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Lewis Acid Catalyzed Highly Stereoselective Domino-Ring-Opening Cyclization of Activated Aziridines with Enolates: Synthesis of Functionalized Chiral γ-Lactams

Manas K. Ghorai* and Deo Prakash Tiwari

Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

mkghorai@iitk.ac.in

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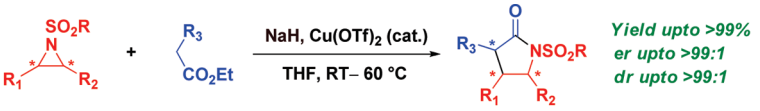
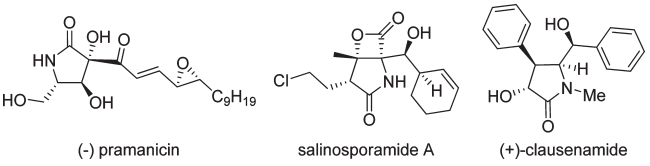


R = 4-MeC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-*t*-BuC$_6$H$_4$; R$_1$ = H, Ph; R$_2$ = H, *i*Pr, Et, *n*-propyl, vinyl, allyl; R$_3$ = CO$_2$Et, COCH$_3$

A highly enantio- and diastereoselective Lewis acid catalyzed S_N2-type ring opening followed by cyclization of aziridines with active methylene carbon nucleophiles to functionalized chiral γ-lactams in a domino fashion has been developed. γ-Lactams have been desulfonated and decarboxylated, providing pyrrolidone-3-carboxylate and *N*-tosylpyrrolidinone derivatives, respectively, in good yields.

Introduction

γ-Lactams are one of the most important and widespread subunits prevalent in many natural products[1] (Figure 1) and serve as pharmacophores in several biologically active compounds.[2] Synthetic utility[3] as well as interesting biological activities[4] of γ-lactam ring structures have led researchers to develop interesting routes toward their synthesis. Those



(-) pramanicin salinosporamide A (+)-clausenamide

FIGURE 1. Some γ-lactam-containing natural products.

strategies include mostly intramolecular cyclization of γ-amino esters,[5] ring expansion,[6] palladium-catalyzed cyclization reactions,[7] cycloaddition,[8] radical cyclization,[9] and cascade or multicomponent reactions,[10] etc. In recent years, attractive routes for the stereoselective synthesis of γ-lactams have been reported.[11,12] There are a few reports for the synthesis

(1) (a) Aoki, S.; Tsukude, T.; Miyazaki, Y.; Takao, K.; Tadano, K. *Heterocycles* **2006**, *69*, 49. (b) Cappi, M. W.; Chen, W. -P.; Flood, R. W.; Liao, Y. -W.; Roberts, S. M.; Skidmore, J.; Smith, J. A.; Williamson, N. M. *Chem. Commun.* **1998**, *10*, 1159. (c) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6244.

(2) (a) Enz, A.; Feuerbach, D.; Frederiksen, M. U.; Gentsch, C.; Hurth, K.; Müller, W.; Nozulak, J.; Roy, B. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1287. (b) Jang, D. S.; Lee, G. Y.; Lee, Y. M.; Kim, Y. S.; Sun, H.; Kim, D.; Kim, J. S. *Chem. Pharm. Bull.* **2009**, *57*, 397.

(3) (a) Padwa, A.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 5139. (b) Loreto, M. A.; Migliorini, A.; Tardella, P. A.; Gambacorta, A. *Eur. J. Org. Chem.* **2007**, 2365. (c) Chouhan, G.; Alper, H. *Org. Lett.* **2008**, *10*, 4987. (d) Pohmakotr, M.; Prateeptongkum, S.; Chooprayoon, S.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2008**, *64*, 2339.

(4) (a) Long, R. D.; Moeller, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 12394. (b) Musonda, C. C.; Gut, J.; Rosenthal, P. J.; Yardley, V.; Carvalho de Souza, R. C.; Chibale, K. *Bioorg. Med. Chem.* **2006**, *14*, 5605.

(5) Wei, Z.-Y.; Knaus, E. E. *Tetrahedron Lett.* **1993**, *34*, 4439.

(6) (a) Park, J.-H.; Ha, J.-R.; Oh, S.-J.; Kim, J.-A.; Shin, D.-S.; Won, T.-J.; Lam, Y.-F.; Ahn, C. *Tetrahedron Lett.* **2005**, *46*, 1755. (b) Dekeukeleire, S.; D'hooghe, M.; De Kimpe, N. *J. Org. Chem.* **2009**, *74*, 1644. (c) Van Brabandt, W.; De Kimpe, N. *J. Org. Chem.* **2005**, *70*, 3369. (d) Van Brabandt, W.; De Kimpe, N. *J. Org. Chem.* **2005**, *70*, 8717.

(7) (a) Xie, X.; Lu, X.; Liu, Y.; Xu, W. *J. Org. Chem.* **2001**, *66*, 6545. (b) Luan, X.; Mariz, R.; Robert, C.; Gatti, M.; Blumentritt, S.; Linden, A.; Dorta, R. *Org. Lett.* **2008**, *10*, 5569. (c) Kammerer, C.; Prestat, G.; Madec, D.; Poli, G. *Chem.—Eur. J.* **2009**, *15*, 4224. (d) Yip, K.-T.; Zhu, N.-Y.; Yang, D. *Org. Lett.* **2009**, *11*, 1911.

(8) (a) Padwa, A.; Nara, S.; Wang, Q. *J. Org. Chem.* **2005**, *70*, 8538. (b) McLaughlin, M.; Takahashi, M.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3912. (c) Sun, P.-P.; Chang, M.-Y.; Chiang, M. Y.; Chang, N.-C. *Org. Lett.* **2003**, *5*, 1761. (d) Romero, A.; Woerpel, K. A. *Org. Lett.* **2006**, *8*, 2127.

(9) (a) Miyabe, H.; Asada, R.; Toyoda, A.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 5863. (b) Ishibashi, H.; Haruki, S.; Uchiyama, M.; Tamura, O.; Matsuo, J. *Tetrahedron Lett.* **2006**, *47*, 6263.

(10) (a) Wei, J.; Shaw, J. T. *Org. Lett.* **2007**, *9*, 4077. (b) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143. (c) Dong, C.; Deng, G.; Wang, J. *J. Org. Chem.* **2006**, *71*, 5560.

(11) Poulsen, T. B.; Dickmeiss, G.; Overgaard, J.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4687.

(12) (a) Lettan, R. B., II; Woodward, C. C.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2294. (b) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131. (c) Scansetti, M.; Hu, X.; McDermott, B. P.; Lam, H. W. *Org. Lett.* **2007**, *9*, 2159. (d) Wiedemann, S. H.; Noda, H.; Harada, S.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 1661. (e) Pohmakotr, M.; Yotapan, N.; Tuchinda, P.; Kuhakarn, C.; Reutrakul, V. *J. Org. Chem.* **2007**, *72*, 5016.

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of γ-lactams from aziridines via ring opening followed by cyclization with enolates.[13,14] Although several reports are known for the opening of aziridines[15] with heteroatom and carbon nucleophiles,[16] enantioselective ring opening of aziridines with enolates is still limited.[17] Recently, we have reported Lewis acid (LA) mediated S_N2-type ring opening of enantiopure 2-aryl-*N*-tosylaziridines and azetidines by a number of nucleophiles to provide nonracemic products.[18] In continuation of our research activities in this area for designing enantioselective ring-opening reactions of chiral aziridines and azetidines toward enantiopure targets, we have developed a simple strategy for the synthesis of chiral functionalized γ-lactams via Lewis acid catalyzed S_N2-type ring opening of enantiopure *N*-sulfonylaziridines by enolates generated from active methylene compounds followed by intramolecular cyclization in a domino fashion. We report herein our results in detail.

Results and Discussion

Our study began with the reaction of (*R*)-2-phenyl-*N*-tosylaziridine **1a** with enolate generated from diethyl malonate (**2a′**, 5.0 equiv) by the treatment of *t*-BuOK (5.0 equiv) in the presence of $Cu(OTf)_2$[19a] (1.0 equiv) in THF at 0 °C−rt for 6.5 h to afford γ-lactam **3a** in 68% yield (Scheme 1) with excellent stereoselectivity (er > 99:1 and dr > 99:1). To improve the yield and reduce the time, the reaction was performed under a variety of conditions (Table 1). Other Lewis acids, e.g., Ti(O-*i*-Pr)$_4$,[19b] $Zn(OTf)_2$,[19c] and $Sc(OTf)_3$, were studied, and in the case of Ti(O-*i*-Pr)$_4$ a reduced er was observed (entry 1).

