JOC The Journal of Organic Chemistry

Article

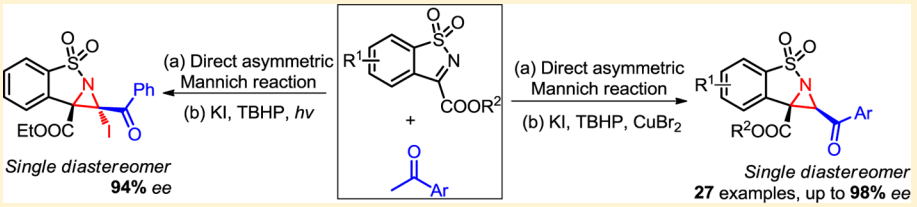
pubs.acs.org/joc

Asymmetric Aziridination of *N*-Sulphonyl Ketimines with Unfunctionalized Ketones: A One-pot Approach to Multisubstituted Fused Aziridines

Sheng Zhang,* Lijun Li, Lilan Xin, Wenmin Liu, and Kun Xu*

College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang 473061, P. R. China

Supporting Information



ABSTRACT: A highly diastereo- and enantioselective aziridination of *N*-sulphonyl ketimines with unfunctionalized ketones was reported. In this efficient method, a sequential direct asymmetric Mannich reaction and oxidative C−H amination were involved, which enabled a straightforward route to multisubstituted-fused aziridines in one pot. More importantly, two different products could be selectively obtained in the reaction by adding or removing a metal additive.

INTRODUCTION

Aziridines as unique nitrogen-containing heterocycles are prevalent in various biologically active natural products (Figure 1).[1] Meanwhile, an estimated 26.7 kcal/mol ringstrain of aziridines facilitates the ring cleavage process initiated by the nucleophilic attack, which makes them versatile building blocks in organic synthesis.[2] Consequently, considerable attention has been devoted to the synthesis of aziridines,[3] and significant advances have been made particularly in the asymmetric aziridination.[4,5] Among the existing strategies to construct enantioenriched aziridines, transfer of a suitable carbon source to aldimines or ketimines has been extensively explored, which was pioneered by Jacobsen,[6a] Jørgensen,[6b] Davis,[6c] and Ruano.[6d] Despite the immense developments in this aspect, the catalytic asymmetric aziridination of ketimines has received far less attention relative to the aziridination of aldimines.[7]

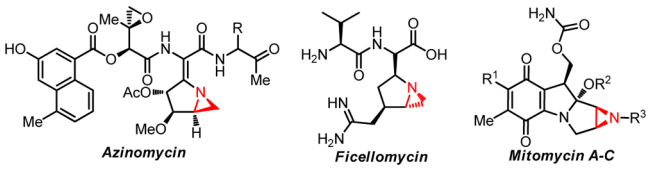


Figure 1. Selected bioactive molecules containing fused aziridines.

The intramolecular C−H amination has been demonstrated as a powerful tool to construct various nitrogen-containing heterocycles.[8] However, successful attempts to construct ring-strained aziridines by intramolecular C−H amination are limited. In 2014, Gaunt and co-workers reported a highly efficient palladium-catalyzed intramolecular C−H amination method to access racemic aziridines (Scheme 1a).[9] Very recently, a remarkable breakthrough was achieved by Ma and co-workers in the asymmetric aziridination of aldimines with β-ketocarboxylic acids (Scheme 1b).[10] Nevertheless, the more accessible unfunctionalized ketones have never been explored as a carbon source to construct aziridines due to the lower reactivity. Herein, we presented an asymmetric aziridination of *N*-sulphonyl ketimines with unfunctionalized ketones, which involved a sequential process of direct Mannich reaction and oxidative C−H amination reaction. This novel method provides a reliable access to synthetically challenging chiral trisubstituted aziridines (Scheme 1c).[5c,7] In this asymmetric aziridination process, two obstacles need to be overcome: (a) the direct asymmetric Mannich reaction of aryl ketones is still an elusive reaction;[11,12] (b) the subsequent C−H amination could induce an obvious racemization.[10]

RESULTS AND DISCUSSION

To conquer the low reactivity of acetophenone, a strategy based on the enamine activation was attempted (Table 1).[13] On the outset, the amino amide **cat A**, which displayed an excellent stereocontrol in a formal Diels−Alder reaction,[14] was tested in the reaction and promising initial result with 85% *ee* was obtained (entry 1). The evaluation on the acid additives showed that the acidity greatly affected the asymmetric induction although there was no linear relationship, and trifluoroacetic acid with a modest acidity led to the highest enantioselectivity and yield (entries 1−4 vs 5). Further optimization on the chiral catalysts failed to give better results (entries 6−7). Increasing the reaction temperature from 25 to

Received: November 26, 2016
Published: February 17, 2017

DOI: 10.1021/acs.joc.6b02827
J. Org. Chem. 2017, 82, 2399−2406

Scheme 1. C−H Amination Strategy in Aziridines Construction

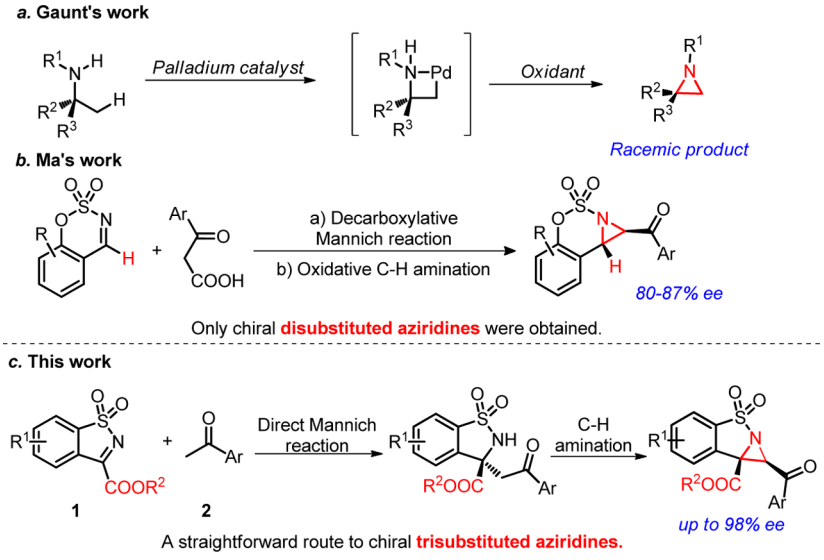
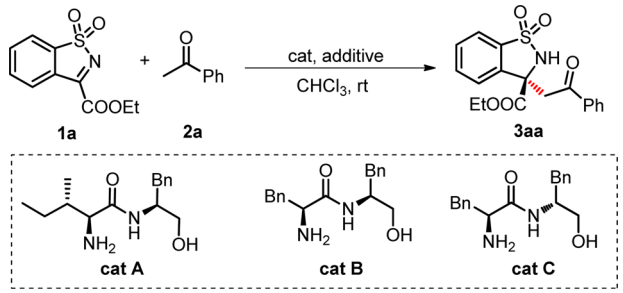


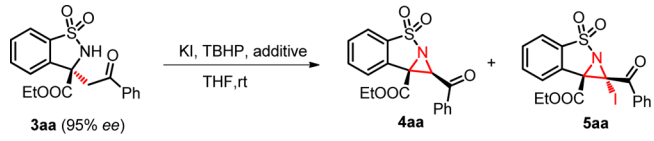
Table 1. Optimization of the Enantioselective Direct Mannich Reaction Conditions[a]



entry	cat	additive	yield (%)[b]	*ee* (%)[c]
1	**cat A**	2,6-$F_2C_6H_3COOH$	54	85
2	**cat A**	PNBA	59	75
3	**cat A**	HOAc	trace	n.d.
4	**cat A**	$MeSO_3H$	trace	n.d.
5[d]	**cat A**	TFA	71 (99)	97 (97)
6	**cat B**	TFA	56	82
7	**cat C**	TFA	47	73
8[e]	**cat A**	TFA	91	95

[a]he reaction of **1a** (0.1 mmol) with **2a** (0.3 mmol) was performed in the presence of catalyst (20 mol%) and additive (20 mol%) in $CHCl_3$ (0.7 mL) at room temperature for 48 h. [b]Yield of isolated product. [c]The *ee* value of the product **3aa** was determined by HPLC on a chiral stationary phase. [d]The data in the parentheses was observed when the reaction was performed at 35 °C. [e]The reaction was performed on 5 mmol with 10 mol% catalyst loading at 35 °C. PNBA = *p*-nitrobenzoic acid.

