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Noncovalent Organocatalytic Synthesis of Enantioenriched Terminal Aziridines with a Quaternary Stereogenic Center

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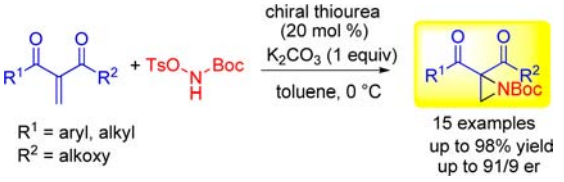
ABSTRACT



A high-yielding and enantioselective access to novel *N*-Boc terminal aziridines, bearing a quaternary stereogenic center, has been developed via an aza-Michael initiated ring-closure (aza-MIRC) reaction of α-acyl acrylates with an *N*-tosyloxy *tert*-butyl carbamate catalyzed by a chiral amino thiourea. The feasibility of the aziridine regioselective ring-opening to valuable α,α-disubstituted α-amino acid esters has been demonstrated.

The development of asymmetric methods for the synthesis of differently substituted aziridines is an area of intensive research in organic chemistry. These small heterocyclic compounds serve as valuable intermediates to obtain a great number of derivatives by regio- and stereoselective ring-opening and ring-expansion reactions.[1] Moreover, they are used as chiral ligands/catalysts in asymmetric synthesis[2] and are present as a key motif in several bioactive compounds and pharmaceuticals.[3] Consequently, over recent decades, many efforts have focused on the development of asymmetric methodologies[4] to prevalently synthesize chiral nonracemic 2,3-disubstituted aziridines. Despite recent developments, up to now only one general method has successfully addressed the highly challenging task of accessing nonracemic terminal aziridines bearing a quaternary stereogenic center.[5] Specifically, Córdova and co-workers developed an organocatalytic asymmetric aziridination of α-alkyl-substituted acryl aldehydes.[6] An aza-Michael approach has been

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(1) (a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (b) Hu, W. E. *Tetrahedron* **2004**, *60*, 2701. (c) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006. (d) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. (e) Florio, S.; Luisi, R. *Chem. Rev.* **2010**, *110*, 5128. (f) Stanković, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; van Speybroeck, V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643.

(2) (a) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2 pp 607. (b) McCoull, M.; Davis, F. A. *Synthesis* **2000**, 1347.

(3) (a) Burrage, T.; Kramer, E.; Brown, F. *Vaccine* **2000**, *18*, 2454. (b) Fürmeier, S.; Metzger, J. O. *Eur. J. Org. Chem.* **2003**, 649. (c) Wakimoto, T.; Asakawa, T.; Akahoshi, S.; Suzuki, T.; Nagai, K.; Kawagishi, H.; Kan, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 1168.

(4) For selected examples, see: (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (b) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chemie, Int. Ed.* **1995**, *34*, 676. (c) Södergren, J. M.; Alonso, D. A.; Andersson, P. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3563. (d) Doyle, M. P.; Chapman, B. J.; Hu, W.; Peterson, C. S.; McKervey, M. A.; Garcia, C. F. *Org. Lett.* **1999**, *1*, 1327. (e) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433. (f) Guthikonda, K.; DuBois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672. (g) Au, S. M.; Huang, J. S.; Yu, W. Y.; Fung, W. H.; Che, C. M. *J. Am. Chem. Soc.* **1999**, *121*, 9120. (h) Katsuki, T. *Synlett* **2003**, 281. (i) Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202. For asymmetric aziridination reaction of 2-substituted terminal alkenes, see: (j) Kawabata, H.; Omura, K.; Uchida, T.; Katsuki, T. *Chem. Asian J.* **2007**, *2*, 248. (k) Minakata, S.; Murakami, Y.; Tsuruoka, R.; Kitanaka, S.; Komatsu, M. *Chem. Commun.* **2008**, 6363. For organocatalytic asymmetric methodologies, see: (l) Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518. (m) Fioravanti, S.; Mascia, M. G.; Pellacani, L.; Tardella, P. *Tetrahedron* **2004**, *60*, 8073. (n) Kano, T.; Hato, Y.; Yamamoto, A.; Maruoka, K. *Tetrahedron* **2008**, *64*, 1197. (o) Akiyama, T.; Suzuki, T.; Mori, K. *Org. Lett.* **2009**, *11*, 2445. (p) Hashimoto, T.; Nakatsu, H.; Yamamoto, K.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 9730. (q) Huang, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 8892. (r) Larson, S. E.; Li, G.; Rowland, G. B.; Junge, D.; Huang, R.; Woodcock, H. L.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 2188. (s) Hayashi, Y.; Urushima, T.; Sakamoto, D.; Torii, K.; Ishikawa, H. *Chem.—Eur. J.* **2011**, *17*, 11715.