With a view to optimizing the reaction conditions further, we utilized the common base NaH for this purpose[20] with different LAs (Table 1, entry 4−9). Combination of NaH along with $Cu(OTf)_2$ provided the best result (yield 93%, er > 99:1, and dr > 99:1) in a comparable reaction time (entry 6). To our delight, the reaction time was drastically reduced to 0.5 h when the reaction was performed at 60 °C (entry 7). We further observed that an even lower amount of enolate (3.0 equiv of NaH and 3.0 equiv of diethyl malonate) and a catalytic amount of $Cu(OTf)_2$ (20 mol %) were sufficient for completion of the reaction (entry 8). When the amount of enolate or the LA was reduced further, the reaction was found to be incomplete after being continued for 2 h. It is worth noting that the reaction was completed within 20 min, and **3a** was obtained with same stereoselectivity as observed previously (er > 99:1, dr > 99:1) with relatively lower yield

SCHEME 1. Lewis Acid Catalyzed Domino-Ring-Opening Cyclization of 2-Phenyl-*N*-tosylaziridine

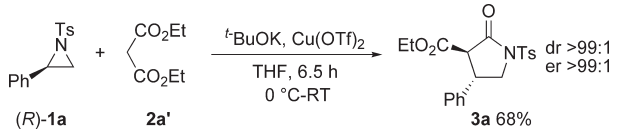
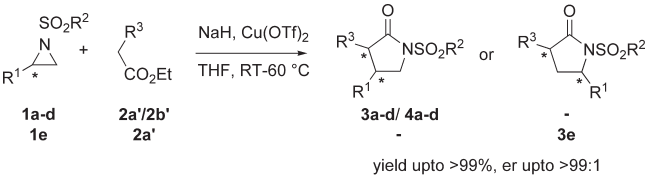


TABLE 1. Optimization Study for Ring-Opening Cyclization of 2-Phenyl-*N*-tosylaziridine with Enolate

entry	conditions	time	yield[d] (%)	er[e,f] (%)
1[a]	^{t}-BuOK, Ti(O-*i*-Pr)$_4$, 0 °C to rt	7.0 h	73	99:1
2[a]	^{t}-BuOK, $Zn(OTf)_2$, 0 °C to rt	11.0 h	68	> 99:1
3[a]	^{t}-BuOK, $Cu(OTf)_2$, 0 °C to rt	6.5 h	68	> 99:1
4[a]	NaH, Ti(O-*i*-Pr)$_4$, 0 °C to rt	7.0 h	76	99:1
5[a]	NaH, $Zn(OTf)_2$, 0 °C to rt	11.0 h	79	> 99:1
6[a]	NaH, $Cu(OTf)_2$, 0 °C to rt	6.0 h	93	> 99:1
7[b]	NaH, $Cu(OTf)_2$, rt to 60 °C	30 min	93	> 99:1
8[c]	NaH, $Cu(OTf)_2$, rt to 60 °C	30 min	93	> 99:1
9[c]	NaH, $Sc(OTf)_3$, rt to 60 °C	< 20 min	84	> 99:1

[a] 5.0 equiv of **2a′**, 5.0 equiv of base, and 1.0 equiv of LA were used. [b] 3.0 equiv of base, 3.0 equiv of **2a′**, and 1.0 equiv of LA were used. [c] Catalytic amount of LA (20 mol %) was used. [d] Yields of isolated products. [e] ee was determined using a Chiralpak AD-H column, hexane−2-propanol 90:10, flow rate 1.0 mL min^{-1}. [f] Product was obtained as a single diastereomer after column chromatographic purification in all cases.

SCHEME 2. Lewis Acid Catalyzed Domino-Ring-Opening Cyclization of *N*-Sulfonylaziridines



a: R^1 = Ph, R^2 = 4-MeC$_6$H$_4$; **b**: R^1 = Ph, R^2 = 4-NO$_2$C$_6$H$_4$; **c, d**: R^1 = Ph, R^2 = 4-*t*-BuC$_6$H$_4$; **e**: R^1 = *i*Pr, R^2 = 4-MeC$_6$H$_4$; **2a'**: R^3 = CO_2Et; **2b'**: R^3 = $COCH_3$

(13) For synthesis of γ-lactam from enantiopure *N*,*O*-ditosylates of amino acids via intermediacy of aziridine, see: (a) Tseng, C. C.; Terashima, S.; Yamada, S. *Chem. Pharm. Bull.* **1977**, *25*, 29. (b) Tseng, C. C.; Terashima, S.; Yamada, S. *Chem. Pharm. Bull.* **1977**, *25*, 166. (c) An inseparable mixture of diastereomers was obtained in the above cases.

(14) For racemic synthesis of γ-lactam from aziridine, see: (a) Stamm, H. *J. Prakt. Chem.* **1999**, *341*, 319 and references cited therein. (b) Stamm, H.; Fiihrling, G. *Tetrahedron Lett.* **1970**, *22*, 1937. (c) Gailius, V.; Stamm, H. *Arch. Pharm.* (*Weinheim*) **1988**, *321*, 337. (d) Stamm, V. H.; Budny, J. *Chem. Ztg.* **1979**, *103*, 156. (e) Stamm, H.; Schneider, L. *Chem. Ber.* **1975**, *108*, 500. (f) Stamm, H. *Arch. Pharm.* (*Weinheim*) **1966**, *299*, 965. (g) Stamm, H. *Chem. Ber.* **1966**, *99*, 2556. For synthesis of ring-fused γ-lactam, see: (h) Smith, P. W.; Whittington, A. R.; Cobley, K. N.; Jaxa-Chamiec, A.; Finch, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 21. (h) Page, M. F. Z.; Jalisatgi, S. S.; Maderna, A.; Hawthorne, M. F. *Synthesis* **2008**, 555.

(15) (a) Nielsen, L. P. C.; Jacobsen, E. N. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; Chapter 7, p 229. For some recent reviews on aziridines, see: (b) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701 and references cited therein. (c) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194. (d) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (e) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. For some recent examples of aziridine ring opening, see: (f) Forbeck, E. M.; Evans, C. D.; Gilleran, J. A.; Li, P.; Joullié, M. M. *J. Am. Chem. Soc.* **2007**, *129*, 14463. (g) Ochoa-Terán, A.; Concellón, J. M.; Rivero, I. A. *ARKIVOC* **2009**, *ii*, 288. (h) Concellón, J. M.; Bernad, P. L.; Suárez, J. R. *J. Org. Chem.* **2005**, *70*, 9411. (i) Couty, F.; Evano, G.; Prim, D. *Tetrahedron Lett.* **2005**, *46*, 2253.

(16) (a) Enders, D.; Janeck, C. F.; Raabe, G. *Eur. J. Org. Chem.* **2000**, 3337. (b) Blyumin, E. V.; Gallon, H. J.; Yudin, A. K. *Org. Lett.* **2007**, *9*, 4677. (c) Minakata, S.; Murakami, Y.; Satake, M.; Hidaka, I.; Okada, Y.; Komatsu, M. *Org. Biomol. Chem.* **2009**, *7*, 641. (e) Ding, C. H.; Dai, L. X.; Hou, X. L. *Tetrahedron* **2005**, *61*, 9586. (f) D'hooghe, M.; Van Nieuwenhove, A.; Van Brabandt, W.; Rottiers, M.; De Kimpe, N. *Tetrahedron* **2008**, *64*, 1064.

