Organic LETTERS

Letter

pubs.acs.org/OrgLett

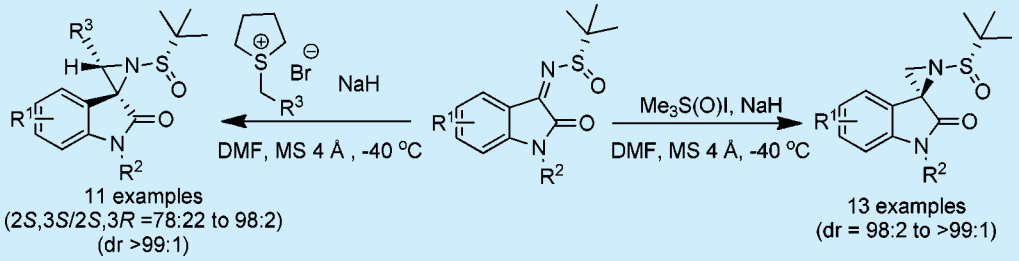
Synthesis of Chiral Spiro-Aziridine Oxindoles via Aza-Corey–Chaykovsky Reaction of Isatin Derived *N-tert*-Butanesulfinyl Ketimines

Saumen Hajra,[*,†] Sk Mohammad Aziz,[§] Bibekananda Jana,[†,§] Prosenjit Mahish,[†,§] and Dhiraj Das[§]

[†]Centre of Biomedical Research, Sanjay Gandhi Post-Graduate Institute of Medical Sciences Campus, Raebareli Road, Lucknow 226014, India

[§]Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur 721302, India

Supporting Information



ABSTRACT: A general and direct strategy for the synthesis of chiral spiro-aziridine oxindoles has been developed via an aza-Corey–Chaykovsky reaction of isatin-derived *N-tert*-butanesulfinyl ketimines with excellent selectivity (dr = 98:2 to >99:1). The method is explored for the synthesis of chiral 3-substituted spiro-aziridine oxindoles with high (2*S*,3*S*)-selectivity over (2*S*,3*R*).

Chiral aziridines are of great synthetic interest because they are important substructural units in many biologically active compounds and are powerful building blocks in organic synthesis.[1,2] This is because the versatile functionality can readily be transformed stereoselectively to a variety of nitrogen-containing compounds. Similar to spiro-epoxy oxindoles,[3] highly strained spiro-aziridine oxindoles are attracting increasing attention because of their potential synthetic utility and bioactivities. However, the synthesis of nonracemic chiral spiro-aziridine oxindoles remains a challenge, and only one report[4] exists on the asymmetric synthesis of spiro-aziridine oxindole via a two-step method.

Over the decades, several methods have been developed for the direct asymmetric synthesis of aziridines, mostly involving the addition of carbon to imines or of nitrogen to olefins.[5] The aza-Corey–Chaykovsky reaction,[6] which involves the addition of sulfur ylides to imines, is an efficient strategy for carbenoid addition in the asymmetric synthesis of aziridines, pioneered by Aggarwal et al.[7] Alternatively, the addition of sulfur ylides to chiral *N*-sulfinyl imines[8] is a straightforward and well-established method providing nonracemic aziridines with controlled stereochemistry, developed by Davis,[9] Garcia-Ruano,[10] and Stockman groups.[11] However, reports on the aza-Corey–Chaykovsky reaction of chiral ketimines are limited in the literature.[12] Our continued interest in aziridine chemistry[13] and recent research in oxindoles[14] drew our attention to the asymmetric synthesis of spiro-aziridine oxindoles. Isatin-derived *N-tert*-butanesulfinyl ketimines[15] can provide the spiro-aziridineoxindoles. During the course of our study, Marsini et al. reported[12c] the aziridination of chiral *N-tert*-butanesulfinyl ketimino esters with excellent stereoselectivities. However, isatin-derived ketimines resulted in poor-to-moderate (dr = 1:1 to 6.6:1) diastereoselectivity (Scheme 1).