Table 2. Optimization of the Intramolecular Oxidative C−H Amination of the Mannich Product[a]



entry	additive	product	yield (%)[b]	*ee* (%)[c]
1[d]		**5aa**	23 (24)	86 (77)
2[e]		**5aa**	24	94
3	$Fe(OTf)_3$ (10 mol%)	**4aa**	73	92
4	$Co(acac)_3$ (10 mol%)	**4aa**	78	93
5	$Ni(OTf)_2$ (10 mol%)	**4aa**	83	93
6	$Cu(OTf)_2$ (10 mol%)	**4aa**	89	94
7	$Zn(OTf)_2$ (10 mol%)	**4aa**	95	90
8[f]	$CuBr_2$ (10 mol%)	**4aa**	94 (92)	95 (94)

[a]The reaction of **3aa** (0.1 mmol), KI (0.2 mmol) with TBHP (0.3 mmol, 5.5 mol/L in decane) was performed in the presence of additives (10 mol%) in THF (1.0 mL) at room temperature for 4 h. [b]Yield of isolated product. [c]The *ee* value of the product was determined by HPLC on a chiral stationary phase. [d]The data in the parentheses was observed when the reaction was performed in darkness. [e]The reaction was performed under the irradiation of 20 W white lamp. [f]The data in the parentheses was observed when the reaction was performed on the 0.3 mmol scale in one pot process.

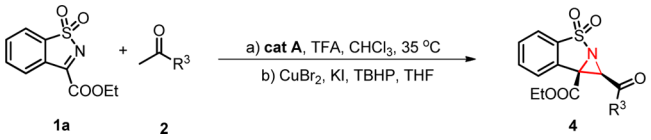
35 °C greatly improved the yield without any observable racemization (entry 5). To further demonstrate the utility of this method, the reaction was scaled up to gram quantities, giving 1.6 g of the product with 95% *ee* (entry 8).

We then turned our attention toward the intramolecular oxidative C−H amination of the Mannich product **3aa**, and a common oxidation system KI/TBHP was employed (Table 2).[15] Interestingly, only an iodinated product **5aa** was observed with the full conversion of reactant (entries 1−2). Moreover, it was found that visible light could significantly suppress the racemization in this step, giving the single diastereomer of the product **5aa** with 94% *ee* and 24% yield (entry 2). Such low yield might be attributed to the instability of the fully substituted aziridine **5aa**.[3a] To obtain the desired aziridine product **4aa**, various metal additives were employed in the reaction (entries 3−8). As expected, the transition metal salts were able to inhibit the iodination process to afford the product **4aa** with more than 90% *ee* values. Among the tested transition metals, $CuBr_2$ could give a high yield with maintained enantiopurity (entry 8). Notably, combining the direct Mannich reaction with the oxidative C−H amination in one-pot could still deliver the product with satisfactory results (92% yield, 94% *ee*, entry 8).

With these optimized conditions identified, the scope of the reaction was explored for both aromatic and aliphatic ketones (Table 3). Electronic variation on *para* substitution showed

DOI: 10.1021/acs.joc.6b02827
J. Org. Chem. 2017, 82, 2399−2406

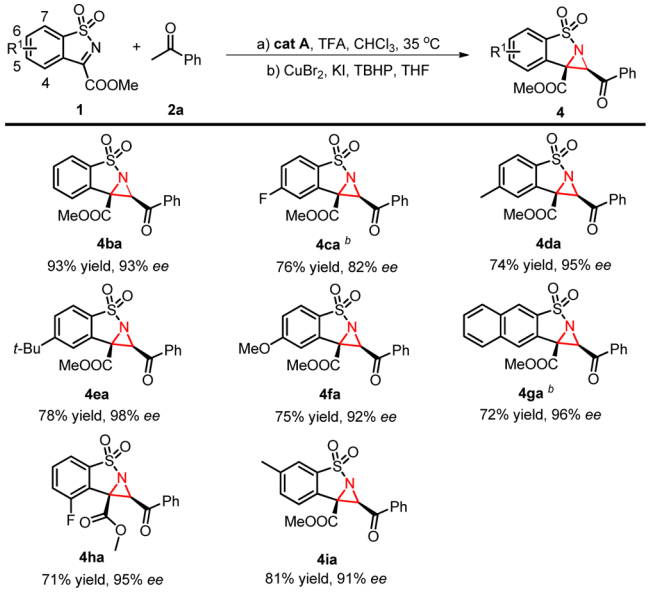
Table 3. Scope of Ketones in the Asymmetric Aziridination[a]



entry	4	R^3	yield (%)[b]	*ee* (%)[c]
1	**4aa**	Ph	92	94
2[d]	**4ab**	*p*-FC_6H_4	80	94
3[d]	**4ac**	*p*-ClC_6H_4	72	94
4[d]	**4ad**	*p*-BrC_6H_4	74	96
5[d]	**4ae**	*p*-$CF_3C_6H_4$	73	98
6	**4af**	*p*-MeC_6H_4	82	94
7	**4ag**	*p*-PhC_6H_4	89	92
8	**4ah**	*p*-^{t}BuC_6H_4	82	89
9	**4ai**	*p*-^{n}BuC_6H_4	85	90
10	**4aj**	*p*-$OMeC_6H_4$	76	87
11[d]	**4ak**	*m*-FC_6H_4	78	97
12	**4al**	*m*-MeC_6H_4	88	94
13	**4am**	*m*-OMe-C_6H_4	92	95
14[d]	**4an**	*o*−F-C_6H_4	62	98
15[d]	**4ao**	3,4-F_2−C_6H_3	69	97
16	**4ap**	3,4-$(OCH_2O)C_6H_3$	89	83
17	**4aq**	2-naphthyl	91	94
18	**4ar**	Cy	68	84
19	**4as**	cyclopropyl	77	96

[a]The reaction of **1a** (0.3 mmol) with **2** (0.9 mmol) was performed in the presence of **cat A** (20 mol%) and TFA (20 mol%) in solvent (2.0 mL) at 35 °C for 48 h. Then, the solvent was evaporated and THF (3 mL), KI (0.6 mmol), TBHP (0.9 mmol, 5.5 mol/L in decane), $CuBr_2$ (10 mol%) were added. The resulting mixture was stirred at room temperature for 4−10 h. [b]Yield of isolated product. [c]The *ee* value of the product was determined by HPLC on a chiral stationary phase. [d]The amount of KI was reduced to 0.3 mmol.

Table 4. Scope of *N*-Sulphonyl Ketimines in the Asymmetric Aziridination[a]



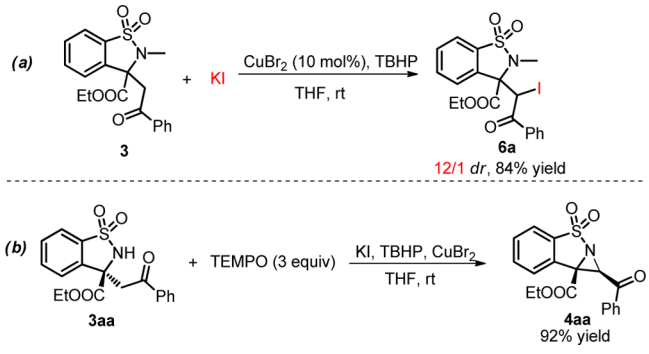
[a]The reaction of **1** (0.3 mmol) with **2a** (0.9 mmol) was performed in the presence of **cat A** (20 mol%) and TFA (20 mol%) in solvent (2.0 mL) at 35 °C for 48 h. Then, the solvent was evaporated and THF (3 mL), KI (0.6 mmol), TBHP (0.9 mmol, 5.5 mol/L in decane), $CuBr_2$ (10 mol%) were added. The resulting mixture was stirred at room temperature for 4−10 h. The product was isolated by column chromatography. The *ee* value of the product was determined by HPLC on a chiral stationary phase. [b]The amount of KI was reduced to 0.3 mmol.

that more electron-deficient aryl ketones (entries 2−5) give better enantioselectivities, while electron-rich derivatives (entries 6−10) provide higher yields. Changing *para* substitutions to *meta* positions had little effect on the reaction performance (entries 11−13). Noteworthily, the *ortho*-substituted ketones proceeded smoothly in this protocol, thereby giving access to the product **4an** with excellent enantioselectivity, albeit with slight erosion of yield (entry 14). To the best of our knowledge, this is the first example using *ortho*-substituted aryl ketones as a substrate in an enamine catalysis reaction.[11] Other substituted aryl ketones were also well tolerated in the transformation providing the desired products with good to excellent enantioselectivities (entries 15−17). With respect to the challenging substrate aliphatic ketones, which contained two reactive sites, the corresponding products **4ar**−**4as** could be obtained with excellent regioselectivities and good to excellent stereoselectivities (entries 18−19).

Subsequently, a range of substituted *N*-sulphonyl ketimines were evaluated to examine the generality of the method (Table 4). As shown in Table 4, replacing the ethyl ester group with a methyl group (**4aa** vs **4ba**) and changing the substitution pattern had little influence on the reaction performance (**4ha**−**4ia**). Specifically, substrate with the substitution close to the reactive site also gave the corresponding product **4ha** in 71% yield and 95% *ee*. On the contrary, the electronic effect seems to be apparent, for the observation of lower *ee* value in the electron-deficient ketimines (**4ca**).