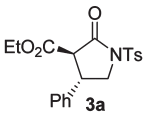
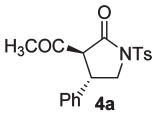
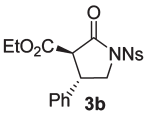
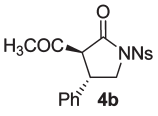
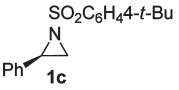
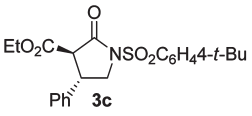
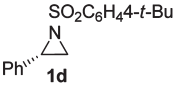
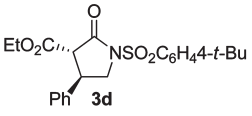
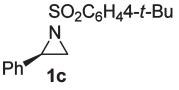
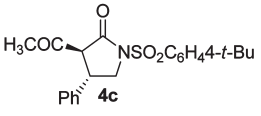
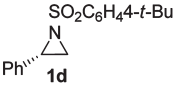
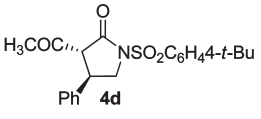
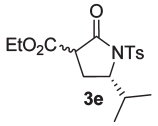
(17) (a) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801. (b) Moss, T. A.; Fenwick, D. R.; Dixon, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 10076. (c) Paixão, M. W.; Nielsen, M.; Jacobsen, C. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2008**, *6*, 3467.

(18) (a) Ghorai, M. K.; Das, K.; Kumar, A.; Ghosh, K. *Tetrahedron Lett.* **2005**, *46*, 4103. (b) Ghorai, M. K.; Das, K.; Kumar, A.; Das, A. *Tetrahedron Lett.* **2006**, *47*, 5393. (c) Ghorai, M. K.; Ghosh, K.; Das, K. *Tetrahedron Lett.* **2006**, *47*, 5399. (d) Ghorai, M. K.; Ghosh, K. *Tetrahedron Lett.* **2007**, *48*, 3191. (e) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, *48*, 4373. (f) Ghorai, M. K.; Das, K.; Shukla, D. *J. Org. Chem.* **2007**, *72*, 5859. (g) Ghorai, M. K.; Kumar, A.; Das, K. *Org. Lett.* **2007**, *9*, 5441. (h) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2009**, *50*, 1105. (i) Ghorai, M. K.; Shukla, D.; Das, K. *J. Org. Chem.* **2009**, *74*, 7013. (j) Ghorai, M. K.; Kumar, A.; Tiwari, D. P. *J. Org. Chem.* **2010**, *75*, 137.

(19) (a) Ma, S.; Han, X.; Krishnan, S.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8037. (b) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527. (c) Shao, H.; Wang, Z.; Lacroix, E.; Wu, S.-H.; Jennings, H. J.; Zou, W. *J. Am. Chem. Soc.* **2002**, *124*, 2130.

(20) Joly, G. J.; Peeters, K.; Mao, H.; Brossette, T.; Hoornaert, G. J.; Compernolle, F. *Tetrahedron Lett.* **2000**, *41*, 2223.

TABLE 2. Lewis Acid Catalyzed Domino-Ring-Opening Cyclization of Monosubstituted Aziridines

entry	aziridine	R^3	product[a,b]	yield[c] (%)	er[d] (%)
1	 **1a**	**2a′**	 **3a**	93	>99:1
2[e]	 **1a**	**2b′**	 **4a**	>99	>99:1
3	 **1b**	**2a′**	 **3b**	48[f]	>99:1
4[e]	 **1b**	**2b′**	 **4b**	64	nd[g]
5	 **1c**	**2a′**	 **3c**	92	>99:1
6	 **1d**	**2a′**	 **3d**	94	>99:1
7[e]	 **1c**	**2b′**	 **4c**	91	>99:1
8[e]	 **1d**	**2b′**	 **4d**	92	>99:1
9	 **1e**	**2a′**	 **3e**	73[h,i]	-

[a]All reactions were performed with 3.0 equiv of nucleophile, 3.0 equiv of NaH, and 20 mol % of $Cu(OTf)_2$. [b]Product was obtained as a single diastereomer in all cases. [c]Yields of isolated products after column chromatographic purification. [d]Determined by chiral HPLC analysis (see the Supporting Information). [e]Product was obtained as a mixture of keto and enol forms. [f]Uncyclized product **5** was also obtained. [g]er of the product could not be determined. [h]Inseparable mixture of diastereomers (dr 4:1) was obtained, and the reaction was completed in 2 h. [i]When $Sc(OTf)_3$ was used as the LA, the reaction was completed in 30 min and higher dr (> 5:1) was observed with relatively lower yield (56%).

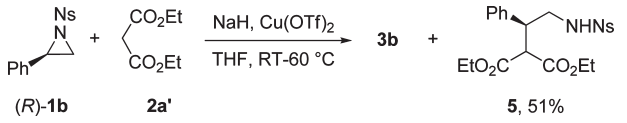
(84%) using $Sc(OTf)_3$ (20 mol %) as the LA (entry 9, Table 1).

The reaction of **1a** proceeds in the absence of a LA but it takes longer time (3.5 h) for completion as compared to 20−30 min using a LA at 60 °C. Without LA, the γ-lactam **3a** was obtained in lower yield (79%) along with some uncharacterized compound (probably other regioisomer), but the stereoselectivity of the crystallized product **3a** remained the same (dr >99:1, er 99:1) as obtained under LA conditions. Furthermore, the reaction without LA was completed in 24 h when performed at room temperature, whereas it took 6 h for completion using $Cu(OTf)_2$ as the LA (entry 6, Table 1).

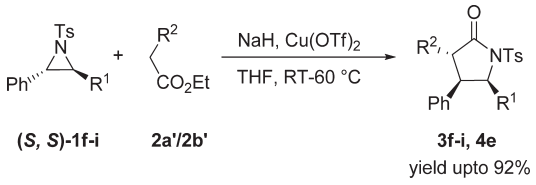
To generalize this strategy, a number of monosubstituted aziridines were studied (Scheme 2), and the results are shown in Table 2. (*R*)-**1a** produced the corresponding γ-lactam in excellent yield and stereoselectivity upon reaction with diethyl malonate (**2a′**) or ethyl acetoacetate (**2b′**) (entries 1 and 2, Table 2).

Substrate (*R*)-**1b** having an easily removable protecting group (*p*-nitrobenzenesulfonyl) on nitrogen produced the corresponding γ-lactam (**3b**) in moderate yield and excellent er (entry 3, Table 2) along with **5** when **2a′** was used as the enolate source. Probably because of of the higher electron-attracting capacity of the nosyl group, lone pair/charge on nitrogen is less available for further cyclization and led to the

SCHEME 3. Lewis Acid Catalyzed Ring-Opening Cyclization of 2-Phenyl-*N*-nosylaziridine



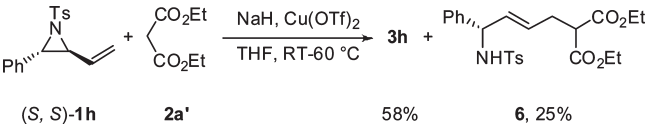
SCHEME 4. Lewis Acid Catalyzed Domino-Ring-Opening Cyclization of *N*-Tosyl-2,3-disubstituted Aziridines



formation of **5** (Scheme 3). However, when **2b′** was used as the enolate source, **4b** was formed in good yield (entry 4, Table 2) along with some uncharacterized compound.

Excellent results were obtained with aziridines bearing a 4-*tert*-butylphenyl sulfonyl group on nitrogen (**1c**,**d**) (entry 5−8, Table 2). Interestingly, the alkylaziridine (*S*)-**1e** produced the corresponding γ-lactam **3e** (entry 9, Table 2) in high yield as an inseparable diastereomeric mixture (4:1).

SCHEME 5. Lewis Acid Catalyzed Domino-Ring-Opening Cyclization of Vinylaziridine



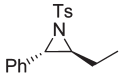
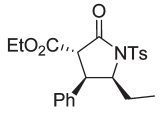
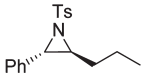
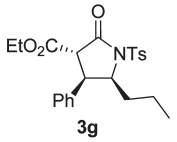
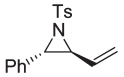
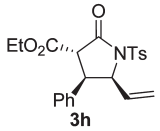
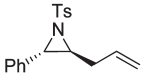
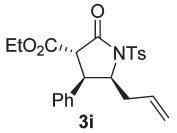
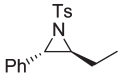
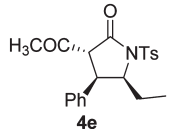
To extend the scope of our methodology, a variety of disubstituted aziridines (*S*,*S*)-**1f-i**[18j] were studied (Scheme 4) and converted into the corresponding γ-lactams (**3f**−**i** and **4e**) with excellent stereoselectivity (Table 3).

