Organic LETTERS

Letter

pubs.acs.org/OrgLett

Diastereoselective Electrophilic α-Hydroxyamination of *N-tert*-Butanesulfinyl Imidates

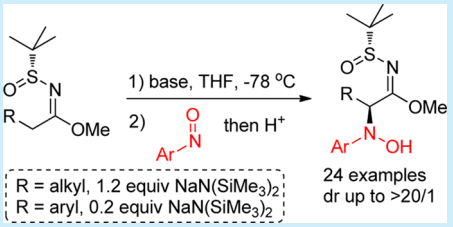
Peng-Ju Ma,[†,‡] Hui Liu,[†] Chong-Dao Lu,[*,†] and Yan-Jun Xu[*,†]

[†]Key Laboratory of Plant Resources and Chemistry of Arid Zones, Xinjiang Technical Institute of Physics & Chemistry, Chinese Academy of Sciences, Urumqi 830011, China

[‡]University of Chinese Academy of Sciences, Beijing 100049, China

Supporting Information

ABSTRACT: Diastereoselective α-hydroxyamination of *N-tert*-butanesulfinyl imidates using nitrosoarenes is reported. A catalytic amount of base effectively promotes the hydroxyamination reaction of α-aryl-substituted imidates, and the resulting α-hydroxyamino imidates can be transformed into a range of synthetically useful intermediates.



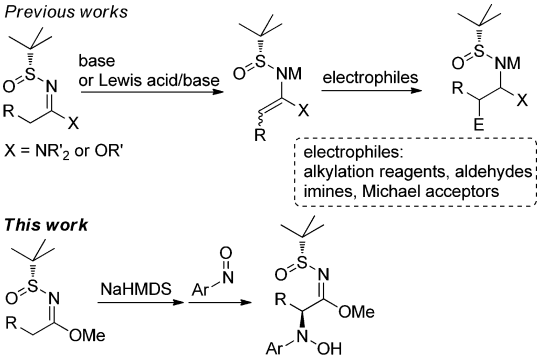
Enantioselective construction of C−N bonds is attractive because of the ubiquity of chiral amines in bioactive natural products and pharmaceuticals. Numerous synthetic approaches have been developed, including nucleophilic substitution, reductive amination, nucleophilic addition to C═N double bonds, transition-metal-catalyzed cross-coupling, and electrophilic amination.[1] A particularly straightforward asymmetric approach toward optically active amino acid derivatives is direct electrophilic amination of chiral metal enolates using suitable nitrogen sources. In 1986, the Evans and Vederas groups succeeded in using dialkyl azodiformates to aminate enolates derived from chiral carboximides,[2] and subsequently, this strategy has been used to aminate several other chiral variants.[3]

Chiral amines are often constructed using *tert*-butanesulfinamide, as first shown by Ellman and co-workers, in a process involving diastereoselective nucleophilic addition to *N-tert*-butanesulfinyl (*N-t*BS) imines.[4] The corresponding nucleophilic addition of enolizable *N-t*BS imines has met with limited success,[5] in part because of a competing self-condensation reaction that occurs at the enolization step in the presence of bases.[6] Replacing *N-t*BS imines with *N′-t*BS amidines or *N-t*BS imidates can avoid this problem, allowing C−C bond formation in such reactions as alkylation,[7] Mannich addition,[8] and Michael addition (Scheme 1).[9] Aldolization is also feasible when $TiCl_2(OiPr)_2/Et_3N$ is used because this species simultaneously promotes enolization and suppresses the reverse reaction of aldol condensation.[10]

To our knowledge, diastereoselective C−N bond formation using *N-t*BS imidates has not been reported. Here, we show that aza-enolates derived from *N-tert*-butanesulfinyl imidates can be intercepted by using aromatic nitroso compounds[11] as electrophiles. This allows highly diastereoselective construction of α-hydroxyamino *N-tert*-butanesulfinyl imidates.[12]

Initially, we screened various bases to promote the hydroxyamination reaction of metallo aza-enolate derived from (R_S)-*N-tert*-butanesulfinyl imidate **1a** with nitrosobenzene (**2a**)