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exploited, taking advantage of the iminium/enamine strategy,[7] using *O*-protected diarylprolinols as catalysts and acylated hydroxycarbamates as an ambiphilic nitrogen source (Figure 1).

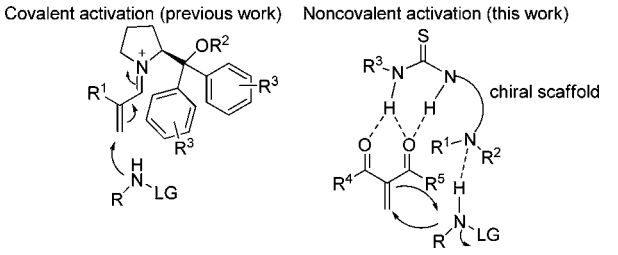


Figure 1. Organocatalytic activation strategies for the asymmetric aza-MIRC reaction to terminal aziridines with a quaternary stereogenic center.

The functionalized terminal aziridines were isolated in moderate to satisfactory yield and up to 99:1 enantiomeric ratio. The increasing demand for efficient methods to produce this class of functionalized aziridines relies on their great synthetic potential for further regioselective ring-opening to α,α-disubstituted α-amino acid derivatives.[8] Indeed, nonproteinogenic α,α-disubstituted amino acids are gaining a lot of importance in various areas such as biochemical and drug discovery research, thanks to their peculiar biological and chemical properties.

With the aim of enlarging access to terminal aziridines functionalized at the quaternary stereogenic center and given our interest in developing asymmetric organocatalytic Michael type reactions,[9] we envisioned a noncovalent approach for the aza-MIRC reaction catalyzed by bifunctional amino thioureas. This class of organocatalysts, as pioneered by the work of Takemoto,[10] were suggested to activate electron-poor alkenes, and nucleophiles by the thiourea and the amine groups, respectively. Then, highly organized transition states are formed leading to high stereocontrol.[11] According to the activation model proposed in amino thioureas catalyzed asymmetric conjugate additions of α,β-unsaturated imides,[12] α-acyl acrylates were supposed to be able to similarly establish multiple hydrogen-bonding interactions with the thiourea group and the nucleophile with the amine moiety of the catalyst. Once formed, the H-bonded prochiral enolate could have undergone preferential ring-closure to an enantiomerically enriched aziridine. Herein, we report our preliminary findings on the asymmetric aziridination of α-acyl acrylates with an *N*-tosyloxy *tert*-butyl carbamate catalyzed by the Takemoto thiourea in the presence of basic additives. Novel terminal aziridines, bearing a quaternary stereocenter, were isolated in high yield and good enantioselectivity. We also showed that these compounds are useful intermediates to access α,α-disubstituted α-amino acid esters via regioselective ring-opening.

The aziridination process on model α-benzoyl ethylacrylate **1a** with different *N*,*O*-protected hydroxylamines **2** was carried out screening a variety of bifunctional promoters (Figure 2), used at stoichiometric loading, in toluene as the solvent (Table 1).

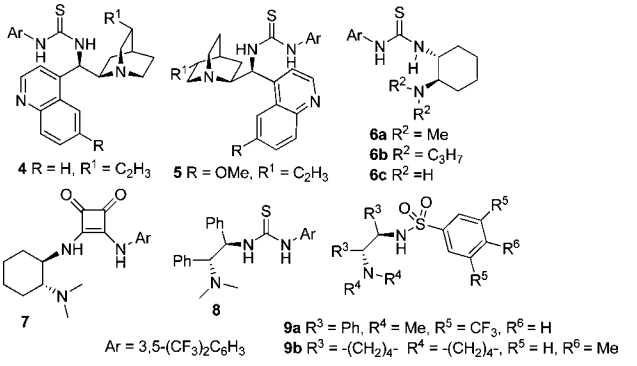


Figure 2. Organocatalysts screened in the aziridination.