It is noteworthy that aziridine (*S, S*)-**1h** under the same reaction condition afforded the corresponding γ-lactam **3h** along with **6** obtained from the attack of the enolate on vinylic carbon[21] (Scheme 5) when **2a′** was used as the enolate source.

Interestingly, when **2b′** was used as the enolate source, the corresponding γ-lactams were obtained as mixture of keto and enol tautomers with keto form being produced predominantly in all the cases (entries 2, 4, 7, and 8, Table 2, and entry 5, Table 3).

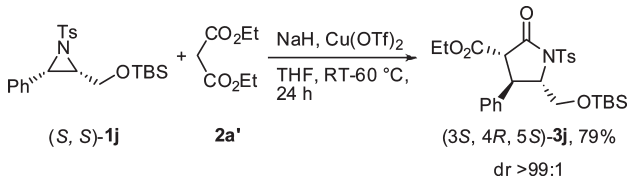
After successful demonstration of the ring-opening cyclization of *trans*-2,3-disubstituted aziridines with active methylene carbon nucleophiles (Scheme 4, Table 3), we next studied the reaction of enantiomerically pure *cis*-2,3-disubstituted aziridine (**1j**).[22] When **1j** was reacted with the Na enolate

TABLE 3. Lewis Acid Catalyzed Domino-Ring-Opening Cyclization of *trans*-*N*-Tosyl-2,3-disubstituted Aziridines

entry	aziridine **1**	R^2	product[a] **3/4**	yield[b,c] (%)
1	 **1f**	CO_2Et (**2a′**)	 **3f**	92
2	 **1g**	CO_2Et (**2a′**)	 **3g**	62
3	 **1h**	CO_2Et (**2a′**)	 **3h**	58[d]
4[e]	 **1i**	CO_2Et (**2a′**)	 **3i**	73
5[f]	 **1f**	$COCH_3$ (**2b′**)	 **4e**	63

[a]All reactions were performed with 3.0 equiv of nucleophile, 3.0 equiv of NaH, and 20 mol % of $Cu(OTf)_2$. [b]Yields of isolated products after column chromatographic purification. [c]Product was obtained as a single diastereomer after column chromatography in all the cases. [d]dr could not be determined (see the Experimental Section). [e]When $Sc(OTf)_3$ was used as the LA, reaction completed in 6 h with relatively lower yield (57%). [f]Product was obtained as mixture of keto and enol forms.

SCHEME 6. Lewis Acid Catalyzed Domino-Ring-Opening Cyclization of *cis*-*N*-Tosyl-2,3-disubstituted Aziridine



of diethyl malonate (**2a**′) under our reaction conditions, the corresponding γ-lactam **3j** was obtained in excellent yield and diastereoselectivity (dr > 99:1) (Scheme 6), although the reaction took a longer time (24 h) for completion.

On the basis of the NOE experiments (see the Supporting Information), the relative stereochemistry as well as the absolute configuration of **3j** could be ascertained (Figure 2), and the NOE was observed between protons H^a-H^{ortho}, H^a-H^c, and H^c-H^{ortho}.

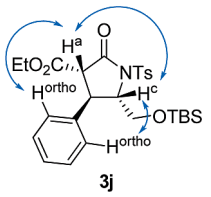


FIGURE 2. NOE experiment for determination of stereochemistry.

All of the new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS data, and the structure of **4a** was confirmed by X-ray crystallographic analysis where **4a** was found to exist in enol form with intramolecular hydrogen bonding (see the Supporting Information).

Based on the experimental facts, we do believe that the ring opening of chiral aziridines **1** with enolates proceed via an S_N2-type pathway (Scheme 7). First, the LA is coordinated to aziridine **1** generating a highly reactive species **A**. Alternatively, **A** might bind to the enolate to generate another reactive species **B**. Next the S_N2-type ring opening by enolate takes place either from **A** or **B** to generate **C**, which finally undergoes lactamization to produce the corresponding γ-lactams (**3** and **4**).

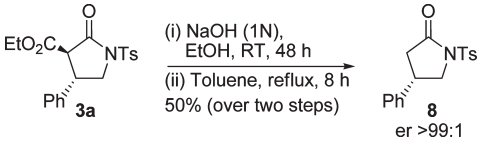
The observed regio- and stereoselectivity for the ring-opening cyclization of 2-phenyl-*N*-tosylaziridines can be explained by considering the electronic effect of the Ph group that plays a vital role in the ring-opening process and overcomes the steric effect. The CN bond becomes more polarized in the presence of a LA as the partial +ve charge at the benzylic position could be stabilized by the Ph group and the nucleophilic opening takes place at this position selectively. Finally, cyclization takes place with the β-ester group to produce the corresponding *trans*-product (**3** and **4**) as a single diastereomer (Scheme 7).

However, in the case of 2-alkyl-*N*-tosylaziridine, both the steric and electronic effects govern the reactivity and thus the ring-opening process. With bulkier alkyl substituents at the 2-position of the aziridine ring, nucleophilic attack takes place at the less substituted position preferably. For example, opening of 2-isopropyl-*N*-tosylaziridine **1e** with enolate from diethyl malonate **2a**′ followed by possible cyclization with any one of the two ester groups led to the formation of the product **3e** as a mixture of diastereomers (entry 9, Table 2).[23]

For wider applicability of the developed methodology, the γ-lactams were desulfonated to the corresponding free γ-lactam derivatives. As representative examples, *N*-tosylpyrrolidinone-3-carboxylate **3a** was detosylated using sodium naphthalide,[24] and *N*-nosylpyrrolidinone-3-carboxylate **3b** was denosylated using K_2CO_3/PhSH[17b] to produce the γ-lactam **7** in free form (Scheme 8).

Furthermore, as a representative example, **3a** was decarboxylated to the corresponding γ-lactam **8** in good yield following a literature report[25] (Scheme 9).

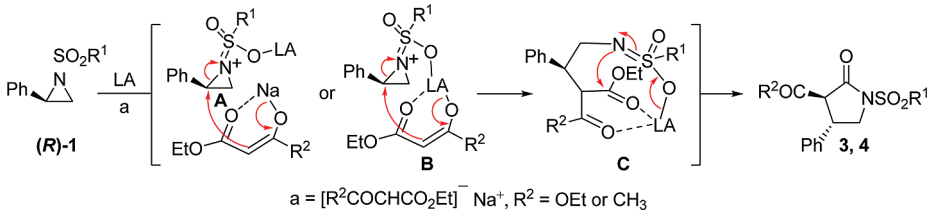
SCHEME 9. Decarboxylation of γ-Lactam



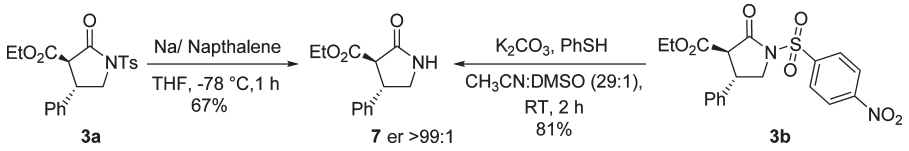
Conclusion

In conclusion, we have developed a simple strategy for the synthesis of highly functionalized chiral γ-lactams via LA-catalyzed S_N2-type ring opening of aziridines with enolates followed by intramolecular cyclization. This method allows the use of a wide range of aziridines and active methylene carbon nucleophiles to construct a variety of γ-lactams in excellent yield and enantioselectivity. These γ-lactams can be

SCHEME 7. Proposed Mechanism of the Reaction



SCHEME 8. Desulfonation of γ-Lactams



desulfonated and decarboxylated to provide the corresponding free pyrrolidinone-3-carboxylate and *N*-tosylpyrrolidinone derivatives, respectively.