Scheme 1. Nucleophilic Reactions of *N-tert*-Butanesulfinyl Imidates

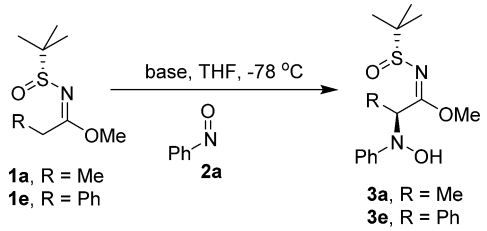


(Table 1). After **1a** was deprotonated using lithium diisopropylamide (LDA), the reaction proceeded smoothly to provide α-hydroxyamino imidate **3a** in 65% yield and 3:1 dr (entry 1). The desired α-hydroxyamination product was obtained exclusively, with no formation of oxygenation product via the O-addition pathway.[13] The same diastereoselectivity was observed when LiHMDS was used as a base (entry 2). The diastereoselectivity was reversed (1:1.4 dr) by adding 1.2 equiv of hexamethylphosphoramide (HMPA) to the reaction, but conversion of only ~40% was observed (entry 3). Reducing the amount of HMPA to 0.20 equiv reversed the diastereoselectivity again (1.4:1 dr) and increased the conversion to ~85% (entry 4). Increasing the amount of HMPA to 6.0 equiv completely suppressed the reaction. Replacing LiHMDS with NaHMDS improved dr to >20:1 and yield to 81% (entry 5). KHMDS can also initiate the reaction: it gave high dr but lower yield (67%, entry 6). Similarly high diastereoselectivity was obtained using NaHMDS as a base

Received: December 23, 2016

DOI: 10.1021/acs.orglett.6b03835
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Initial Attempts to α-Hydroxyaminate *N-tert*-Butanesulfinyl Imidates[a]



entry	base (equiv)/HMPA (equiv)	imidate	product (yield)[b]	dr[c]
1	LDA (1.2)	**1a**	**3a** (65%)	3:1
2	LiHMDS (1.2)	**1a**	**3a** (78%)	3:1
3[d]	LiHMDS (1.2)/1.2	**1a**	**3a** (ni)[e]	1:1.4
4[d]	LiHMDS (1.2)/0.20	**1a**	**3a** (ni)[e]	1.4:1
5	NaHMDS (1.2)	**1a**	**3a** (81%)	>20:1
6	KHMDS (1.2)	**1a**	**3a** (67%)	>20:1
7	NaHMDS (1.2)	**1e**	**3e** (65%)	>20:1
8	NaHMDS (0.20)	**1e**	**3e** (85%)	>20:1
9	LiHMDS (0.20)	**1e**	**3e** (80%)	>20:1
10	NaHMDS (0.20)	**1a**	**3a** (ni)[e]	na[f]

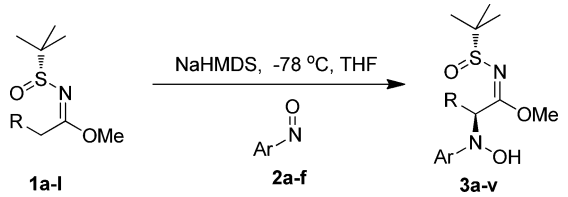
[a]Reaction conditions: **1** (0.30 mmol), **2a** (0.39 mmol), and base in anhydrous THF (3.0 mL) under argon at −78 °C; the reaction was complete within 30 min, unless otherwise noted. [b]Isolated yield after silica gel chromatography. [c]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d]Reaction mixture was stirred for 3 h before quenching. [e]Not isolated. [f]Not analyzed. Since TLC analysis indicated most of the starting material **1a** was intact, no NMR analysis of the crude reaction mixture to determine diastereoselectivity was conducted.

and α-phenyl-substituted imidate **1e** as substrate (entry 7), although the yield of the corresponding α-hydroxyaminination product **3e** was only 65%, reflecting a competing reaction in which adduct **3e** was dehydrated under basic conditions to afford the corresponding *N*-phenyl α-imino imidate.[14]

This side reaction could be suppressed using a catalytic amount of base. The hydroxyamination reaction of **1e** could be effectively promoted using 0.20 equiv of NaHMDS, which led to higher yield (85%, entry 8) than a stoichiometric amount of base (65%, entry 7). In fact, 0.20 equiv of LiHMDS was also effective, giving **3e** in 80% yield with excellent stereocontrol (entry 9). However, a catalytic amount of base was not sufficient for hydroxyamination of α-alkyl-substituted imidate **1a**, for which only low conversion was observed (entry 10). This result indicates that the anion derived from the addition of α-alkyl imidate **1a** to **2a** cannot extract the α-proton of **1a** to complete the catalytic cycle.