To shed light on the reaction mechanism, control experiments were performed as shown in Scheme 2. First, the *N*-methyl Mannich product **3** was employed in the oxidative C−H amination process to detect the intermediate in the reaction (Scheme 2a). Unsurprisingly, a monoiodinated product **6a** as the major intermediate was observed in a good yield (84%). Additionally, it is noteworthy that a high level of diastereocontrol (12/1 *dr*) was also achieved in this iodination process (Scheme 2a). This extraordinary diastereoselectivity indicated that this reaction was unlikely to proceed through a pathway involving Hoffmann−Löffler−Freytag-type reaction, which is one of the most classical radical reactions.[16] In order to further elucidate the nature of this reaction, a common radical scavenger TEMPO was tested in this reaction and no significant

Scheme 2. Control Experiments

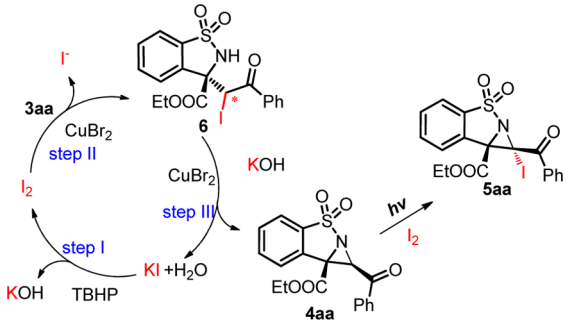


DOI: 10.1021/acs.joc.6b02827
J. Org. Chem. 2017, 82, 2399−2406

change in the yield was detected (Scheme 2b). Consequently, a possible radical pathway was excluded by these observations.

On the basis of these data and the related mechanism study,[8f−h,15,17] a plausible catalytic cycle was proposed (Scheme 3). Initially, the oxidation of potassium iodide generates

Scheme 3. Plausible Catalytic Cycle in the Oxidative C−H Amination Process



molecular iodine and potassium hydroxide. The *in situ* generated iodine is captured by the Mannich product **3aa** via a diastereoselective nucleophilic addition process, giving the chiral iodinated intermediate **6**. Then, an intramolecular cyclization is initiated in the presence of potassium hydroxide, and the fused aziridine **4aa** is formed as the final product. In this catalytic cycle, the copper salt plays a decisive role in controlling a further iodination process according to Wu's study.[18] Meanwhile, a sequential iodination process was proposed in the absence of metal additives to rationalize the formation of product **5aa**.

CONCLUSIONS

In conclusion, a sequential method involving asymmetric Mannich reaction and intramolecular C−H amination was developed for the synthesis of multisubstituted chiral fused aziridines. A broad range of challenging substrates, unfunctionalized ketones, could be readily employed in this reaction to give aziridines with excellent enantioselectivities. Moreover, the metal additives proved to be a crucial role in altering the product distribution. Further investigations into the mechanism and applications of this transformation are underway.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR and ^{13}C NMR were recorded on a 400 MHz Spectrometer (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz) using TMS as the reference. The chemical shifts (δ) and coupling constants (J) were expressed in ppm and Hz, respectively. High-resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and the time-of-flight (TOF) mass analyzer. Commercially available compounds were used without further purification. All solvents were purified according to the standard procedures unless otherwise noted. Substrate **1a−1i**,[11b] **cat A**,[14] **cat B**,[14] and **cat C**[14] were prepared according to the literature procedures.

Gram Scale Mannich Reaction. To a mixture of cyclic ketimine **1a** (1.20 g, 5 mmol) and acetophenone **2a** (1.8 mL, 15 mmol) in 20 mL of chloroform were added **cat A** (132.2 mg, 0.5 mmol) and TFA (37.0 μL, 0.5 mmol). After stirring the mixture at 35 °C for 48 h, the solvent was evaporated in vacuo. Purification of the residue by column chromatography (PE/EA = 6/1−2/1) afforded the desired Mannich product **3aa** in 91% yield (1.63 g) with 95% *ee*. (Chiralcel IC, *i*-PrOH/hexanes =50/50, 1.0 mL/min, λ = 230 nm: t_R = 11.6 min (minor), t_R = 15.2 min (major))

General Working Procedure for the Asymmetric Aziridination. To a mixture of *N*-sulphonyl ketimine **1a** (72 mg, 0.3 mmol) and acetophenone **2a** (105 μL, 0.9 mmol) in 2.0 mL of chloroform were added **cat A** (16.0 mg, 0.06 mmol) and TFA (4.4 μL, 0.06 mmol). After stirring the mixture at 35 °C for 48 h, the solvent was evaporated in vacuo. To the residue were added $CuBr_2$ (6.6 mg, 0.03 mmol), KI (100 mg, 0.6 mmol), and 3 mL THF (for products **4ab−4ae**, **4ak**, **4an−4ao**, **4ca**, **4ga**, the amount of KI was reduced to 50 mg (0.3 mmol)). After stirring the mixture at room temperature for 30 min, the oxidant TBHP (165 μL, 5.5 mol/L in *n*-decane) was added in portions during 4 h. After completion of the reaction (monitored by TLC), the solvent was evaporated in vacuo. Purification of the residue by column chromatography (PE/EA = 15/1−5/1) afforded the desired aziridine product **4aa** in 92% yield with 94% *ee*. (Chiralcel OD-H, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 215 nm: t_R = 10.7 min (minor), t_R = 11.4 min (major))

Experimental Data of the Aziridine Products, Mannich Product. *(R)-Ethyl 3-(2-oxo-2-Phenylethyl)-2,3-dihydrobenzo[d]-isothiazole-3-carboxylate 1,1-Dioxide (**3aa**).* The title product was obtained as a white solid in 91% yield, 1.63 g, mp 57−58 °C. $[\alpha]_D^{20}$ + 121.6 (c = 1.3, $CHCl_3$, 95% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =50/50, 1.0 mL/min, λ = 230 nm: t_R = 11.6 min (minor), t_R = 15.2 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92−7.90 (d, J = 7.6 Hz, 2H), 7.83−7.81 (d, J = 7.6 Hz, 1H), 7.72−7.68 (m, 2H), 7.66−7.58 (m, 2H), 7.48−7.44 (t, J = 7.7 Hz, 2H), 6.10 (s, 1H), 4.37−4.26 (m, 2H), 4.12−4.07 (d, J = 17.7 Hz, 1H), 3.75−3.71 (d, J = 17.7 Hz, 1H), 1.32−1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 169.6, 136.9, 135.5, 134.0, 133.6, 130.8, 128.7, 128.1, 124.2, 121.8, 65.4, 63.5, 49.1, 13.9; IR (film, ν/cm^{-1}): 3280, 2982, 1739, 1683, 1451, 1304, 1228, 1169, 1056, 758, 688.

*(1R,7bS)-Ethyl 1-Benzoyl-1,7b-dihydroazirino[1,2-b]benzo[d]-isothiazole-7b-carboxylate 3,3- Dioxide (**4aa**).* The title product was obtained as a light yellow oil in 92% yield, 98.9 mg. $[\alpha]_D^{20}$ −56.9 (c = 1.6, EtOAc, 94% *ee*); HPLC: Chiralcel OD-H, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 215 nm: t_R = 10.7 min (minor), t_R = 11.4 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23−8.21 (m, 1H), 8.11−8.09 (m, 2H), 7.80−7.75 (m, 2H), 7.70−7.64 (m, 2H), 7.55−7.51 (m, 2H), 4.37−4.24 (m, 2H), 3.94 (s, 1H), 1.27−1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6, 163.4, 134.61, 134.57, 134.0, 133.5, 133.1, 131.2, 129.1, 129.0, 127.2, 123.3, 63.0, 59.8, 53.6, 13.7; IR (film, ν/cm^{-1}): 2985, 1740, 1694, 1470, 1451, 1349, 1177, 758, 691; HRMS (ESI) m/z calcd for $C_{18}H_{15}NO_5S$ $[M+H]^+$ 358.0744, found 358.0750.

*(1R,7bS)-Ethyl 1-(4-Fluorobenzoyl)-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**4ab**).* The title product was obtained as a light yellow oil in 80% yield, 90.3 mg. $[\alpha]_D^{20}$ −44.7 (c = 1.9, EtOAc, 94% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 215 nm: t_R = 19.1 min (minor), t_R = 23.0 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24−8.22 (d, J = 7.8 Hz, 1H), 8.19−8.15 (m, 2H), 7.80−7.75 (m, 2H), 7.70−7.66 (m, 1H), 7.23−7.19 (m, 2H), 4.38−4.25 (m, 2H), 3.89 (s, 1H), 1.28−1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.2, 167.8−165.3 (d, J = 256.6 Hz), 163.3, 134.1, 133.4, 133.0, 132.1−132.0 (d, J = 9.7 Hz), 131.2, 131.08−131.06 (d, J = 2.8 Hz), 127.3, 123.3, 116.4−116.2 (d, J = 22.1 Hz), 63.1, 59.8, 53.5, 13.7; IR (film, ν/cm^{-1}): 2925, 1739, 1696, 1596, 1449, 1350, 1234, 1176, 765; HRMS (ESI) m/z calcd for $C_{18}H_{14}FNO_5S$ $[M+H]^+$ 376.0650, found 376.0655.