Experimental Section

General Experimental Procedure for the Synthesis of Chiral γ-Lactam. To a suspension of sodium hydride (3.0 equiv) in THF (2.0 mL) was added diethyl malonate/ethyl acetoacetate (3.0 equiv) at room temperature under nitrogen atmosphere. Subsequently, solutions of *N*-sulfonylaziridine (100 mg, 1.0 equiv) and $Cu(OTf)_2$ (20 mol %) in THF were added to the reaction mixture. The reaction mixture was then stirred at 60 °C for the appropriate time. After complete consumption of starting compound (monitored by TLC), the reaction was quenched by addition of saturated aqueous NH_4Cl (1.0 mL) solution. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 1.0 mL). The combined extracts were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in petroleum ether as the eluent to give the pure γ-lactam.

(3*R*,4*S*)-Ethyl 2-Oxo-4-phenyl-1-tosylpyrrolidine-3-carboxylate (3a).[13b] The general method described above was followed when (*R*)-**1a** (100 mg, 0.366 mmol) was reacted with enolate from diethyl malonate [diethyl malonate (0.17 mL, 1.098 mmol), NaH (44 mg, 1.098 mmol)] in the presence of $Cu(OTf)_2$ (26 mg, 0.07 mmol) at 60 °C for 30 min to afford **3a** (133 mg, 0.34 mmol) as a white solid in 93% yield: mp 108−110 °C; R_f 0.38 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D = +34.5$ (*c* 0.20, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 2919, 1755, 1730, 1352, 1167, 1138, 758, 697, 673, 582, 545; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.2 Hz, 3H), 2.40 (s, 3H), 3.54 (d, *J* = 9.9 Hz, 1H), 3.72 (dd, *J* = 9.8, 9.1 Hz, 1H), 3.91 (q, *J* = 8.6 Hz, 1H), 4.05−4.14 (m, 2H), 4.29 (dd, *J* = 9.6, 8.3 Hz, 1H), 7.10 (d, *J* = 6.5 Hz, 2H), 7.23−7.30 (m, 5H), 7.87 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 21.8, 41.1, 51.7, 56.5, 62.3, 126.9, 128.1, 128.3, 129.3, 129.9, 134.7, 137.9, 145.8, 167.1, 167.5; HRMS (ESI) for $C_{20}H_{21}NO_5S$ $(M + H)^+$ found 388.1218, calcd 388.1219; er >99:1. The enantiomeric ratio was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol 90:10, flow rate = 1.0 mL/min; t_R (1) = 29.74 min (minor), t_R (2) = 54.15 min (major).

(3*S*,4*S*)-3-Acetyl-4-phenyl-1-tosylpyrrolidin-2-one (4a). The general method described above was followed when (*R*)-**1a** (100 mg, 0.366 mmol) was reacted with enolate from ethyl acetoacetate [ethyl acetoacetate (0.14 mL, 1.098 mmol), NaH (44 mg, 1.098 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (26 mg, 0.073 mmol) at 60 °C for 8 h to afford **4a** (132 mg, 0.369 mmol) as a white crystalline solid in >99% yield: mp 154−156 °C; R_f 0.37 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D = +21.9$ (*c* 0.16, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 3032, 2923, 1752, 1715, 1342, 1167, 1129, 1089, 978, 814, 757, 698, 671, 579, 547; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.40 (s, 3H), 3.67 (d, *J* = 9.0 Hz, 1H), 3.75 (dd, *J* = 9.8, 7.6 Hz, 1H), 3.95−4.02 (m, 1H), 4.22 (dd, *J* = 9.8, 8.6 Hz, 1H), 7.05−7.31 (m, 7H), 7.85 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) (mixture of keto and enol forms) δ 19.2, 21.9, 29.8, 30.5, 38.3, 39.0, 51.8, 54.2, 63.6, 103.4, 126.9, 127.0, 127.6, 127.9, 128.1, 128.3, 128.7, 129.2, 129.9, 130.0, 134.7, 135.2, 139.2, 142.9, 145.3, 145.8, 167.8, 171.5, 171.8, 199.9; HRMS (ESI) for $C_{19}H_{19}NO_4S$ $(M + H)^+$ found 358.1114, calcd 358.1113; er >99:1. The enantiomeric ratio was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol 90:10, flow rate = 1.0 mL/min; t_R (1) = 35.95 min (minor), t_R (2) = 74.38 min (major).

(3*R*,4*S*)-Ethyl 1-(4-Nitrophenylsulfonyl)-2-oxo-4-phenylpyrrolidine-3-carboxylate (3b). The general method described above was followed when (*R*)-**1b** (100 mg, 0.329 mmol) was reacted with enolate from diethyl malonate [diethyl malonate (0.15 mL, 0.99 mmol), NaH (40 mg, 0.99 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (23.8 mg, 0.066 mmol) at 60 °C for 15 min to afford **3b** (66.5 mg, 0.159 mmol) as a white solid in 48% yield along with **5** (78 mg, 0.168 mmol) as a colorless thick liquid in 51% yield. Data for **3b**: mp 129−131 °C; R_f 0.37 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D = -9.2$ (*c* 0.13, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 2942, 1746, 1723, 1369, 1214, 1172, 1119, 1090, 1020, 948, 840, 817, 752, 659, 579, 544; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.2 Hz, 3H), 3.59 (d, *J* = 9.8 Hz, 1H), 3.79 (dd, *J* = 10.0, 8.6 Hz, 1H), 3.93 (q, *J* = 8.6 Hz, 1H), 4.04−4.17 (m, 2H), 4.32 (dd, *J* = 10.0, 8.3 Hz, 1H), 7.10−7.31 (m, 5H), 8.20 (d, *J* = 8.6 Hz, 2H), 8.34 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 41.3, 51.9, 56.3, 62.6, 124.5, 126.9, 128.4, 129.4, 129.9, 137.4, 142.9, 151.2, 166.8, 167.8; HRMS (ESI) for $C_{19}H_{18}N_2O_7S$ $(M - H)^+$ found 417.0758, calcd 417.0757. The enantiomeric ratio of **3b** was determined from the denosylated compound **7** (Scheme 8).

Procedure for Denosylation of Compound 3b. Compound **3b** (31 mg, 0.074 mmol) dissolved in CH_3CN (1.0 mL) was added to the suspension of K_2CO_3 (40.9 mg, 0.296 mmol, 4.0 equiv) in CH_3CN (1.9 mL), and PhSH (23.0 μL, 0.222 mmol, 3.0 equiv) was added at room temperature under nitrogen atmosphere. Next, DMSO (0.1 mL) was added to the reaction mixture, and stirring was continued at room temperature for 2 h. After complete consumption of the starting compound, the reaction was quenched with water. The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 2.0 mL). The combined extracts were dried on anhydrous sodium sulfate and evaporated to dryness. After column chromatographic purification on silica gel (230−400 mesh) using 40% ethyl acetate in petroleum ether as the eluent, pyrrolidinone-3-carboxylate **7** was obtained as white solid. The corresponding racemic product **7** was obtained by detosylation of the racemic **3a** following the reaction conditions shown in Scheme 8. The enantiomeric ratio (er >99:1) was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol 90:10, flow rate = 1.0 mL/min; t_R (1) = 19.48 min (minor), t_R (2) = 24.48 min (major).

Data for (*S*)-diethyl 2-(2-(4-nitrophenylsulfonamido)-1-phenylethyl) malonate (5): R_f 0.23 (20% ethyl acetate in petroleum ether); IR ν_{max} (neat, cm^{-1}) 3360, 2923, 1733, 1597, 1533, 1456, 1403, 1265, 1166, 1093, 1023, 745, 704, 614, 535, 464; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 3.23−3.28 (m, 1H), 3.41−3.46 (m, 1H), 3.62 (d, *J* = 10.0 Hz, 1H), 3.82−3.86 (m, 2H), 4.14−4.20 (m, 2H), 4.53 (m, 1H), 6.99−7.23 (m, 5H), 7.86 (d, *J* = 8.6 Hz, 2H), 8.23 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 14.0, 44.9, 46.5, 55.2, 61.6, 62.1, 124.3, 128.0, 128.2, 129.0, 129.9, 137.5, 147.2, 150.0, 167.2, 168.1; HRMS (ESI) for $C_{21}H_{24}N_2O_8S$ $(M + H)^+$ found 465.1333, calcd 465.1332.