Pleasingly, aziridine **3a** was isolated in 90% and 92% yield[13] and moderate enantiomeric ratio when using compound **2a** and cinchona thioureas **4** and **5**, respectively (entries 1 and 2).

Remarkably, highly reactive and sensitive Michael acceptor **1a** did not undergo competitive formation of

(5) For recent reviews on the asymmetric construction of quaternary stereogenic centers, see: (a) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (c) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583. (d) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295. (e) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593.

(6) (a) Deiana, L.; Zhao, G.-L.; Lin, S.; Dziedzic, P.; Zhang, Q.; Leijonmarck, H.; Córdova, A. *Adv. Synth. Catal.* **2010**, *352*, 3201. (b) Deiana, L.; Dziedzic, P.; Zhao, G.-L.; Vesely, J.; Ibrahem, I.; Rios, R.; Sun, J.; Córdova, A. *Chem.—Eur. J.* **2011**, *17*, 7904. (c) Desmarchelier, A.; Pereira de Sant'Ana, D.; Terrasson, V.; Campagne, J. M.; Moreau, X.; Greck, C.; Marcia de Figueiredo, R. *Eur. J. Org. Chem.* **2011**, 4046. (d) For the first organocatalytic report on asymmetric aziridination by *O*-protected diaryl prolinols, see:Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778.

(7) For recent reviews on aminocatalysis provided by *O*-protected diaryl prolinols, see: (a) Xu, L.-W.; Li, L.; Shi, Z.-H. *Adv. Synth. Catal.* **2010**, *352*, 243. (b) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248.

(8) For reviews, see: (a) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406. (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569.

(9) (a) Lattanzi, A. *Org. Lett.* **2005**, *7*, 2579. (b) Russo, A.; Perfetto, A.; Lattanzi, A. *Adv. Synth. Catal.* **2009**, *351*, 3067. (c) De Fusco, C.; Tedesco, C.; Lattanzi, A. *J. Org. Chem.* **2011**, *76*, 676. (d) Lattanzi, A.; De Fusco, C.; Russo, A.; Poater, A.; Cavallo, L. *Chem. Commun.* **2012**, *48*, 1650. (e) Russo, A.; Galdi, G.; Croce, G.; Lattanzi, A. *Chem.—Eur. J.* **2012**, *18*, 6152.

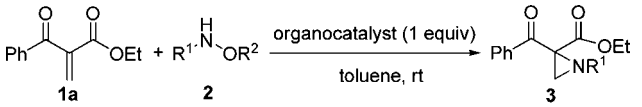
(10) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

(11) For reviews on amino thioureas organocatalyzed reactions, see: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Connon, S. J. *Synlett* **2009**, 354. (d) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632.

(12) (a) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (b) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413.

(13) Carbamate-protected aziridines reported in ref 6 were found to be sensitive to silica gel purification and underwent significant decomposition.

Table 1. Aziridination of Alkene **1a** with **2** Promoted by Bifunctional Organocatalysts[a]



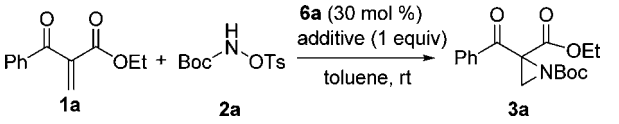
R^1 = Boc, R^2 = Ts **2a**
R^1 = Cbz, R^2 = Ts **2b**
R^1 = Boc, R^2 = $PO(Ph)_2$ **2c**
R^1 = Boc, R^2 = Ac **2d**
R^1 = Ts, R^2 =Ts **2e**

entry	organocatalyst	**2**	time (h)	yield[b] (%)	er[c] (%)
1	**4**	**2a**	5	92	75.5/24.5
2	**5**	**2a**	2	90	−78/22
3	**6a**	**2a**	7	76	86/14
4	**6b**	**2a**	2	97	78/22
5	**6c**	**2a**	5	42	rac
6[d]	**7**	**2a**	5	43	57/43
7	**8**	**2a**	2	50	68/32
8	**9a**	**2a**	21	71	−55/45
9	**9b**	**2a**	20	96	−55/45
10	**quinine**	**2a**	2	90	54.5/45.5
11	**4**	**2b**	3	72	72/28
12	**5**	**2b**	4	77	−72.5/27.5
13	**6a**	**2b**	6	59	86/14
14	**6a**	**2c**	1	40	−62/38
15	**6a**	**2d**	5	<10	
16	**6a**	**2e**	20	61	68/32