Herein, we report the direct asymmetric synthesis of spiro-aziridine oxindoles via the aza-Corey–Chaykovsky reaction of isatin-derived *N-tert*-butanesulfinyl ketimines with excellent selectivity (dr = 98:2 to >99:1) and high (2*S*,3*S*)-selectivity for the substituted spiro-aziridine oxindoles.

We began our investigation by exploring the reaction of (*S*)-ketimine **1a** with in situ generated sulfur ylide from trimethylsulfonium iodide and NaH (Table 1). To our delight, reaction in DMF proceeded rapidly at rt and within 10 min produced the spiro-aziridine **2a** with good diastereoselectivity (dr = 90:10) in 42% yield (Table 1, entry 1). However, the reaction in DMSO gave only 18% of the desired product with poor diastereoselectivity (dr = 60:40) along with a mixture of uncharacterized compounds (entry 2). Lowering the temperature of the reaction in DMF improves both the yield and selectivity (entries 3–5). At −40 °C, a 62% yield with a dr of 97:3 (entry 5) was observed. The reaction in THF provided yield and selectivity at −40 °C (entry 6) comparable to the ones in the reaction in DMF, but both yield and selectivity dropped in dioxane (entry 7). Interestingly, changing the ylide reagent to trimethylsulfoxonium iodide ($Me_3S(O)I$) afforded excellent selectivities (dr >99:1) with improved yields in both

Received: December 16, 2015
Published: January 19, 2016

DOI: 10.1021/acs.orglett.5b03564
Org. Lett. 2016, 18, 532–535

Scheme 1. Asymmetric Synthesis of Spiro-Aziridine Oxindoles

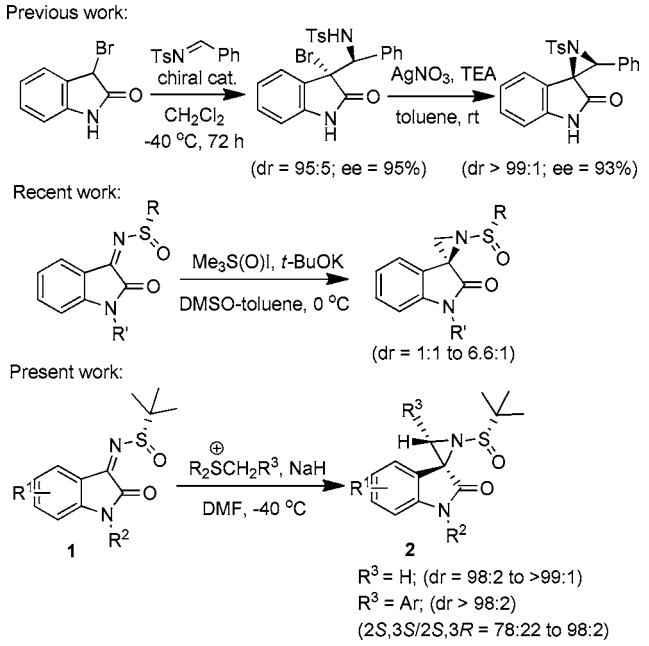
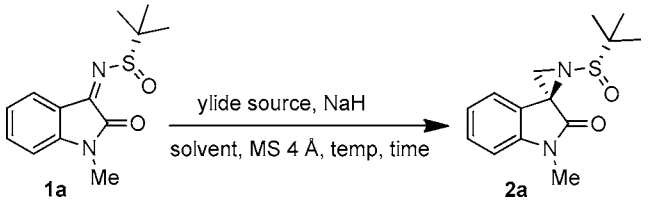


Table 1. Optimization of Reaction Conditions[a]