(3*S*,4*S*)-3-Acetyl-1-(4-nitrophenylsulfonyl)-4-phenylpyrrolidine-2-one (4b). The general method described above was followed when (*R*)-**1b** (100 mg, 0.329 mmol) was reacted with enolate from ethyl acetoacetate [ethyl acetoacetate (0.13 mL, 0.99 mmol), NaH (40 mg, 0.99 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (23.8 mg, 0.066 mmol) at 60 °C for 1.5 h to afford **4b** (81.5 mg,

(21) Fujii, N.; Nakai, K.; Tamamura, H.; Otaka, A.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1359.
(22) Righi, P.; Scardovi, N.; Marotta, E.; ten Holte, P.; Zwanenburg, B. *Org. Lett.* **2002**, *4*, 497.
(23) For the mechanism of ring-opening cyclization of alkylaziridine, see the Supporting Information.
(24) Closson, W. D.; Wriede, P.; Bank, S. *J. Am. Chem. Soc.* **1966**, *88*, 1581.
(25) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

0.209 mmol) as a white solid in 64% yield: mp 146−149 °C; R_f 0.36 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = +41.4 (*c* 0.21, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 3449, 2925, 2855, 1749, 1714, 1532, 1356, 1310, 1267, 1212, 1162, 1131, 1086, 964, 854, 759, 737, 699, 628, 566, 527, 460; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.77−3.80 (m, 1H), 3.87 (dd, *J* = 10.0, 7.8 Hz, 1H), 4.07−4.11 (m, 1H), 4.22−4.36 (m, 1H), 7.10−7.32 (m, 5H), 8.25 (d, *J* = 9.0 Hz, 2H), 8.41 (dd, *J* = 8.8, 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of keto and enol forms) δ 19.1, 30.4, 38.5, 38.9, 51.9, 54.2, 63.1, 102.8, 124.3, 124.4, 126.8, 126.9, 127.5, 127.7, 128.1, 129.3, 129.5, 129.7, 138.5, 142.4, 142.9, 143.7, 150.6, 150.61, 168.0, 170.7, 172.9, 199.3; HRMS (ESI) for $C_{18}H_{16}N_2O_6S$ (M + H)$^+$ found 389.0839, calcd 389.0807. The er of the compound **4b** could not be determined due to it is insolubility in the available HPLC condition.

(3*R*, 4*S*)-Ethyl 1-(4-*tert*-Butylphenylsulfonyl)-2-oxo-4-phenylpyrrolidine-3-carboxylate (3c). The general method described above was followed when (*R*)-**1c** (100 mg, 0.317 mmol) was reacted with enolate from diethyl malonate [diethyl malonate (0.14 mL, 0.95 mmol), NaH (38 mg, 0.95 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (23.0 mg, 0.063 mmol) at 60 °C for 1 h to afford **3c** (125 mg, 0.291 mmol) as a white solid in 92% yield: mp 129−131 °C; R_f 0.36 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = +26.4 (*c* 0.42, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 2965, 2925, 1753, 1726, 1461, 1366, 1337, 1278, 1203, 1177, 1126, 1086, 1016, 841, 763, 704, 629, 581, 548; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 9H), 3.56 (d, *J* = 10.0 Hz, 1H), 3.73 (dd, *J* = 9.5, 9.3, 1H), 3.92 (q, *J* = 8.5 Hz, 1H), 4.02−4.17 (m, 2H), 4.30 (dd, *J* = 9.9, 8.1 Hz, 1H), 7.10−7.29 (m, 5H), 7.48−7.51 (m, 2H), 7.89−7.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 31.0, 35.3, 41.0, 51.6, 56.4, 62.2, 126.3, 126.8, 128.0, 129.2, 134.5, 137.8, 150.2, 158.4, 167.0, 167.3; HRMS (ESI) for $C_{23}H_{27}NO_5S$ (M + H)$^+$ found 430.1684, calcd 430.1688; er >99:1. The enantiomeric ratio was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol 90:10, flow rate = 1.0 mL/min; t_R (1) = 20.18 min (minor), t_R (2) = 28.97 min (major).

(3*S*,4*R*)-Ethyl 1-(4-*tert*-Butylphenylsulfonyl)-2-oxo-4-phenylpyrrolidine-3-carboxylate (3d). The general method described above was followed when (*S*)-**1d** (100 mg, 0.317 mmol) was reacted with enolate from diethyl malonate [diethyl malonate (0.14 mL, 0.95 mmol), NaH (38 mg, 0.95 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (23.0 mg, 0.063 mmol) at 60 °C for 1 h to afford **3d** (128 mg, 0.298 mmol) in 94% yield: $[\alpha]^{25}_D$ = −24.8 (*c* 0.32, $CHCl_3$); er >99:1. The enantiomeric ratio was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol 90:10, flow rate = 1.0 mL/min; t_R (1) = 18.78 min (major), t_R (2) = 29.09 min (minor).

(3*S*,4*S*)-3-Acetyl-1-(4-*tert*-butylphenylsulfonyl)-4-phenylpyrrolidin-2-one (4c). The general method described above was followed when (*R*)-**1c** (100 mg, 0.317 mmol) was reacted with enolate from ethyl acetoacetate [ethyl acetoacetate (0.12 mL, 0.95 mmol), NaH (38.0 mg, 0.95 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (23.0 mg, 0.063 mmol) at 60 °C for 9 h to afford **4c** (116 mg, 0.290 mmol) as a white solid in 91% yield: mp 149−152 °C; R_f 0.37 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = −2.3 (*c* 0.33, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 3443, 2966, 1737, 1712, 1594, 1402, 1364, 1210, 1179, 1127, 1086, 958, 837, 766, 703, 627, 585, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.29 (s, 3H) 3.72 (d, *J* = 8.6 Hz, 1H), 3.79 (t, *J* = 8.9 Hz, 1H), 3.99−4.04 (m, 1H), 4.15−4.28 (m, 1H), 7.06−7.10 (m, 2H), 7.22−7.26 (m, 3H), 7.51−7.55 (m, 2H), 7.92 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of keto and enol forms) δ 19.1, 30.4, 31.0, 35.3, 35.4, 38.2, 38.8, 51.6, 54.0, 63.5, 103.4, 126.2, 126.3, 126.9, 127.0, 127.7, 127.8, 128.0, 129.0, 129.1, 134.5, 135.0, 139.1, 142.8, 158.0, 167.7, 171.4, 171.6, 199.9; HRMS (ESI) for $C_{22}H_{25}NO_4S$ (M + H)$^+$ found 400.1581, calcd 400.1583; er >99:1. The enantiomeric ratio was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol 90:10, flow rate = 1.0 mL/min; t_R (1) = 19.18 min (minor), t_R (2) = 59.17 min (major).

(3*R*,4*R*)-3-Acetyl-1-(4-*tert*-butylphenylsulfonyl)-4-phenylpyrrolidin-2-one (4d). The general method described above was followed when (*S*)-**1d** (100 mg, 0.317 mmol) was reacted with enolate from ethyl acetoacetate [ethyl acetoacetate (0.12 mL, 0.95 mmol), NaH (38.0 mg, 0.95 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (23.0 mg, 0.063 mmol) at 60 °C for 9 h to afford **4d** (117.0 mg, 0.293 mmol) in 92% yield; er >99:1. The enantiomeric ratio was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol 90:10, flow rate 1.0 mL/min; t_R (1) = 19.57 min (major), t_R (2) = 56.39 min (minor).

(*S*)-Ethyl 5-Isopropyl-2-oxo-1-tosylpyrrolidine-3-carboxylate (3e).[13a] The general method described above was followed when (*S*)-**1e** (100 mg, 0.418 mmol) was reacted with enolate from diethyl malonate [diethyl malonate (0.19 mL, 1.25 mmol), NaH (50.0 mg, 1.25 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (30.0 mg, 0.084 mmol) at 60 °C for 2 h to afford **3e** (108.0 mg, 0.306 mmol) as a colorless thick liquid as an inseparable diastereomeric mixture (4:1) in 73% yield: R_f 0.37 (20% ethyl acetate in petroleum ether); IR ν_{max} (neat, cm^{-1}) 2964, 1729, 1596, 1393, 1169, 1138, 1089, 815, 665, 559; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.69 (d, *J* = 6.9 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 2.08−2.13 (m, 1H), 2.42 (s, 3H), 2.46−2.55 (m, 2H), 3.47 (dd, *J* = 11.0, 9.3 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.38−4.41 (m, 1H), 7.31(d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 15.1, 19.0, 21.8, 22.8, 31.2, 49.2, 62.2, 63.3, 128.6, 129.6, 135.3, 145.3, 168.2, 169.0; HRMS (ESI) for $C_{17}H_{23}NO_5S$ (M + H)$^+$ found 354.1371, calcd 354.1375.