With the optimal reaction conditions in hand, we investigated the scope of imidate and nitrosoarene substrates. Imidates bearing α-alkyl substitutions such as ethyl, propyl, and benzyl were all suitable coupling partners, giving the desired products **3b–d** in good yields with excellent diastereoselectivities (Table 2, entries 2–4). α-Aryl-substituted imidates with electron-neutral, electron-donating, or electron-withdrawing groups attached to the aryl group underwent hydroxyamination in the presence of a catalytic amount of base, providing α-(*N*-phenyl hydroxyamino)arylacetimidates **3f–l** with excellent asymmetric induction (entries 6–12). The reaction of **1e** was easily carried out on a preparative scale using 0.1 equiv of NaHMDS, affording product **3e** in 76% yield without erosion of dr (entry 5). Enantiomers of **3a** and **3e** were easily accessed by replacing (*R*)-

Table 2. Substrate Scope of the α-Hydroxyamination of *N-tert*-Butanesulfinyl Imidates[a]



entry	imidate (R)	nitrosoarenes (Ar)	product	yield (%)[b]	dr[c]
1	**1a** (Me)	**2a** (Ph)	**3a**	81	>20:1
2	**1b** (Et)	**2a** (Ph)	**3b**	76	>20:1
3	**1c** (Pr)	**2a** (Ph)	**3c**	81[e]	>20:1
4	**1d** (Bn)	**2a** (Ph)	**3d**	80	>20:1
5	**1e** (Ph)	**2a** (Ph)	**3e**	85 (76)[f]	>20:1
6	**1f** (4-MeC$_6$H$_4$)	**2a** (Ph)	**3f**	87	>20:1
7	**1g** (3-MeC$_6$H$_4$)	**2a** (Ph)	**3g**	45[e]	>20:1
8	**1h** (2-MeC$_6$H$_4$)	**2a** (Ph)	**3h**	79	>20:1
9	**1i** (4-MeOC$_6$H$_4$)	**2a** (Ph)	**3i**	88	>20:1
10	**1j** (4-BrC$_6$H$_4$)	**2a** (Ph)	**3j**	64	>20:1
11	**1k** (4-FC$_6$H$_4$)	**2a** (Ph)	**3k**	81	>20:1
12	**1l** (3,4-diClC$_6$H$_4$)	**2a** (Ph)	**3l**	76	>20:1
13	*ent*-**1a** (Me)[d]	**2a** (Ph)	*ent*-**3a**	75	>20:1
14	*ent*-**1e** (Ph)[d]	**2a** (Ph)	*ent*-**3e**	71	>20:1
15	**1a** (Me)	**2b** (3-MeC$_6$H$_4$)	**3m**	80	>20:1
16	**1a** (Me)	**2c** (2-MeC$_6$H$_4$)	**3n**	80	>20:1
17	**1a** (Me)	**2d** (4-ClC$_6$H$_4$)	**3o**	60	>20:1
18	**1a** (Me)	**2e** (4-BrC$_6$H$_4$)	**3p**	62	>20:1
19	**1a** (Me)	**2f** (4-MeOC$_6$H$_4$)	**3q**	76[e]	5:1
20	**1e** (Ph)	**2b** (3-MeC$_6$H$_4$	**3r**	82	>20:1
21	**1e** (Ph)	**2c** (2-MeC$_6$H$_4$)	**3s**	90	>20:1
22	**1e** (Ph)	**2d** (4-ClC$_6$H$_4$)	**3t**	68	>20:1
23	**1e** (Ph)	**2e** (4-BrC$_6$H$_4$)	**3u**	68	17:1
24	**1e** (Ph)	**2f** (4-MeOC$_6$H$_4$)	**3v**	69[e]	>20:1

[a]Reaction conditions: **1** (0.30 mmol), NaHMDS (0.36 mmol for imidates **1a–d**; 0.060 mmol for **1e–l**), and **2** (0.39 mmol) in anhydrous THF (3.0 mL) under argon at −78 °C, unless otherwise noted. [b]Isolated yield after silica gel chromatography. [c]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d](*S*)-Enantiomer of *N-tert*-butanesulfinyl imidate was used. [e]Refers to the N–O cleavage product; for details, see the Supporting Information. [f]Reaction on 1 g scale using 0.10 equiv of NaHMDS.

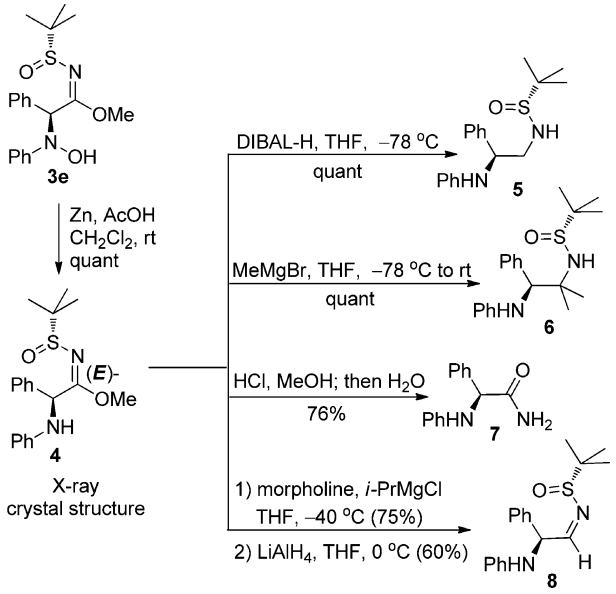
tert-butanesulfinyl imidates **1a** and **1e** with the (*S*)-enantiomers as starting material (entries 13 and 14).