*(1R,7bS)-Ethyl 1-(4-Chlorobenzoyl)-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**4ac**).* The title product was obtained as a light yellow oil in 72% yield, 85.0 mg. $[\alpha]_D^{20}$ −32.0 (c = 1.2, EtOAc, 94% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 215 nm: t_R = 19.5 min (minor), t_R = 22.8 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24−8.22 (d, J = 7.8 Hz, 1H), 8.09−8.06 (m, 2H), 7.80−7.75 (m, 2H), 7.71−7.67 (m, 1H), 7.53−7.50 (m, 2H), 4.38−4.25 (m, 2H), 3.88 (s, 1H), 1.28−1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.8, 163.3, 141.4, 134.1, 133.3, 132.94, 132.87, 131.3, 130.5, 129.4, 127.3, 123.3, 63.2, 59.7, 53.5, 13.8; IR (film, ν/cm^{-1}): 2924, 1741, 1691, 1589, 1351, 1177, 1092, 1013, 732; HRMS (ESI) m/z calcd for $C_{18}H_{14}{}^{35}ClNO_5S$

DOI: 10.1021/acs.joc.6b02827
J. Org. Chem. 2017, 82, 2399−2406

$[M+H]^+$ 392.0354, found 392.0360; HRMS (ESI) m/z calcd for $C_{18}H_{14}{}^{37}ClNO_5S$ $[M+H]^+$ 394.0330, found 394.0332.

*(1R,7bS)-Ethyl 1-(4-Bromobenzoyl)-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**4ad**).* The title product was obtained as a light yellow oil in 74% yield, 96.8 mg. $[\alpha]_D{}^{20}$ −38.4 (c = 2.2, EtOAc, 96% *ee*); HPLC: Chiralcel AD-H, *i*-PrOH/hexanes =20/70, 0.8 mL/min, λ = 206 nm: t_R = 18.7 min (major), t_R = 23.0 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23−8.21 (d, J = 7.8 Hz, 1H), 8.00−7.97 (m, 2H), 7.80−7.75 (m, 2H), 7.70−7.67 (m, 3H), 4.37−4.25 (m, 2H), 3.88 (s, 1H), 1.28−1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.9, 163.2, 134.1, 133.3, 132.9, 132.3, 131.3, 130.5, 130.2, 127.2, 123.3, 63.1, 59.6, 53.5, 13.7; IR (film, ν/cm^{-1}): 2983, 1741, 1694, 1586, 1470, 1350, 1206, 1177, 1071, 768; HRMS (ESI) m/z calcd for $C_{18}H_{14}{}^{79}BrNO_5S$ $[M+H]^+$ 435.9849, found 435.9858; HRMS (ESI) m/z calcd for $C_{18}H_{14}{}^{81}BrNO_5S$ $[M+H]^+$ 437.9834, found 437.9837.

*(1R,7bS)-Ethyl 1-(4-(Trifluoromethyl)benzoyl)-1,7b-dihydro-azirino[1,2-b]benzo[d]isothi-azole-7b-carboxylate 3,3-Dioxide (**4ae**).* The title product was obtained as a light yellow oil in 73% yield, 93.6 mg. $[\alpha]_D{}^{20}$ −62.4 (c = 1.9, EtOAc, 98% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 254 nm: t_R = 13.0 min (minor), t_R = 14.8 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25−8.21 (m, 3H), 7.82−7.77 (m, 4H), 7.72−7.68 (m, 1H), 4.37−4.26 (m, 2H), 3.92 (s, 1H), 1.28−1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.3, 163.1, 137.2, 136.0−135.0 (q, J = 32.7 Hz), 134.2, 133.1, 132.9, 131.4, 129.5, 127.3, 126.1−125.9 (q, J = 3.6 Hz), 124.6−121.9 (d, J = 271.4 Hz), 123.4, 63.2, 59.6, 53.6, 13.7; IR (film, ν/cm^{-1}): 2984, 1745, 1699, 1352, 1326, 1134, 1092, 1068, 769; HRMS (ESI) m/z calcd for $C_{19}H_{14}F_3NO_5S$ $[M+H]^+$ 426.0618, found 426.0619.

*(1R,7bS)-Ethyl 1-(4-Methylbenzoyl)-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**4af**).* The title product was obtained as a light yellow oil in 82% yield, 91.8 mg. $[\alpha]_D{}^{20}$ −39.6 (c = 0.9, EtOAc, 94% *ee*); HPLC: Chiralcel OD-H, *i*-PrOH/hexanes =10/90, 0.8 mL/min, λ = 215 nm: t_R = 22.4 min (major), t_R = 24.8 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23−8.22 (d, J = 7.8 Hz, 1H), 8.01−7.99 (d, J = 8.3 Hz, 2H), 7.80−7.74 (m, 2H), 7.70−7.66 (m, 1H), 7.33−7.31 (d, J = 8.0 Hz, 2H), 4.38−4.24 (m, 2H), 3.92 (s, 1H), 2.44 (s, 3H), 1.28−1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.1, 163.5, 145.9, 134.0, 133.5, 133.1, 132.1, 129.7, 129.2, 127.1, 123.3, 63.0, 59.9, 53.6, 21.8, 13.7; IR (film, ν/cm^{-1}): 2926, 1740, 1689, 1606, 1450, 1350, 1206, 1177, 1020, 912, 733; HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_5S$ $[M+H]^+$ 372.0900, found 372.0909.

*(1R,7bS)-Ethyl 1-([1,1′-Biphenyl]-4-carbonyl)-1,7b-dihydro-azirino[1,2-b]benzo[d]isothiazole-7b-carboxylate 3,3-Dioxide (**4ag**).* The title product was obtained as a white foam in 89% yield, 115.7 mg. $[\alpha]_D{}^{20}$ −32.1 (c = 2.3, EtOAc, 92% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 215 nm: t_R = 35.8 min (minor), t_R = 46.2 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24−8.22 (d, J = 7.8 Hz, 1H), 8.19−8.16 (m, 2H), 7.80−7.72 (m, 4H), 7.69−7.61 (m, 3H), 7.49−7.45 (m, 2H), 7.43−7.40 (m, 1H), 4.39−4.25 (m, 2H), 3.95 (s, 1H), 1.29−1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.2, 163.4, 147.2, 139.3, 134.0, 133.5, 133.2, 133.1, 131.2, 129.7, 129.0, 128.5, 127.5, 127.2, 123.3, 63.0, 59.9, 53.6 13.7; IR (film, ν/cm^{-1}): 2985, 1740, 1687, 1603, 1469, 1452, 1350, 1235, 1204, 1177, 766, 735, 698; HRMS (ESI) m/z calcd for $C_{24}H_{19}NO_5S$ $[M+H]^+$ 434.1057, found 434.1065.

*(1R,7bS)-Ethyl 1-(4-(tert-Butyl)benzoyl)-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole-7b-carboxylate 3,3-Dioxide (**4ah**).* The title product was obtained as a light yellow oil in 82% yield, 101.8 mg. $[\alpha]_D{}^{20}$ −33.0 (c = 1.7, EtOAc, 89% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 240 nm: t_R = 23.3 min (minor), t_R = 30.4 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25−8.23 (d, J = 7.8 Hz, 1H), 8.06−8.04 (m, 2H), 7.80−7.76 (m, 2H), 7.70−7.68 (m, 1H), 7.55−7.53 (m, 2H), 4.36−4.27 (m, 2H), 3.93 (s, 1H), 1.35 (s, 9H), 1.28−1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.2, 163.5, 158.7, 134.0, 133.5, 133.1, 132.0, 131.1, 129.1, 127.2, 126.0, 123.3, 63.0, 60.0, 53.6, 35.3, 30.9, 13.7; IR (film, ν/cm^{-1}): 2965, 1740, 1689, 1604, 1470, 1351, 1241, 1204, 1177, 770; HRMS (ESI) m/z calcd for $C_{22}H_{23}NO_5S$ $[M+H]^+$ 414.1370, found 414.1376.

