successively. The mixture was filtered through a Celite® pad, and extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification on preparative silica gel TLC (*n*-hexane-AcOEt = 2:1 as an eluent) gave methyl 3-(4-methoxyphenylamino)-3-phenyl-2-((*p*-tosylamino)methyl)propionate (**5b**) (60.6 mg, 86 %) as a pale brown oil and an inseparable mixture of diastereomers. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 2.40 (s, 3H), 3.08-3.27 (m, 3H), 3.55 (s, 3H), 3.66 (s, 3H), 4.60 (d, *J* = 5.9 Hz, 1H), 5.21-5.37 (m, 1H), 6.46-6.66 (m, 4H), 7.16-7.26 (m, 7H), 7.60-7.65 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 21.5, 41.4, 42.8, 51.7, 51.9, 52.1, 52.2, 55.6, 58.0, 59.2, 114.6, 114.7, 126.5, 126.7, 127.0, 127.1, 127.7, 128.7, 129.7, 136.3, 139.6, 140.0, 140.2, 140.3, 143.5, 152.4, 152.5, 172.6, 173.0.