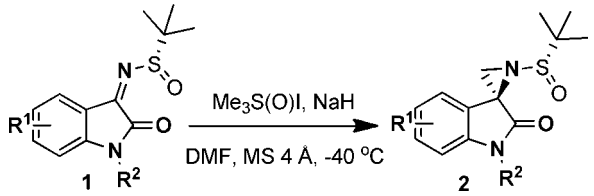
entry	ylide source	solvent	temp (°C)	time (min)	yield[b] (%)	dr[c]
1	Me_3SI	DMF	25	10	42	90:10
2	Me_3SI	DMSO	25	30	18[d]	60:40
3	Me_3SI	DMF	0	20	57	95:5
4	Me_3SI	DMF	−20	30	60	95:5
5	Me_3SI	DMF	−40	30	62	97:3
6	Me_3SI	THF	−40	60	60	97:3
7	Me_3SI	dioxane	−40	60	45	95:5
8	**$Me_3S(O)I$**	**DMF**	**-40**	**30**	**73**	**>99:1**
9	$Me_3S(O)I$	THF	−40	60	72	>99:1
10	$Me_3S(O)I$	DMSO	25	30	72	81:19

[a]Ylide source (1.25 mmol, 2.5 equiv) and NaH (60% in mineral oil; 1.25 mmol, 2.5 equiv) in solvent (2.5 mL) were stirred for 30 min in the presence of MS 4 Å and added to ketimine **1a** (0.5 mmol) and MS 4 Å in solvent (2.0 mL) at specified temperature. [b]Isolated yield otherwise noted. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Determined by ^{1}H NMR analysis of the crude reaction mixture with naphthalene as internal standard.

DMF and THF (entries 8 and 9). Reaction in THF takes more time than that in DMF. Reaction with $Me_3S(O)I$ in DMSO is clean and provided very good yield of the aziridine **2a** with a dr of 81:19 (entry 10).

To test the generality of this method, a series of chiral ketimines derived from a number of isatins and (*S*)-*tert*-butanesulfinamide was investigated under the optimized reaction conditions (Table 2). All the ketimines, irrespective of whether they possessed electron-rich or -withdrawing substituents and the nature of the protecting group, underwent a smooth reaction and provided very good yields of the desired spiroaziridine-2,3′-oxindoles with excellent diastereoselectivities (dr = 98:2 to >99:1).

Table 2. Generalization for the Synthesis of Spiroaziridine Oxindoles 2[a]



entry	R^1	R^2	time (min)	product **2**	yield[b] (%)	dr[c]
1	H	Me	30	**2a**	73	>99:1
2	H	Bn	30	**2b**	72	>99:1
3	5-F	Me	30	**2c**	75	99:1
4	5-F	Bn	30	**2d**	69	>99:1
5	7-F	Me	40	**2e**	70	>99:1
6	7-F	Bn	30	**2f**	72	99:1
7	5-Br	Me	30	**2g**	78	98:2
8	5-Cl	Me	30	**2h**	76	>99:1
9	5-Cl	Bn	45	**2i**	68	99:1
10	5-OMe	Me	45	**2j**	72	98:2
11	5-OMe	Bn	30	**2k**	73	98:2
12	5,7-Me	Me	45	**2l**	67	99:1
13	5,7-Me	Bn	50	**2m**	66	98:2

[a]$Me_3S(O)I$ (1.25 mmol, 2.5 equiv) and NaH (60% in mineral oil; 1.25 mmol, 2.5 equiv) in solvent (2.5 mL) were stirred for 30 min in the presence of MS 4 Å and added to ketimine **1** (0.5 mmol) and MS 4 Å in solvent (2.0 mL) at specified temperature. [b]Isolated yield. [c]Determined by the ^{1}H NMR analysis of crude reaction mixture.

After the successful synthesis of nonracemic chiral spiroaziridine-2,3′-oxindoles **2**, the synthesis of 3-substituted spiroaziridine oxindoles was attempted. By employing a method similar to the ones developed by the groups of Hou, Dai,[16] and Stockman,[12a,17] the reaction of benzyl sulfur ylides generated from *S*-benzyl tetrahydrothiophenium bromide with chiral *tert*-butanesulfinyl ketimines provided access to a series of nonracemic chiral 3-substituted spiro-aziridinoxindoles **3** with high (2*S*,3*S*)-selectivities and excellent diastereoselectivities (Scheme 2).