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.1 mmol), organocatalyst (0.1 mmol) in 2 mL of toluene. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] 5 mol % of catalyst **7** was used in the presence of K_2CO_3 (0.1 mmol).

polymeration byproduct.[14] A significant improvement of the enantioselectivity up to 86/14 er was observed when employing thiourea **6a** (entry 3). Whereas thiourea **6b** proved to be more active, but less enantioselective, as a catalyst (entry 4), thiourea **6c**, bearing a primary amine group, yielded a racemic product (entry 5). Squaramide **7** was checked under catalytic conditions, employing K_2CO_3 (1 equiv) as a scavenger for the *p*-toluensulfonic acid formed as side product (entry 6). It proved to be moderately active but considerably less efficient than catalyst **6a**. Thiourea **8** afforded compound **3a** in moderate yield and er value (entry 7). Bifunctional catalysts containing a single H-bond donor moiety, such as sulfonamides **9a**,**b** and quinine, proved to be fairly good promoters in term of activity but poorly effective in term of enantioselectivity (entries 8−10). These findings appear to confirm the hypothesis that multiple hydrogen-bonding interactions are necessary to achieve satisfactory stereocontrol as postulated in Figure 1. The nature of the protecting group on nitrogen and the leaving group in reagent **2** had a significant impact on the outcome of the aziridination when using the best promoters **4**, **5**, and **6a** (entries 11−16). *N*-Tosyloxy *tert*-butyl carbamate **2a** was found to be the most effective reagent (entry 3).[15] To develop a catalytic process, a variety of basic additives were checked, employing 30 mol % of catalyst **6a** in the aziridination of **1a** with **2a** (Table 2). Different organic and inorganic bases (entries 1−7) were screened, and the use of 1 equiv of K_2CO_3 enabled the isolation of product **3a** in good yield and er (entry 7).

Table 2. Optimization Study on the Aziridination of Alkene **1a** with **2a** Catalyzed by Thiourea **6a**[a]



entry	additive	time (h)	yield[b] (%)	er[c] (%)
1	Et_3N	1	40	73/27
2	Proton Sponge	0.5	58	79/21
3	AcONa	2	69	89/11
4	$PhCO_2Na$	1.5	48	89/11
5	Na_2CO_3	3	68	82/18
6	$NaHCO_3$	16	70	82.5/17.5
7	K_2CO_3	2	72	89/11
8[d]	K_2CO_3	1.5	67	83/17
9[e]	K_2CO_3	2.5	83	84/16
10[f]	K_2CO_3	2	69	77/23
11[g]	K_2CO_3	2	39	79/21
12[h]	K_2CO_3	24	91	83/17
13[i]	K_2CO_3	3.5	95	89/11

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), and **6a** (0.03 mmol) in 2 mL of toluene. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] K_2CO_3 (3 equiv). [e] Diethyl ether as solvent. [f] $CHCl_3$ as solvent. [g] Chlorobenzene as solvent. [h] 20 mol % of catalyst used at −20 °C. [i] 20 mol % of catalyst used at 0 °C.

An excess of K_2CO_3 (3 equiv) proved to be deleterious (entry 8).[16] A solvent screening confirmed toluene as the optimum medium (entries 9−11). The reaction carried out in toluene at −20 °C with 20 mol % of **6a** furnished the aziridine in high yield although without improvement of the asymmetric induction (entry 12). However, an excellent conversion to the product with 89/11 er value could be achieved working at 0 °C with 20 mol % of catalyst loading (entry 13).

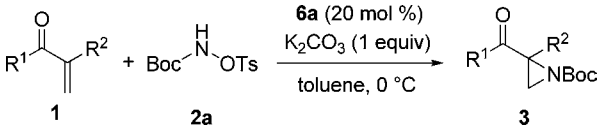
With the optimized conditions in hand, the scope of the aziridination was next investigated (Table 3). The nature of the ester group in alkene **1** slightly influenced the stereochemical outcome, with the corresponding aziridines being obtained in good to high yield (entries 1−4). Different electron-donating or withdrawing substituents on the phenyl ring at *para*, *meta*, and *ortho*-positions or heteroaromatic groups were tolerated leading to the aziridine in generally high yield and up to 91/9 er (entries 5−12). The cyclohexenyl derivative **1o** was regioselectively converted

(14) Acrylates of type **1** suffer easy polymerization on standing and consequently need to be used freshly prepared.