*(1R,7bS)-Ethyl 1-(4-Butylbenzoyl)-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**4ai**).* The title product was obtained as a Light yellow oil in 85% yield, 105.6 mg. $[\alpha]_D{}^{20}$ −41.8 (c = 1.2, EtOAc, 90% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 215 nm: t_R = 23.0 min (minor), t_R = 38.7 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24−8.22 (d, J = 7.8 Hz, 1H), 8.03−8.01 (m, 2H), 7.80−7.74 (m, 2H), 7.69−7.65 (m, 1H), 7.34−7.31 (d, J = 8.3 Hz, 2H), 4.38−4.24 (m, 2H), 3.92 (s, 1H), 2.71−2.67 (t, J = 7.6 Hz, 2H), 1.66−1.58 (m, 2H), 1.38−1.33 (m, 2H), 1.28−1.24 (t, J = 7.1 Hz, 3H), 0.95−0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.1, 163.4, 150.7, 134.0, 133.6, 133.1, 132.3, 131.1, 129.3, 129.0, 127.2, 123.3, 63.0, 60.0, 53.6, 35.8, 33.0, 22.2, 13.8, 13.7; IR (film, ν/cm^{-1}): 2932, 2859, 1738, 1688, 1605, 1351, 1234, 1205, 1176, 913.4, 768; HRMS (ESI) m/z calcd for $C_{22}H_{23}NO_5S$ $[M+H]^+$ 414.1370, found 414.1373.

*(1R,7bS)-Ethyl 1-(4-Methoxybenzoyl)-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carboxylate 3,3-Dioxide (**4aj**).* The title product was obtained as a white solid in 76% yield, 88.7 mg, mp 103−105 °C. $[\alpha]_D{}^{20}$ −27.4 (c = 2.6, EtOAc, 87% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 240 nm: t_R = 37.4 min (minor), t_R = 49.3 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24−8.22 (d, J = 7.8 Hz, 1H), 8.10−8.08 (m, 2H), 7.79−7.74 (m, 2H), 7.69−7.67 (m, 1H), 7.00−6.97 (d, J = 9.0 Hz, 2H), 4.38−4.25 (m, 2H), 3.90 (s, 1H), 3.89 (s, 3H), 1.28−1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.8, 164.7, 163.5, 134.0, 133.6, 133.0, 131.6, 131.1, 127.6, 127.1, 123.2, 114.2, 62.9, 60.0, 55.6, 53.5, 13.7; IR (film, ν/cm^{-1}): 2983,1739, 1682, 1600, 1574, 1349, 1248, 1206, 1179, 1023, 768; HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_6S$ $[M+H]^+$ 388.0849, found 388.0855.

*(1R,7bS)-Ethyl 1-(3-Fluorobenzoyl)-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**4ak**).* The title product was obtained as a light yellow oil in 78% yield, 87.8 mg. $[\alpha]_D{}^{20}$ −63.1 (c = 1.0, EtOAc, 97% *ee*); HPLC: Chiralcel AD-H, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 230 nm: t_R = 10.8 min (minor), t_R = 12.8 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23−8.21 (m, 1H), 7.97−7.94 (m, 1H), 7.81−7.75 (m, 3H), 7.71−7.67 (m, 1H), 7.55−7.51 (m, 1H), 7.37−7.36 (m, 1H), 4.38−4.26 (m, 2H), 3.89 (s, 1H), 1.29−1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.70−186.67 (d, J = 2.2 Hz), 164.0−161.5 (d, J = 247.9 Hz), 163.2, 136.45−136.38 (d, J = 6.6 Hz), 134.1, 133.2, 132.9, 131.3, 130.9−130.8 (d, J = 7.6 Hz), 127.2, 125.2−125.1 (d, J = 2.9 Hz), 123.3, 121.9−121.7 (d, J = 21.3 Hz), 115.6−115.4 (d, J = 22.6 Hz), 63.2, 59.5, 53.6 13.7; IR (film, ν/cm^{-1}): 2984, 1740, 1694, 1585, 1445, 1346, 1256, 1171, 1090, 1016, 759; HRMS (ESI) m/z calcd for $C_{18}H_{14}FNO_5S$ $[M+H]^+$ 376.0650, found 376.0656.

*(1R,7bS)-Ethyl 1-(3-methylbenzoyl)-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**4al**).* The title product was obtained as a light yellow oil in 88% yield, 98.2 mg. $[\alpha]_D{}^{20}$ −55.6 (c = 1.2, EtOAc, 94% *ee*); HPLC: Chiralcel AD-H, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 215 nm: t_R = 10.6 min (minor), t_R = 11.4 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23−8.21 (d, J = 7.8 Hz, 1H), 7.91−7.90 (m, 2H), 7.80−7.74 (m, 2H), 7.70−7.66 (m, 1H), 7.48−7.46 (d, J = 7.6 Hz, 1H), 7.43−7.39 (m, 1H), 4.38−4.26 (m, 2H), 3.93 (s, 1H), 2.43 (s, 3H), 1.29−1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.7, 163.4, 138.9, 135.5, 134.5, 134.0, 133.5, 133.0, 131.2, 129.5, 128.8, 127.1, 126.4, 123.3, 63.0, 59.9, 53.7, 21.3, 13.7; IR (film, ν/cm^{-1}): 2985, 2929, 1738, 1687, 1591, 1459, 1344, 1255, 1167, 1091, 759; HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_5S$ $[M+H]^+$ 372.0900, found 372.0906.

*(1R,7bS)-Ethyl 1-(3-Methoxybenzoyl)-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carboxylate 3,3-Dioxide (**4am**).* The title product was obtained as a white solid in 92% yield, 107.2 mg, mp 60−62 °C. $[\alpha]_D{}^{20}$ −61.7 (c = 2.5, EtOAc, 95% *ee*); HPLC: Chiralcel AD-H, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 230 nm: t_R = 12.6 min (minor), t_R = 14.1 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23−8.21 (d, J = 7.7 Hz, 1H), 7.79−7.75 (m, 2H), 7.70−7.66 (m, 2H), 7.60−7.59 (m, 1H), 7.44−7.40 (t, J = 8.0 Hz, 1H), 7.20−7.18 (m, 1H), 4.38−4.25 (m, 2H), 3.93 (s, 1H), 3.86 (s, 3H), 1.29−1.26 (t,

DOI: 10.1021/acs.joc.6b02827
J. Org. Chem. 2017, 82, 2399−2406

J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.3, 163.3, 159.8, 135.6, 134.1, 133.4, 132.9, 131.2, 130.0, 127.1, 123.2, 121.7, 121.6, 112.5, 63.0, 59.9, 55.5, 53.6, 13.7; IR (film, ν/cm^{-1}): 2981, 2926, 1740, 1691, 1597, 1488, 1464, 1349, 1266, 1205, 1177, 1028, 813, 768; HRMS (ESI) m/z calcd for $C_{19}H_{17}NO_6S$ $[M+H]^+$ 388.0849, found 388.0856.

*(1R,7bS)-Ethyl 1-(2-Fluorobenzoyl)-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**4an**).* The title product was obtained as a light yellow oil in 62% yield, 70.0 mg. $[\alpha]_D^{20}$ −83.9 (c = 0.9, EtOAc, 98% *ee*); HPLC: Chiralcel AD-H, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 240 nm: t_R = 12.4 min (major), t_R = 14.6 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07−8.05 (m, 1H), 8.00−7.96 (m, 1H), 7.79−7.75 (m, 2H), 7.70−7.62 (m, 2H), 7.33−7.29 (m, 1H), 7.21−7.16 (m, 1H), 4.29−4.20 (m, 2H), 3.92−3.91 (d, J_{F-H} = 3.4 Hz, 1H), 1.21−1.17 (t, J = Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.7−184.6 (d, J = 3.3 Hz), 163.4−160.9 (d, J = 254.2 Hz), 163.2, 136.4−136.3 (d, J = 9.2 Hz), 133.9, 133.5−133.3 (d, J = 15.6 Hz), 131.2, 130.99−130.98 (d, J = 1.3 Hz), 127.0, 125.01−124.98 (d, J = 3.2 Hz), 123.29−123.17 (d, J = 11.8 Hz), 123.21, 116.9, 116.6, 63.2, 62.06−62.00 (d, J = 6.6 Hz), 54.65−54.62 (d, J = 3.4 Hz), 13.6; IR (film, ν/cm^{-1}): 1741, 1693, 1606, 1453, 1347, 1277, 1168, 1095, 1017, 945, 760; HRMS (ESI) m/z calcd for $C_{18}H_{14}FNO_5S$ $[M+H]^+$ 376.0650, found 376.0655.