To determine the absolute stereochemistry of the spiro-center, aziridine **2e** was recrystallized from ethyl acetate−hexanes and was subjected to X-ray crystallographic analysis. The crystal structure unambiguously confirms the stereochemistry of the spiro-center as an (*S*)-configuration derived from (*S*)-*tert*-butanesulfinyl ketimine **1e** (Figure 1a). Recently Marsini et al. also observed the same stereochemical outcome from (*S*)-*tert*-butanesulfinyl ketimino ester.[12c] The stereochemistry of the major isomer of the 3-substituted spiro-aziridine oxindoles **3** was determined by NOESY experiment of the spiro-aziridine **3k**, where interaction of the C4′-H of the oxindole unit and the C3−H of aziridine indicated the formation of the (2*S*,3*S*)-isomer as the major product (Figure 1b). The high (2*S*,3*S*)-selectivity for the substituted spiroaziridines and excellent diastereoselectivity observed in the aziridination may be due to the high stereodirecting effect of the bulky *tert*-butanesulfinyl group and the cyclic transition state,[12] with both solvent and temperature playing important roles.

DOI: 10.1021/acs.orglett.5b03564
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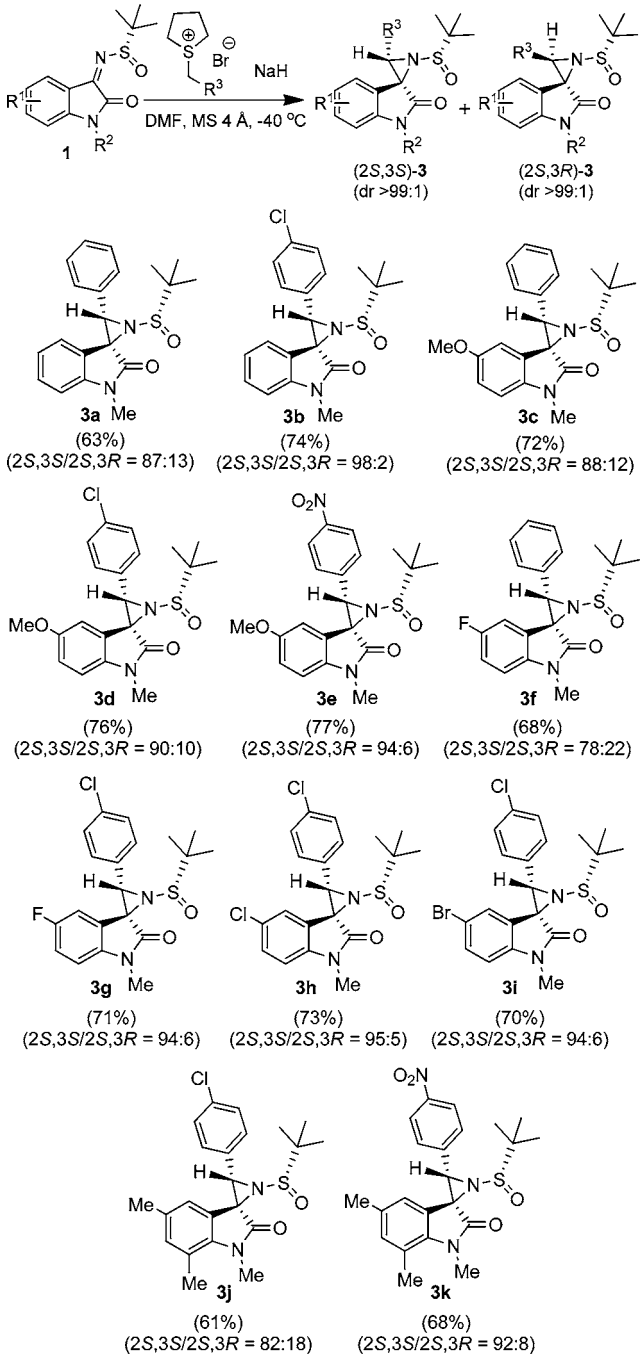
Scheme 2. Substrate Scope for the Synthesis of 3-Substitued Spiroaziridine Oxindoles 3



Next, cleavage of the sulfinyl group was attempted. According to the reported method,[15f,17b] spiro-aziridine **2a** was reacted with HCl in dioxane at rt to provide the unprotected spiro-aziridine oxindole **4a** in good yield with high optical purity (Scheme 3).