(3*S*,4*R*,5*S*)-Ethyl 5-Ethyl-2-oxo-4-phenyl-1-tosylpyrrolidine-3-carboxylate (3f). The general method described above was followed when (*S*,*S*)-**1f** (100 mg, 0.33 mmol) was reacted with enolate from diethyl malonate [diethyl malonate (0.15 mL, 0.99 mmol), NaH (40.0 mg, 0.99 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (23.8 mg, 0.066 mmol) at 60 °C for 12 h to afford **3f** (126 mg, 0.30 mmol) as a colorless thick liquid in 92% yield: R_f 0.42 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = −31.8 (*c* 0.38, $CHCl_3$); IR ν_{max} (neat, cm^{-1}) 2978, 2934, 1748, 1729, 1362, 1172, 1059, 815, 702, 670, 542, 503, 466; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.46 (t, *J* = 7.6 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H), 1.39−1.44 (m, 1H), 1.60−1.66 (m, 1H), 2.38 (s, 3H), 3.97 (d, *J* = 13.4 Hz, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 4.18 (dd *J* = 13.4, 7.9 Hz, 1H), 4.60−4.64 (m, 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 7.22 −7.31 (m, 5H), 7.91 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 23.8, 29.7, 46.4, 51.6, 62.1, 63.2, 127.4, 127.9, 128.5, 129.0, 129.6, 134.4, 135.3, 145.4, 167.3, 168.0; HRMS (ESI) for $C_{22}H_{25}NO_5S$ (M + H)$^+$ found 416.1531, calcd 416.1532.

(3*S*,4*R*,5*S*)-Ethyl 2-Oxo-4-phenyl-5-propyl-1-tosylpyrrolidine-3-carboxylate (3g). The general method described above was followed when (*S*,*S*)-**1g** (100 mg, 0.317 mmol) was reacted with enolate from diethyl malonate [diethyl malonate (0.14 mL, 0.95 mmol), NaH (38.0 mg, 0.95 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (23.0 mg, 0.063 mmol) at 60 °C for 26 h to afford **3g** (85.0 mg, 0.198 mmol) as a white solid in 62% yield: R_f 0.41 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ = −25.0 (*c* 0.40, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 2962, 2874, 1748, 1730, 1597, 1454, 1362, 1171, 1120, 1087, 1030, 814, 763,702, 665, 584, 556; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.62 (t, *J* = 7.3 Hz, 3H), 0.69−0.75 (m, 1H), 0.99−1.06 (m, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.37−1.44 (m, 1H), 1.51−1.56 (m, 1H), 2.44 (s, 3H), 4.02 (d, *J* = 13.3 Hz, 1H), 4.12 (q, *J* = 7.4 Hz, 2H), 4.22 (dd, *J* = 13.3, 7.8 Hz, 1H), 4.66−4.70 (m, 1H), 7.18 (d, *J* = 7.4 Hz, 2H), 7.28−7.37 (m, 5H), 7.96 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.0, 18.4, 21.7, 33.1, 46.6, 51.6, 62.1, 62.2, 127.5, 127.9, 128.5, 129.0, 129.6, 134.4, 135.4, 145.4, 167.2,

168.0; HRMS (ESI) for $C_{23}H_{27}NO_5S$ $(M + H)^+$ found 430.1685, calcd 430.1688.

(3*S*,4*R*,5*S*)-Ethyl 2-Oxo-4-phenyl-1-tosyl-5-vinylpyrrolidine-3-carboxylate (3h). The general method described above was followed when (*S*,*S*)-**1h** (100 mg, 0.334 mmol) was reacted with enolate from diethyl malonate [diethyl malonate (0.15 mL, 1.00 mmol), NaH (40.0 mg, 1.00 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (24.1 mg, 0.067 mmol) at 60 °C for 8.5 h to afford **3h** (80 mg, 0.193 mmol) as a colorless thick liquid in 58% yield along with **6** (38 mg, 0.083 mmol) as a colorless thick liquid in 25% yield. Data for **3h**: R_f 0.43 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D = -9.37$ (*c* 0.21, $CHCl_3$); IR ν_{max} (neat, cm^{-1}) 2924, 2853, 1750, 1730, 1597, 1455, 1369, 1310, 1172, 1115, 1089, 1020, 815, 702, 667, 573; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 2.39 (s, 3H), 3.59 (d, J = 12.4 Hz, 1H), 3.77−3.81 (m, 1H), 4.17−4.25 (m, 2H), 4.95−4.99 (m, 2H), 5.11−5.16 (m, 1H), 5.46 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 7.3 Hz, 2H), 7.15−7.29 (m, 5H), 7.56 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 21.8, 46.5, 52.8, 62.2, 64.7, 119.8, 127.3, 128.6, 128.8, 128.9, 129.3, 132.8, 134.9, 135.3, 145.4, 167.0, 167.8; HRMS (ESI) for $C_{22}H_{23}NO_5S$, $(M + H)^+$ found 414.1374, calcd 414.1375. Dr of the compound **3h** could not be determined as it was found to contain some impurity (or diastereomer) which could not be separated after column chromatographic purification (see ^1H NMR spectrum in Supporting Information).

Data for (*S*,*E*)-diethyl 2-(4-(4-methylphenylsulfonamido)-4-phenylbut-2-enyl)malonate (6): R_f 0.29 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D = -14.2$ (*c* 0.12, $CHCl_3$); IR ν_{max} (neat, cm^{-1}) 3282, 2923, 1732, 1598, 1330, 1159, 1093, 1020, 814, 700, 669, 562; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J = 7.1 Hz, 6H), 2.33 (s, 3H), 2.44 (dd, J = 7.3, 6.6 Hz, 2H), 3.19 (t, J = 7.5 Hz, 1H), 4.02−4.11 (m, 4H), 4.67 (d, J = 6.8 Hz, 1H), 4.80 (dd, J = 6.6, 6.1 Hz, 1H), 5.38−5.51 (m, 2H), 6.99−7.17 (m, 7H), 7.54 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 21.6, 31.3, 51.5, 59.4, 61.6, 127.0, 127.3, 127.9, 128.7, 128.7, 129.5, 132.3, 137.7, 139.7, 143.4, 168.8; HRMS (ESI) for $C_{24}H_{29}NO_6S$ $(M + Na)^+$ found 482.1613, calcd 482.1613.

(3*S*,4*R*,5*S*)-Ethyl 5Allyl-2-oxo-4-phenyl-1-tosylpyrrolidine-3-carboxylate (3i). The general method described above was followed when (*S*,*S*)-**1i** (100 mg, 0.319 mmol) was reacted with enolate from diethyl malonate [diethyl malonate (0.15 mL, 0.957 mmol), NaH (38.0 mg, 0.957 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (23.0 mg, 0.064 mmol) at 60 °C for 24 h to afford **3i** (99.0 mg, 0.232 mmol) as a colorless thick liquid in 73% yield: R_f 0.46 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D = -11.1$ (*c* 0.18, $CHCl_3$); IR ν_{max} (neat, cm^{-1}) 2924, 1748, 1730, 1597, 1365, 1172, 1121, 1089, 1019, 702, 663, 555, 542; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, J = 7.2 Hz, 3H), 2.04−2.10 (m, 1H), 2.38 (s, 3H), 2.41−2.49 (m, 1H), 4.03 (d, J = 13.4 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 4.21 (dd, J = 13.4, 8.0 Hz, 1H), 4.60 (d, J = 17.1 Hz, 1H), 4.73−4.77 (m, 1H), 4.82 (d, J = 10.3 Hz, 1H), 5.15−5.25 (m, 1H), 7.11 (d, J = 7.3 Hz, 2H), 7.22−7.31 (m, 5H), 7.93 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.7, 34.7, 46.3, 51.7, 61.7, 62.1, 120.1, 127.6, 127.9, 128.6, 128.9, 129.2, 129.6, 131.5, 134.4, 145.4, 167.3, 168.0; HRMS (ESI) for $C_{23}H_{25}NO_5S$ $(M + H)^+$ found 428.1535, calcd 428.1532.