*(1R,7bS)-Ethyl 1-(3,4-Difluorobenzoyl)-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole-7b-carboxylate 3,3-Dioxide (**4ao**).* The title product was obtained as a light yellow oil in 69% yield, 81.7 mg. $[\alpha]_D^{20}$ −54.1 (c = 2.0, EtOAc, 97% *ee*); HPLC: Chiralcel AD-H, *i*-PrOH/hexanes =10/90, 0.8 mL/min, λ = 215 nm: t_R = 24.0 min (minor), t_R = 25.9 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23−8.21 (d, J = 7.7 Hz, 1H), 8.01−7.98 (m, 1H), 7.96−7.91 (m, 1H), 7.81−7.77 (m, 2H), 7.72−7.68 (m, 1H), 7.38−7.31 (m, 1H), 4.38−4.26 (m, 2H), 3.86 (s, 1H), 1.29−1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.6, 163.1, 155.9−153.2 (dd, J = 12.9 Hz, 258.7 Hz), 151.8−149.2 (dd, J = 13.1 Hz, 251.0 Hz), 134.2, 133.1, 132.8, 131.6−131.5 (t, J = 4.1 Hz), 131.4, 127.3, 126.8−126.7 (dd, J = 3.6 Hz, 7.9 Hz), 123.3, 118.3−118.1 (dd, J = 1.9 Hz, 18.2 Hz), 118.2−118.0 (d, J = 17.8 Hz), 63.2, 59.4, 53.5, 13.7; IR (film, ν/cm^{-1}): 2987, 1743, 1697, 1607, 1516, 1434, 1348, 1286, 1674, 770; HRMS (ESI) m/z calcd for $C_{18}H_{13}F_2NO_5S$ $[M+H]^+$ 394.0555, found 394.0564.

*(1R,7bS)-Ethyl 1-(Benzo[d][1,3]dioxole-5-carbonyl)-1,7b-dihydroazirino[1,2-b]benzo[d]iso-thiazole-7b-carboxylate 3,3-Dioxide (**4ap**).* The title product was obtained as a white solid in 89% yield, 108.0 mg, mp 141−143 °C. $[\alpha]_D^{20}$ −39.0 (c = 0.7, EtOAc, 83% *ee*); HPLC: Chiralcel AD-H, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 230 nm: t_R = 17.8 min (minor), t_R = 21.5 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25−8.23 (d, J = 7.8 Hz, 1H), 7.81−7.74 (m, 3H), 7.69−7.65 (m, 1H), 7.51−7.50 (d, J = 1.7 Hz, 1H), 6.93−6.91 (d, J = 8.2 Hz, 1H), 6.09 (s, 2H), 4.40−4.26 (m, 2H), 3.86 (s, 1H), 1.30−1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.5, 163.5, 153.2, 148.5, 134.1, 133.6, 133.0, 131.2, 129.3, 127.2, 126.6, 123.3, 108.4, 108.2, 102.2, 63.0, 60.0, 53.5, 13.8; IR (film, ν/cm^{-1}): 1741, 1681, 1606, 1498, 1448, 1347, 1258, 1174, 1032, 922, 767; HRMS (ESI) m/z calcd for $C_{19}H_{15}NO_7S$ $[M+H]^+$ 402.0642, found 402.0648.

*(1R,7bS)-Ethyl 1-(2-Naphthoyl)-1,7b-dihydroazirino[1,2-b]benzo-[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**4aq**).* The title product was obtained as a white solid in 91% yield, 111.4 mg, mp 68−70 °C. $[\alpha]_D^{20}$ −29.6 (c = 2.7, EtOAc, 94% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 215 nm: t_R = 30.6 min (minor), t_R = 42.3 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.26−8.24 (d, J = 7.8 Hz, 1H), 8.05−7.97 (m, 2H), 7.92−7.85 (m, 2H), 7.82−7.75 (m, 2H), 7.70−7.61 (m, 2H), 7.58−7.54 (m, 1H), 4.39−4.25 (m, 2H), 4.06 (s, 1H), 1.28−1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.4, 163.4, 136.0, 134.1, 133.5, 133.0, 132.2, 132.1, 131.8, 131.2, 130.0, 129.4, 128.9, 127.8, 127.13, 127.10, 123.4, 123.3, 63.0, 59.9, 53.6, 13.7; IR (film, ν/cm^{-1}): 2983, 1740, 1687, 1627, 1469, 1350, 1279, 1177, 1129, 812, 755; HRMS (ESI) m/z calcd for $C_{22}H_{17}NO_5S$ $[M+H]^+$ 408.0900, found 408.0903.

*(1R,7bS)-Ethyl 1-(Cyclohexanecarbonyl)-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole-7b-carboxylate 3,3-Dioxide (**4ar**).* The title product was obtained as a light yellow oil in 68% yield, 74.7 mg. $[\alpha]_D^{20}$ −44.9 (c = 2.4, EtOAc, 84% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 240 nm: t_R = 12.1 min (minor), t_R = 12.8 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04−8.02 (m, 1H), 7.75−7.71 (m, 2H), 7.67−7.63 (m, 1H), 4.36−4.30 (m, 2H), 3.33(s, 1H), 2.95−2.91 (m, 1H), 2.19−2.16 (m, 1H), 1.86−1.79 (m, 3H), 1.72−1.68 (m, 1H), 1.48−1.36 (m, 2H), 1.35−1.31 (t, J = 7.1 Hz, 3H), 1.30−1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.2, 163.3, 133.8, 133.3, 133.0, 131.1, 127.2, 123.2, 63.3, 60.2, 54.0, 48.3, 27.7, 26.4, 25.7, 24.8, 13.8; IR (film, ν/cm^{-1}): 2931, 2856, 1740, 1455, 1348, 1176, 1016, 806, 765; HRMS (ESI) m/z calcd for $C_{18}H_{21}NO_5S$ $[M+H]^+$ 364.1213, found 364.1213.

*(1R,7bS)-Ethyl 1-(Cyclopropanecarbonyl)-1,7b-dihydroazirino-[1,2-b]benzo[d]isothiazole-7b-carboxylate 3,3-Dioxide (**4as**).* The title product was obtained as a white solid in 77% yield, 74.7 mg, mp 158−160 °C. $[\alpha]_D^{20}$ −61.0 (c = 1.0, EtOAc, 96% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 215 nm: t_R = 16.2 min (minor), t_R = 19.1 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04−8.02 (m, 1H), 7.76−7.72 (m, 2H), 7.68−7.64 (m, 1H), 4.37−4.31 (m, 2H), 3.38 (s, 1H), 2.56−2.52 (m, 1H), 1.36−1.32 (t, J = 7.2 Hz, 1H), 1.26−1.17 (m, 2H), 1.15−1.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.6, 163.0, 133.9, 133.3, 132.9, 131.2, 127.1, 123.2, 63.3, 61.5, 54.1, 19.2, 14.0, 13.9, 12.9; IR (film, ν/cm^{-1}): 3020, 1749, 1695, 1449, 1341, 1171, 1086, 1018, 761; HRMS (ESI) m/z calcd for $C_{15}H_{15}NO_5S$ $[M+H]^+$ 322.0744, found 322.0746.

*(1R,7bS)-Methyl 1-Benzoyl-1,7b-dihydroazirino[1,2-b]benzo[d]-isothiazole-7b-carboxylate 3,3-Dioxide (**4ba**).* The title product was obtained as a light yellow oil in 93% yield, 95.4 mg. $[\alpha]_D^{20}$ −59.5 (c = 2.0, EtOAc, 93% *ee*); HPLC: Chiralcel OD-H, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 215 nm: t_R = 12.0 min (minor), t_R = 13.8 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22−8.20 (m, 1H), 8.10−8.08 (m, 2H), 7.80−7.75 (m, 2H), 7.70−7.64 (m, 2H), 7.54−7.51 (m, 2H), 3.96 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.8, 163.9, 134.7, 134.5, 134.1, 133.2, 133.0, 131.3, 129.1, 129.0, 127.0, 123.3, 59.6, 53.6, 53.4; IR (film, ν/cm^{-1}): 2957, 1747, 1693, 1597, 1469, 1351, 1230, 1173, 915, 758, 691; HRMS (ESI) m/z calcd for $C_{17}H_{13}NO_5S$ $[M+H]^+$ 344.0587, found 344.0592.

*(1R,7bS)-Methyl 1-Benzoyl-6-fluoro-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**4ca**).* The title product was obtained as a light yellow oil in 76% yield, 82.5 mg. $[\alpha]_D^{20}$ −36.0 (c = 0.6, EtOAc, 82% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 254 nm: t_R = 16.9 min (minor), t_R = 23.8 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11−8.09 (m, 2H), 7.96−7.93 (dd, J = 2.2 Hz, 8.3 Hz, 1H), 7.81−7.77 (dd, J = 4.6 Hz, 8.3 Hz, 1H), 7.67−7.65 (m, 1H), 7.56−7.52 (m, 2H), 7.39−7.37 (m, 1H), 3.99 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.5, 167.1−164.5 (d, J = 256.1 Hz), 163.7, 136.7−136.6 (d, J = 10.5 Hz), 134.9, 134.4, 129.2, 129.1, 129.0, 125.7−125.6 (d, J = 10.2 Hz), 119.4−119.2 (d, J = 24.1 Hz), 115.0−114.7 (d, J = 25.8 Hz), 59.8, 53.6, 52.5; IR (film, ν/cm^{-1}): 2925, 1742, 1691, 1584, 1349, 1229, 1155, 809, 687; HRMS (ESI) m/z calcd for $C_{17}H_{12}FNO_5S$ $[M+H]^+$ 362.0493, found 362.0496.