In summary, we have developed a highly efficient, versatile protocol for the synthesis of nonracemic chiral spiro-aziridine oxindoles via the aza-Corey–Chaykovsky reaction of chiral isatin-derived *tert*-butanesulfinyl ketimines. The method has a broad scope and provides access to both terminal and substituted spiro-aziridine oxindoles in good yields with excellent diastereoselectivities. Successful sulfinyl cleavage afforded the unprotected spiro-aziridine oxindole without any significant loss in optical purity. Application of this spiro-aziridine in the synthesis of nitrogen-heterocycles is underway and will be reported in due course.

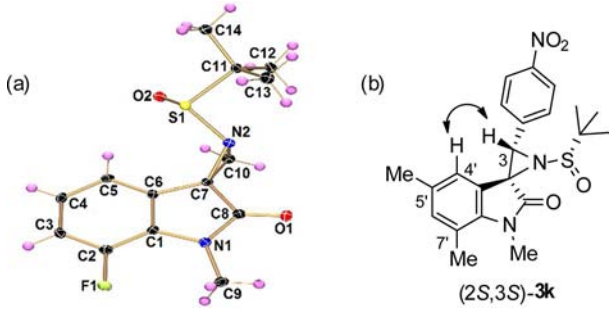
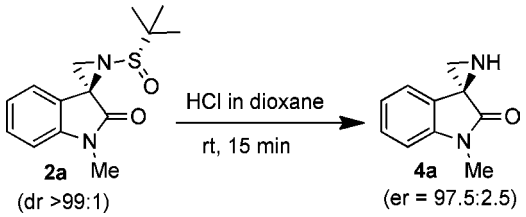


Figure 1. (a) ORTEP diagram of spiro-aziridine oxindole **2e**; (b) Interaction of C4′-H of oxindole unit and C3–H of aziridine in NOESY experiment of compound (**2S,3S**)-**3k**.

Scheme 3. Synthesis of Enantiomeric Pure Spiroaziridine Oxindole 4a



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03564.

Experimental details, spectroscopic and analytical data for all new compounds (PDF)

X-ray crystallographic data for compound **2e** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: saumen.hajra@cbmr.res.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank DST, New Delhi (SR/S1/OC-97/2012) and CBMR, Lucknow for providing financial support. S.M.A. thanks CSIR, New Delhi, and B.J. and P.M. thank UGC, New Delhi for their fellowships. We thank the Director, CBMR for research facilities.

■ REFERENCES

(1) For leading reviews on aziridine-containing natural products and biologically active molecules, see: (a) Lowden, P. A. S. Aziridine Natural Products—Discovery, Biological Activity and Biosynthesis. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; Chapter 11, p 399. (b) Ismail, F. M. D.; Levitsky, D. O.; Dembitsky, V. M. *Eur. J. Med. Chem.* **2009**, *44*, 3373.

(2) For leading reviews on aziridines as synthetic intermediates, see: (a) Callebaut, G.; Meiresonne, T.; De Kimpe, N.; Mangelinckx, S. *Chem. Rev.* **2014**, *114*, 7954. (b) Stankovic, S.; D'hooghe, M.; Catak,

DOI: 10.1021/acs.orglett.5b03564
Org. Lett. 2016, 18, 532–535

S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H.-H. *Chem. Soc. Rev.* **2012**, *41*, 643. (c) Schneider, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2082. (d) Hodgson, D. M.; Humphreys, P. G.; Hughes, S. R. *Pure Appl. Chem.* **2007**, *79*, 269. (e) Ohno, H. Vinylaziridines in Organic Synthesis. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K.; Ed.; Wiley-VCH: Weinheim, 2006; Chapter 2, p 37. (f) Ping Zhou, P.; Chen, B.-C.; Davis, F. A. Asymmetric Syntheses with Aziridinecarboxylate and Aziridinephosphonate Building Block. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; Chapter 3, p 73. (g) Pineschi, M. *Eur. J. Org. Chem.* **2006**, *2006*, 4979. (h) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. (i) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (j) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (k) McCoull, W.; Davis, F. A. *Synthesis* **2000**, *2000*, 1347. (l) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (m) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519.