(15) Reactions performed with phase-transfer catalysts proceeded with low enantioselectivity (see the Supporting Information for details).

(16) A control experiment performed in absence of **6a** and using 1 equiv of K_2CO_3 led to the formation of **3a** in 30% yield after 2 h.

Table 3. Asymmetric Aziridination of Alkenes **1** with **2a** Catalyzed by Thiourea **6a**/K_2CO_3 System[a]



entry	R^1	R^2	time (h)	3	yield (%)[b]	er (%)[c]
1	Ph	CO_2Et	3.5	**3a**	95	89/11
2	Ph	CO_2Me	6	**3d**	79	89/11
3	Ph	CO_2tBu	5	**3e**	83	88/12
4	Ph	CO_2Bn	4	**3f**	79	86/14
5	4-MeC_6H_4	CO_2Et	8	**3g**	84	89/11
6	3-MeC_6H_4	CO_2Et	18	**3h**	80	91/9
7	2-MeC_6H_4	CO_2Et	8	**3i**	91	75/25
8	4-$MeOC_6H_4$	CO_2Et	29	**3j**	93	90/10
9	4-ClC_6H_4	CO_2Et	20	**3k**	98	89/11
10	3-BrC_6H_4	CO_2Et	16	**3l**	87	85/15
11	2-naphthyl	CO_2Et	15	**3m**	93	87/13
12	2-furyl	CO_2Et	19	**3n**	86	87/13
13		CO_2Et	24	**3o**	67	87/13
14	NHBn	CO_2Et	18	**3p**	82	86/14
15	Ph	$PO(OEt)_2$	15	**3q**	72	75/25

[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.1 mmol), **6a** (0.02 mmol), K_2CO_3 (0.1 mmol) in 2 mL of toluene. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis.

into the product in good yield and 87/13 er (entry 13). Alkenes bearing amido or phosphonate groups were also suitable substrates for the aziridination reaction (entries 14 and 15).

The absolute configuration of *N*-Boc aziridines was determined to be *R* by single-crystal X-ray analysis on compound **3m**.[17]

Finally, the synthetic potential of aziridines **3** as intermediates to access α,α-disubstituted α-amino acid esters was investigated (Figure 3). Enantiomerically enriched **3a** was deprotected with tetrabutyl ammonium fluoride (TBAF) to aziridine **10a** in excellent yield. Ring-opening of compound **10a** with an ethereal solution of HCl led regioselectively to the α-amino ester **11a** in high yield.

(17) See the Supporting Information for details.

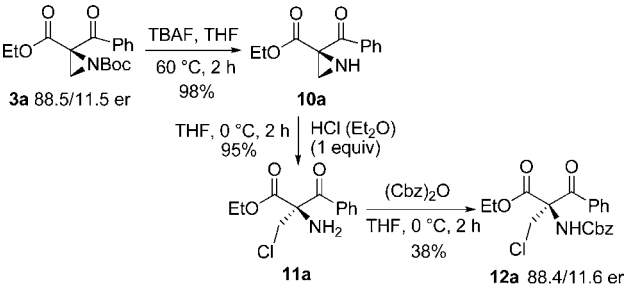


Figure 3. Synthesis of α,α-disubstituted-α-amino acid ester **11a** via deprotection/regioselective ring-opening.

No racemization was observed in deprotection/ring-opening sequence as attested by chiral HPLC analysis on the corresponding *N*-Cbz derivative **12a** obtained after treatment of compound **11a** with dibenzyl dicarbonate (Cbz_2O).

It is important to note that the present methodology enables access to either protected or unprotected terminal aziridines bearing a quaternary stereocenter.

In conclusion, we have disclosed an effective amino thiourea-mediated enantioselective organocatalytic approach to terminal aziridines containing a functionalized quaternary stereocenter. These difficult to access targets also underwent regioselective ring-opening to valuable α, α-disubstituted amino acid esters. Further studies to broaden the substrate scope of the aziridination and the synthetic elaboration of aziridines are ongoing in our laboratory and will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, ^1H and ^{13}C NMR spectra for new compounds and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.