*(1R,7bS)-Methyl 1-Benzoyl-6-methyl-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**4da**).* The title product was obtained as a light yellow oil in 74% yield, 79.1 mg. $[\alpha]_D^{20}$ − 46.3 (c = 1.9, EtOAc, 95% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 254 nm: t_R = 28.9 min (minor), t_R = 42.2 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10−8.07 (m, 2H), 7.984−7.980 (m, 1H), 7.67−7.64 (m, 2H), 7.54−7.50 (m, 2H), 7.48−7.46 (m, 1H), 3.95 (s, 1H), 3.85 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.9,164.0, 145.6, 134.62, 134.56, 133.6, 132.1, 130.2, 129.04, 128.95, 127.2, 123.0, 59.4, 53.5, 53.4, 21.8; IR (film, ν/cm^{-1}): 2957, 1748, 1692, 1593, 1446, 1348, 1230, 1189, 1156, 815, 767, 691; HRMS (ESI) m/z calcd for $C_{18}H_{15}NO_5S$ $[M+H]^+$ 358.0744, found 358.0745.

*(1R,7bS)-Methyl 1-Benzoyl-6-(tert-butyl)-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole-7b-carboxylate 3,3-Dioxide (**4ea**).* The title product was obtained as a white solid in 78% yield, 93.8 mg, mp 182−185 °C. $[\alpha]_D^{20}$ −47.2 (c = 1.3, EtOAc, 98% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 206 nm: t_R = 18.7 min (minor), t_R = 27.4 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ

DOI: 10.1021/acs.joc.6b02827
J. Org. Chem. 2017, 82, 2399−2406

8.21−8.20 (m, 1H), 8.12−8.10 (m, 2H), 7.71−7.70 (d, J = 0.8 Hz, 2H), 7.65−7.64 (m, 1H), 7.54−7.50 (m, 2H), 3,97 (s, 1H), 3.87 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.1, 164.2, 158.8, 134.62, 134.60, 133.5, 130.1, 129.1, 128.9, 128.8, 123.7, 122.8, 59.5, 53.5, 53.3, 35.6, 31.0; IR (film, ν/cm^{-1}): 2966, 1735, 1685, 1593, 1448, 1351, 1186, 1103, 1013, 905, 763; HRMS (ESI) m/z calcd for $C_{21}H_{21}NO_5S$ [M+Na]$^+$ 422.1033, found 422.1032.

*(1R,7bS)-Methyl 1-Benzoyl-6-methoxy-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole-7b-carboxylate 3,3-Dioxide (**4fa**).* The title product was obtained as a light yellow oil in 75% yield, 84.0 mg. $[\alpha]_D^{20}$ −44.8 (c = 1.1, EtOAc, 92% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 215 nm: t_R = 31.3 min (minor), t_R = 45.0 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11−8.09 (d, J = 8.3 Hz, 2H), 7.67−7.65 (m, 3H), 7.54−7.51 (t, J = 7.6 Hz, 2H), 7.14−7.12 (d, J = 8.7 Hz, 1H), 3.97 (s, 1H), 3.94 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.0, 164.2, 164.1, 136.1, 134.7, 134.5, 129.1, 129.0, 124.6, 124.5, 118.3, 110.8, 59.5, 56.1, 53.4, 52.9; IR (film, ν/cm^{-1}): 2927, 1743, 1691, 1587, 1447, 1343, 1235, 1154, 1060, 813, 688; HRMS (ESI) m/z calcd for $C_{18}H_{15}NO_6S$ [M+H]$^+$ 374.0693, found 374.0693.

*(1R,9bS)-Methyl 1-Benzoyl-1,9b-dihydroazirino[1,2-b]naphtho-[2,3-d]isothiazole-9b-carb-oxylate 3,3-Dioxide (**4ga**).* The title product was obtained as a light yellow oil in 72% yield, 85.2 mg. $[\alpha]_D^{20}$ −23.5 (c = 1.4, EtOAc, 96% *ee*); HPLC: Chiralcel AD-H, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 245 nm: t_R = 25.7 min (minor), t_R = 37.1 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.34 (s, 1H), 8.12−8.09 (m, 2H), 8.04−8.00 (m, 2H), 7.73−7.63 (m, 3H), 7.54−7.50 (m, 2H), 4.02 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.9, 164.3, 135.3, 134.7, 133.3, 130.6, 129.8, 129.3, 129.1, 129.0, 128.8, 128.6, 128.0, 127.0, 124.7, 58.8, 53.8, 53.5; IR (film, ν/cm^{-1}): 2926, 1747, 1691, 1447, 1349, 1225, 1171, 1087, 1016, 888, 757; HRMS (ESI) m/z calcd for $C_{21}H_{15}NO_5S$ [M+H]$^+$ 394.0744, found 394.0749.

*(1R,7bS)-Methyl 1-Benzoyl-7-fluoro-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**4ha**).* The title product was obtained as a light yellow oil in 71% yield, 77.0 mg. $[\alpha]_D^{20}$ −65.4 (c = 0.6, EtOAc, 95% *ee*); HPLC: Chiralcel AD-H, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 240 nm: t_R = 11.9 min (major), t_R = 14.9 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03−8.01 (m, 2H), 7.76−7.71 (m, 1H), 7.66−7.60 (m, 2H), 7.54−7.46 (m, 3H), 3.99 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.3, 162.6, 160.1−157.6 (d, J = 257.5 Hz), 136.66−136.64 (d, J = 2.3 Hz), 135.0, 134.31, 134.26, 129.0, 128.6, 121.4−121.2 (d, J = 19.8 Hz), 121.0−120.8 (d, J = 19.1 Hz), 119.42−119.37 (d, J = 4.1 Hz), 59.2, 53.9, 52.50−52.48 (d, J = 2.3 Hz); IR (film, ν/cm^{-1}): 2923, 1755, 1699, 1592, 1476, 1356, 1255, 1224, 1171, 1091, 914, 790; HRMS (ESI) m/z calcd for $C_{17}H_{12}FNO_5S$ [M+H]$^+$ 362.0493, found 362.0497.

*(1R,7bS)-Methyl 1-Benzoyl-5-methyl-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**4ia**).* The title product was obtained as a light yellow oil in 81% yield, 86.4 mg. $[\alpha]_D^{20}$ −63.3 (c = 0.8, EtOAc, 91% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =30/70, 0.8 mL/min, λ = 240 nm: t_R = 31.0 min (minor), t_R = 41.3 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10−8.05 (m, 3H), 7.67−7.64 (t, J = 7.3 Hz, 1H), 7.58−7.51 (m, 4H), 3.93 (s, 1H), 3.85 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.0, 164.1, 142.3, 135.1, 134.7, 134.6, 133.2, 130.6, 129.1, 129.0, 126.7, 123.2, 59.7, 53.5, 53.4, 21.3; IR (film, ν/cm^{-1}): 2926, 1743, 1690, 1445, 1345, 1218, 1164, 1089, 806, 689; HRMS (ESI) m/z calcd for $C_{18}H_{15}NO_5S$ [M+H]$^+$ 358.0744, found 358.0745.

*(1S,7bR)-Ethyl 1-Benzoyl-1-iodo-1,7b-dihydroazirino[1,2-b]-benzo[d]isothiazole-7b-carb-oxylate 3,3-Dioxide (**5aa**).* The title product was obtained as a light yellow solid in 24% yield, 34.5 mg, mp 106−109 °C. $[\alpha]_D^{20}$ + 37.5 (c = 0.4, EtOAc, 94% *ee*); HPLC: Chiralcel IC, *i*-PrOH/hexanes =20/80, 0.8 mL/min, λ = 215 nm: t_R = 13.8 min (minor), t_R = 16.9 min (major); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36−8.34 (d, J = 7.8 Hz, 1H), 8.21−8.19 (d, J = 8.1 Hz, 2H), 7.86−7.82 (t, J = 7.6 Hz, 1H), 7.79−7.73 (m, 2H), 7.68−7.64 (t, J = 7.0 Hz, 1H), 7.57−7.53 (t, J = 7.2 Hz, 2H), 4.34−4.18 (m, 2H), 1.24−1.20 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.2, 162.6, 135.1, 134.6, 134.3, 134.1, 132.0, 130.7, 130.6, 128.9, 128.3, 122.6, 63.3, 56.2, 47.8, 13.7; IR (film, ν/cm^{-1}): 2924, 2854, 1749, 1683, 1451, 1344, 1263, 1204, 1175, 1094, 1052, 1026, 802, 754. HRMS (ESI) m/z calcd for $C_{18}H_{14}INO_5S$ [M+Na]$^+$ 505.9535, found 505.9545.