(3) For leading references on biology and synthesis of spiro-epoxy oxindoles, see: (a) Kuang, Y.; Lu, Y.; Tang, Y.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2014**, *16*, 4244. (b) Boucherif, A.; Yang, Q. Q.; Wang, Q.; Chen, J. R.; Lu, L. Q.; Xiao, W. J. *J. Org. Chem.* **2014**, *79*, 3924. (c) Cheng, D. J.; Ishihara, Y.; Tan, B.; Barbas, C. F., III. *ACS Catal.* **2014**, *4*, 743. (d) Fu, Q.; Yan, C. G. *Beilstein J. Org. Chem.* **2013**, *9*, 918. (e) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023. (f) Muthusamy, S.; Karikalan, T. *Tetrahedron* **2012**, *68*, 1443. (g) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060. (h) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. (i) Shmidt, M. S.; Perillo, I. A.; Gonzalez, M.; Blanco, M. M. *Tetrahedron Lett.* **2012**, *53*, 2514. (j) Gasperi, T.; Loreto, M. A.; Migliorini, A.; Ventura, C. *Eur. J. Org. Chem.* **2011**, *2011*, 385. (k) Palumbo, C.; Mazzeo, G.; Mazziotta, A.; Gambacorta, A.; Loreto, M. A.; Migliorini, A.; Superchi, S.; Tofani, D.; Gasperi, T. *Org. Lett.* **2011**, *13*, 6248. (l) Dandia, A.; Singh, R.; Bhaskaran, S. *Ultrason. Sonochem.* **2011**, *18*, 1113. (m) Muthusamy, S.; Karikalan, T.; Suresh, E. *Tetrahedron Lett.* **2011**, *52*, 1934. (n) Muthusamy, S.; Ramkumar, R.; Mishra, A. K. *Tetrahedron Lett.* **2011**, *52*, 148. (o) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discovery* **2010**, *13*, 758. (p) Schulz, V.; Davoust, M.; Lemarie, M.; Lohier, J. F.; Santos, J. S. D.; Metzner, P.; Briere, J. F. *Org. Lett.* **2007**, *9*, 1745. (q) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, *2003*, 2209. (r) Kikumoto, R.; Kobayashi, T. *Tetrahedron* **1966**, *22*, 3337. (s) Gasperi, T.; Loreto, M. A.; Migliorini, A.; Ventura, C. *Eur. J. Org. Chem.* **2011**, *2011*, 385. (t) Dandia, A.; Singh, R.; Saha, M.; Shivpuri, A. *Pharmazie* **2002**, *57*, 602. (u) Marx, K. A.; O'Neil, P.; Hoffman, P.; Ujwal, M. L. J. *J. Chem. Inf. Model.* **2003**, *43*, 1652.

(4) Li, J.; Du, T.; Zhang, G.; Peng, Y. *Chem. Commun.* **2013**, *49*, 1330.

(5) For leading reviews on the asymmetric synthesis of aziridines, see: Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. *Chem. Rev.* **2014**, *114*, 8199. (b) Pellissier, H. *Adv. Synth. Catal.* **2014**, *356*, 1899. (c) Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881. (d) Pellissier, H. *Tetrahedron* **2010**, *66*, 1509. (d) Singh, G. S.; D'Hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. (e) Hou, X. L.; Wu, J.; Fan, R. H.; Ding, C. H.; Luo, Z. B.; Dai, L. X. *Synlett* **2006**, 181. (f) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247.

(6) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(7) (a) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem.* **1996**, *61*, 8368. (b) Aggarwal, V. K.; Alonso, E.; Fang, G. Y.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433. (c) Li, A.-H.; Zhou, Y.-G.; Dai, L.-X.; Xia, L.-J.; Lin, L. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1317.