(3*S*,4*R*,5*S*)-3-Acetyl-5-ethyl-4-phenyl-1-tosylpyrrolidin-2-one (4e). The general method described above was followed when (*S*,*S*)-**1f** (100 mg, 0.33 mmol) was reacted with enolate from ethyl acetoacetate [ethyl acetoacetate (0.13 mL, 0.99 mmol), NaH (40.0 mg, 0.99 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (23.8 mg, 0.066 mmol) at 60 °C for 24 h to afford **4e** (80 mg, 0.207 mmol) as a white solid in 63% yield: mp 135−137 °C; R_f 0.39 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}_D = +22.0$ (*c* 0.15, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 2926, 1733, 1713, 1596, 1362, 1340, 1178, 1156, 1088, 1059, 957, 814, 664, 559; ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (t, J = 7.4 Hz, 3H), 1.48−1.54 (m, 1H), 1.63−1.71 (m, 1H), 2.33 (s, 3H), 2.43 (s, 3H), 4.13 (d, J = 12.9 Hz, 1H), 4.20 (dd, J = 12.6, 8.0 Hz, 1H), 4.58−4.63 (m, 1H), 7.11 (d, J = 7.1 Hz, 2H), 7.26−7.34 (m, 5H), 7.93 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.6, 21.7, 24.2, 30.8, 44.1, 57.6, 62.9, 127.0, 127.8, 128.4, 128.9, 129.6, 134.8, 135.3, 145.4, 168.4, 200.3; HRMS (ESI) for $C_{21}H_{23}NO_4S$ $(M + H)^+$ found 386.1428, calcd 386.1426.

(3*S*,4*R*,5*S*)-Ethyl-5-((*tert*-butyldimethylsilyloxy)methyl)-2-oxo-4-phenyl-1-tosylpyrrolidine-3-carboxylate (3j). The general method described above was followed when (*S*,*S*)-**1j** (100 mg, 0.239 mmol) was reacted with enolate from diethyl malonate [diethyl malonate (0.11 mL, 0.718 mmol), NaH (29.0 mg, 0.718 mmol)] in the presence of 20 mol % of $Cu(OTf)_2$ (17.0 mg, 0.048 mmol) at 60 °C for 24 h to afford **3i** (100.0 mg, 0.188 mmol) as a white solid in 79% yield: mp 75−78 °C; R_f 0.33 (10% ethyl acetate in petroleum ether); $[\alpha]^{25}_D = -36.6$ (*c* 0.80, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 2962, 2928, 1757, 1598, 1471, 1358, 1282, 1260, 1172, 1142, 1121, 1087, 1034, 976, 948, 833, 814, 775, 761, 670, 655, 663, 573, 543, 518; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 6H), 1.15 (t, J = 7.3 Hz, 3H), 2.38 (s, 3H), 3.45 (d, J = 6.4 Hz, 1H), 3.82 (d, J = 10.3 Hz, 1H), 3.93−4.01 (m, 2H), 4.07−4.15 (m, 3H), 6.92−6.94 (m, 2H), 7.16−7.18 (m, 3H), 7.24 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.5, 0.9, 13.9, 18.2, 21.7, 25.8, 42.2, 56.3, 62.2, 62.6, 67.1, 126.9, 127.7, 128.4, 129.2, 129.6, 135.2, 141.1, 145.4, 167.1, 168.4; HRMS (ESI) for $C_{27}H_{37}NO_6SSi$ $(M + H)^+$ found 532.2186, calcd 532.2189.

Procedure for the Synthesis of (3*R*,4*S*)-Ethyl 2-Oxo-4-phenylpyrrolidine-3-carboxylate (7)[24,26]. Na (30 mg, 1.29 mmol) in dry THF (1.0 mL) was treated with naphthalene (207 mg, 1.61 mmol) in dry THF (1.0 mL) and stirred at room temperature for 2 h. Compound **3a** (100 mg, 0.258 mmol), dissolved in dry THF (1.0 mL), was treated with the above-mentioned solution of sodium naphthalide at −78 °C, and the reaction mixture was stirred at this temperature for 1 h. After completion of the reaction (monitored by TLC), the reaction was quenched with an aqueous saturated solution of NH_4Cl. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 2.0 mL), the combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. After column chromatographic purification on silica gel (230−400 mesh) using ethyl acetate in petroleum ether as the eluent, pyrrolidinone 3-carboxylate **7** (40.5 mg, 0.174 mmol) was obtained as a white solid in 67% yield: mp 53−55 °C; R_f 0.32 (40% ethyl acetate in petroleum ether); $[\alpha]^{25}_D = +45.3$ (*c* 0.29, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 3253, 2982, 2926, 1708, 1492, 1451, 1371, 1335, 1263, 1172, 1049, 1028, 760, 701, 549; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 3.44 (dd, J = 9.3, 8.6, 1H), 3.56 (d, J = 9.5 Hz, 1H), 3.82 (dd, J = 9.5, 8.6, 1H), 4.11 (q, J = 8.6 Hz, 1H), 4.21−4.29 (m, 2H), 6.6 (brs, 1H) 7.25−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 44.3, 47.6, 55.2, 61.8, 126.9, 127.6, 128.9, 139.8, 169.2, 172.7; HRMS (ESI) for $C_{13}H_{15}NO_3$ $(M + H)^+$ found 234.1132, calcd 234.1130; er >99:1. The enantiomeric ratio was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−2-propanol 97:3, flow rate = 1.0 mL/min; t_R = 15.89 min.

Procedure for the Synthesis of (*S*)-4-Phenyl-1-tosylpyrrolidin-2-one (8)[25,27]. Compound **3a** (100 mg, 0.258 mmol) dissolved in EtOH (1.0 mL) was treated with 1.0 N NaOH (0.40 mL), and the reaction was stirred for 48 h at room temperature. The reaction mixture was concentrated under reduced pressure, acidified with

(26) The enantiomer of compound **7** is known; see: Wang, J.; Li, W.; Liu, Y.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. *Org. Lett.* **2010**, *12*, 1280.

(27) For racemic compound **8**, see: Andreeva, O. A.; Zobacheva, M. M. *Sint., Str. Khim. Prevrashch. Org. Soedin. Azota: Nitrosoedin., Aminov Aminokislot* **1991**, 3.

5% HCl, and extracted with ethyl acetate (3 × 2.0 mL), the organic layer was dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure. The crude product was refluxed in toluene (1.0 mL) for 8 h. Solvent was removed under reduced pressure, and after column chromatographic purification on silica gel (230−400 mesh) using ethyl acetate in petroleum ether as the eluent, pyrrolidinone **8** (41 mg, 0.13 mmol) was obtained as a white solid in 50% yield (over two steps): mp 110−112 °C; R_f 0.42 (20% ethyl acetate in petroleum ether); $[\alpha]^{25}{}_D$ = +4.88 (*c* 0.20, $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 2922, 1739, 1336, 1163, 1132, 1087, 959, 819,764, 741, 702, 666, 613, 563, 543; ^1H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.62 (dd, *J* = 17.3, 9.3 Hz, 1H), 2.85 (dd, *J* = 17.5, 8.4 Hz, 1H), 3.56−3.65 (m, 1H), 3.79 (dd, *J* = 9.9, 7.9 Hz, 1H), 4.33 (dd, *J* = 10.0, 7.8 Hz, 1H), 7.09−7.36 (m, 7H), 7.94 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 37.1, 39.5, 53.6, 126.5, 127.6, 128.1, 129.0, 129.7, 135.0, 139.8, 145.3, 172.1; HRMS (ESI) for $C_{17}H_{17}NO_3S$ $(M + H)^+$ found 316.1008, calcd 316.1007; er > 99:1. The enantiomeric ratio was determined by chiral HPLC analysis (Chiralcell OD-H column), hexane−2-propanol 90:10, flow rate = 1.0 mL/min; t_R = 20.36 min.

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Supporting Information Available: X-ray crystallographic data of **4a**, copies of ^1H and ^{13}C spectra for all compounds, and HPLC chromatograms for er determination. This material is available free of charge via the Internet at http://pubs.acs.org.