*Ethyl 3-(1-Iodo-2-oxo-2-phenylethyl)-2-methyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-Dioxide (**6a**).* The title product was obtained as a white solid in 84% yield, 84.2 mg, mp 167−170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06−8.03 (m, 2H), 7.94−7.92 (d, J = 7.1 Hz, 1H), 7.76−7.74 (m, 2H), 7.73−7.70 (m, 1H), 7.65−7.61 (m, 1H), 7.54−7.50 (t, J = 7.9 Hz, 2H), 6.39 (s, 1H), 4.23−4.08 (m, 2H), 3.31 (s, 3H), 1.17−1.13 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 166.2, 134.09, 134.07, 134.0, 133.9, 133.7, 131.2, 128.84, 128.79, 122.7, 122.0, 72.1, 63.4, 36.5, 27.0, 13.8. HRMS (ESI) m/z calcd for $C_{19}H_{18}INO_5S$ [M+Na]$^+$ 521.9848, found 521.9847.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02827.

HPLC profiles and crystallographic data of compound **5aa** (CIF)

^{1}H NMR and ^{13}C NMR spectra for all the products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: shengzhang@nynu.edu.cn

*E-mail: xukun@nynu.edu.cn

ORCID

Sheng Zhang: 0000-0002-9686-3921

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the Natural Science Foundation of China (21602119, U1504208), and acknowledge the financial support from He'nan Provincial Department of Science and Technology (152300410117).

■ REFERENCES

(1) For reviews of bioactive aziridines, see: (a) *Mitomycin C: Current Status and New Developments*; Carter, S. K., Crooke, S. T., Eds.; Academic: New York, 1979; p 254. (b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (c) Nakao, Y.; Fujita, M.; Warabi, K.; Matsunaga, S.; Fusetani, N. *J. Am. Chem. Soc.* **2000**, *122*, 10462. (d) Ismail, F. M. D.; Levitsky, D. O.; Dembitsky, V. M. *Eur. J. Med. Chem.* **2009**, *44*, 3373.

(2) For reviews of aziridines in organic synthesis, see: (a) Yudin, A. K. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Botuha, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A. *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, 2011; pp 3. (c) Stankovic, 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. (d) Callebaut, G.; Meiresonne, T.; De Kimpe, N.; Mangelinckx, S. *Chem. Rev.* **2014**, *114*, 7954. (e) Dolfen, J.; Yadav, N. N.; De Kimpe, N.; D'hooghe, M.; Ha, H.-J. *Adv. Synth. Catal.* **2016**, *358*, 3485. For the ringstrain of aziridines, see: (f) Bach, R. D.; Dmitrenko, O. *J. Org. Chem.* **2002**, *67*, 3884.

(3) For the synthesis of aziridines, see: (a) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. (b) Sweeney, J. *Eur. J. Org. Chem.* **2009**, *2009*, 4911. (c) Reddy, A. R.; Zhou, C.-Y.; Che, C.-M. *Org. Lett.* **2014**, *16*, 1048. (d) Chen, J.; Yan, W.-Q.; Lam, C.-M.; Zeng, C.-C.; Hu, L.-M.; Little, R. D. *Org. Lett.* **2015**, *17*, 986. (e) Jiang, J.; Liu, H.; Lu, C.-D.; Xu, Y.-J. *Org. Lett.* **2016**, *18*, 880. (f) Jiang, H.-L.;

DOI: 10.1021/acs.joc.6b02827
J. Org. Chem. 2017, 82, 2399−2406

Lang, K.; Lu, H.-J.; Wojtas, L.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 11604.
(4) For the asymmetric synthesis of aziridines, see: (a) Denolf, B.; Mangelinckx, S.; Törnroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129. (b) Pellissier, H. *Tetrahedron* **2010**, *66*, 1509. (c) Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881. (d) Hajra, S.; Aziz, S. M.; Jana, B.; Mahish, P.; Das, D. *Org. Lett.* **2016**, *18*, 532.
(5) The impressive work of Wulff, see: (a) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099. (b) Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518. (c) Huang, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 8892. (d) Huang, L.; Zhang, Y.; Staples, R. J.; Huang, R.-H.; Wulff, W. D. *Chem. - Eur. J.* **2012**, *18*, 5302.
(6) For the pioneering work of Jacobsen, Jørgensen, Davis, and Ruano, see: (a) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676. (b) Rasmussen, K. G.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1995**, *0*, 1401. (c) Davis, F. A.; Zhou, P.; Liang, C.-H.; Reddy, R. E. *Tetrahedron: Asymmetry* **1995**, *6*, 1511. (d) Ruano, J. L. G.; Fernández, I.; Hamdouchi, C. *Tetrahedron Lett.* **1995**, *36*, 295.
(7) The previously reported work, see: Hashimoto, T.; Nakatsu, H.; Yamamoto, K.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 9730.
(8) For reviews on intramolecular C-H amination, see: (a) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. (b) Driver, T. G. *Nat. Chem.* **2013**, *5*, 736. (c) Jeffrey, J. L.; Sarpong, R. *Chem. Sci.* **2013**, *4*, 4092. (d) Zatolochnaya, O. V.; Gevorgyan, V. *Nat. Chem.* **2014**, *6*, 661. (e) Guo, X.-X.; Gu, D.-W.; Wu, Z.-X.; Zhang, W.-B. *Chem. Rev.* **2015**, *115*, 1622. Recent examples, see: (f) Paz, N. R.; Rodríguez-Sosa, D.; Valdés, H.; Marticorena, R.; Melián, D.; Copano, M. B.; González, C. C.; Herrera, A. J. *Org. Lett.* **2015**, *17*, 2370. (g) Martínez, C.; Muńiz, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 8287. (h) Wappes, E. A.; Fosu, S. C.; Chopko, T. C.; Nagib, D. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 9974. (i) Lu, H.-L.; Lang, K.; Jiang, H.-L.; Wojtas, L.; Zhang, X. P. *Chem. Sci.* **2016**, *7*, 6934.
(9) (a) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129. (b) Zakrzewski, J.; Smalley, A. P.; Kabeshov, M. A.; Gaunt, M. J.; Lapkin, A. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 8878.
(10) Lai, B.-N.; Qiu, J.-F.; Zhang, H.-X.; Nie, J.; Ma, J.-A. *Org. Lett.* **2016**, *18*, 520.
(11) For the direct Mannich reaction of aryl ketones, see: (a) Ren, Y.-Y.; Wang, Y.-Q.; Liu, S.; Pan, K. *ChemCatChem* **2014**, *6*, 2985. (b) Zhang, S.; Li, J.-L.; Hu, Y.-B.; Zha, Z.-G.; Wang, Z.-Y.; Loh, T.-P. *Org. Lett.* **2015**, *17*, 1050. (only one example of aryl ketone provided a moderate *ee*). (c) Zhang, S.; Li, L.-J.; Hu, Y.-B.; Li, Y.-N.; Yang, Y.; Zha, Z.-G.; Wang, Z.-Y. *Org. Lett.* **2015**, *17*, 5036.
(12) Other related reactions involving *N*-sulphonyl imines, see: (a) Zhang, H.-X.; Nie, J.; Cai, H.; Ma, J.-A. *Org. Lett.* **2014**, *16*, 2542. (b) An, Q.-J.; Shen, J.-F.; Butt, N.; Liu, D.-L.; Liu, Y.-G.; Zhang, W.-B. *Org. Lett.* **2014**, *16*, 4496. (c) Qiao, B.; Huang, Y.-J.; Nie, J.; Ma, J.-A. *Org. Lett.* **2015**, *17*, 4608. (d) Nakamura, S.; Sano, M.; Toda, A.; Nakane, D.; Masuda, H. *Chem. - Eur. J.* **2015**, *21*, 3929. (e) Yu, J.-S.; Zhou, J. *Org. Chem. Front.* **2016**, *3*, 298.
(13) For enamine activation in the Mannich reaction of acetophenone and for reviews, see: (a) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580. (b) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29.
(14) Zhang, S.; Cha, L.-D.; Li, L.-J.; Hu, Y.-B.; Li, Y.-N.; Zha, Z.-G.; Wang, Z.-Y. *J. Org. Chem.* **2016**, *81*, 3177.
(15) For the mechanism study involving I-/TBHP, see (a) Shi, E.-B.; Shao, Y.; Chen, S.-L.; Hu, H.-Y.; Liu, Z.-J.; Zhang, J.; Wan, X.-B. *Org. Lett.* **2012**, *14*, 3384. (b) Wu, X.-F.; Gong, J.-L.; Qi, X.-X. *Org. Biomol. Chem.* **2014**, *12*, 5807.
(16) (a) Hofmann, A. W. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 558. (b) Löffler, K.; Freytag, C. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3427.
(17) The absolute configuration of the products was proven by X-ray crystal structure analysis of product **5aa**. See Section 1.3 (page S4-S9) of the Supporting Information. CCDC 1510069 (**5aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(18) Yin, G.-D.; Zhou, B.-H.; Meng, X.-G.; Wu, A.-X.; Pan, Y.-J. *Org. Lett.* **2006**, *8*, 2245.

DOI: 10.1021/acs.joc.6b02827
J. Org. Chem. 2017, 82, 2399−2406