(8) For leading reviews on sulfinimine chemistry, see: (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600. (b) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162. (c) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (d) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993. (e) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (f) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (g) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13.

(9) Davis, F. A.; Zhou, P.; Liang, C.-H.; Reddy, R. E. *Tetrahedron: Asymmetry* **1995**, *6*, 1511.

(10) Garcia-Ruano, J. L.; Fernandez, I.; Catalina, M. d-P.; Cruz, A. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407.

(11) (a) Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Synlett* **2003**, 1985. (b) Forbes, D. C.; Bettigeri, S. V.; Amin, S. R.; Bean, C. J.; Law, A. M.; Stockman, R. A. *Synth. Commun.* **2009**, *39*, 2405.

(12) (a) Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Chem. Commun.* **2006**, 1833. (b) Yang, Y.; Huang, Y.; Qing, F.-L. *Tetrahedron Lett.* **2013**, *54*, 3826. (c) Marsini, M. A.; Reeves, J. T.; Desrosiers, J.-N.; Herbage, M. A.; Savoie, J.; Li, Z.; Fandrick, K. R.; Sader, C. A.; McKibben, B.; Gao, D. A.; Cui, J.; Gonnella, N. C.; Lee, H.; Wei, X.; Roschangar, F.; Lu, B. Z.; Senanayake, C. H. *Org. Lett.* **2015**, *17*, 5614.

(13) (a) Hajra, S.; Maji, B.; Sinha, D.; Bar, S. *Tetrahedron Lett.* **2008**, *49*, 4057. (b) Hajra, S.; Maji, B.; Mal, D. *Adv. Synth. Catal.* **2009**, *351*, 859. (c) Hajra, S.; Bar, S. *Chem. Commun.* **2011**, *47*, 3981. (d) Hajra, S.; Sinha, D. *J. Org. Chem.* **2011**, *76*, 7334. (e) Hajra, S.; Aziz, S. M.; Akhtar, S. M. S. *Chem. Commun.* **2014**, *50*, 6913.

(14) Hajra, S.; Maity, S.; Maity, R. *Org. Lett.* **2015**, *17*, 3430.

(15) For leading references on uses of istatin derived *N*-sulfinyl ketamines, see: (a) Chen, D.; Xu, M.-H. *J. Org. Chem.* **2014**, *79*, 7746. (b) Rao, V. U. B.; Jadhav, A. P.; Garad, D.; Singh, R. P. *Org. Lett.* **2014**, *16*, 648. (c) Chen, D.; Xu, M.-H. *Chem. Commun.* **2013**, *49*, 1327. (d) Yan, W.; Wang, D.; Feng, J.; Li, P.; Wang, R. *J. Org. Chem.* **2012**, *77*, 3311. (e) Jung, H. H.; Buesking, A. W.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 3912. (f) Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537.

(16) (a) Li, A.-H.; Dai, L.-X.; Hou, X.-L. *Chem. Commun.* **1996**, 491. (b) Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Chen, M.-B. *J. Org. Chem.* **1996**, *61*, 4641. (c) Wang, D.-K.; Dai, L.-X.; Hou, X.-L. *Chem. Commun.* **1997**, 1231. (d) Li, A.-H.; Zhou, Y.-G.; Dai, L.-X.; Hou, X.-L.; Xia, L.-J.; Tang, M.-H. *J. Org. Chem.* **1998**, *63*, 4338. (e) Hou, X.-L.; Yang, X.-F.; Dai, L.-X. *Chem. Commun.* **1998**, 747.

(17) (a) Arini, L. G.; Sinclair, A.; Szeto, P.; Stockman, R. A. *Tetrahedron Lett.* **2004**, *45*, 1589. (b) Morton, D.; Pearson, D.; Field, R. A.; Stockman, R. A. *Org. Lett.* **2004**, *6*, 2377.

DOI: 10.1021/acs.orglett.5b03564
Org. Lett. 2016, 18, 532−535