Various nitrosoarenes could trap deprotoned **1a** and **1e**, leading to the corresponding α-(*N*-aryl hydroxyamino) imidates (entries 15–19 and 20–24). We failed in our attempts to extend the reaction to nitrosoarenes containing two potential electrophilic sites, such as 4-AcC$_6$H$_4$-NO and 4-MeO$_2$CC$_6$H$_4$-NO; these reactions led to unidentified mixtures. In the reactions to produce α-hydroxyamination products **3c**, **3g**, **3q**, and **3v**, which show poor stability at room temperature,[15] the residues obtained after common workup were immediately mixed with Zn/AcOH to cleave the N–O bond and thereby afford the corresponding α-arylamino products, which could be characterized (entries 3, 7, 19, and 24).

We crystallized the N–O bond cleavage product **4** derived from **3e**, via the reaction with Zn/AcOH, which gave quantitative yield (Scheme 2). X-ray diffraction analysis of **4** showed that the

DOI: 10.1021/acs.orglett.6b03835
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 2. Cleavage of the N−O Bond in α-Hydroxyamino *N*-*t*BS Imidate and Further Manipulations

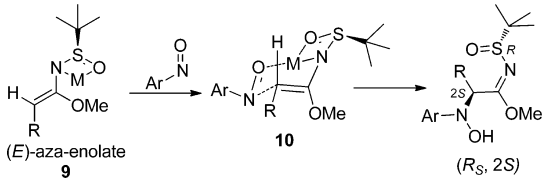


aminated α-carbon adopts the *S*-configuration,[16] indicating that the absolute configuration of **3e** is (R_S,2*S*). Configurations of other hydroxyamination products were determined by analogy. The crystal structure showed an *E*-configuration for the *N*-*t*BS imidate, with the *t*BS and methoxy groups on opposite sides of the C═N bond. Because all *N*-*t*BS imidate derivatives of known configuration are (*E*)-isomers,[17] we infer that the hydroxyamino imidates **3** adopt the same geometry.

To illustrate the synthetic utilities of this method, we investigated further transformations of α-hydroxyamino imidate **3e** (Scheme 2). Using **4** as a starting material, we transformed the *N*-*t*BS imidate group into *N*-*t*BS α-primary and α-tertiary amine, amide, and imine groups. We were able to obtain optically active diamines **5** and **6**, α-phenylamino amide **7**, and α-phenylamino *N*-*t*BS aldimine **8**. Aldimine **8** is a suitable precursor for further transformation into structurally diverse chiral 1,2-diamines.

The observed stereochemistry can be rationalized by postulating *si*-face addition of (*E*)-aza-enolate **9** to aromatic nitroso compounds via a well-known Ellman's chelated chairlike 6/4-membered bicyclic transition state[5b] **10** to afford the (R_S,2*S*)-products (Scheme 3). The formation of (*E*)-aza-enolate **9** is favored, in which the R and bulky *N*-*t*BS groups are on opposite sides of the C═C bond to minimize steric hindrance.

Scheme 3. Rationalization of Stereochemistry



In summary, we have described a highly diastereoselective α-hydroxyamination of chiral *N*-*tert*-butanesulfinyl imidates. We have further transformed the hydroxyamination products into a range of synthetically useful intermediates. Our protocol is the first example of α-heterofunctionalization of *N*-*tert*-butanesulfinyl imidates and the first demonstration that nucleophilic addition of α-aryl substituted *N*-*tert*-butanesulfinyl imidates can be realized by using a catalytic amount of base.[18]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03835.

Experimental details, characterization data of all new compounds (PDF)

X-ray crystal structure of compound **4** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: clu@ms.xjb.ac.cn.

*E-mail: xuyj@ms.xjb.ac.cn.

ORCID

Chong-Dao Lu: 0000-0001-8968-0134

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (U1403301, 21372255, and 21572262), the Recruitment Program of Global Experts (Xinjiang Program), and the Director Foundation of XTIPC (2015RC014).

■ REFERENCES

(1) (a) *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2007. (b) *Amino Group Chemistry: From Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2008. (c) Mailyan, A. K.; Eickhoff, J. A.; Minakova, A. S.; Gu, Z.; Lu, P.; Zakarian, A. *Chem. Rev.* **2016**, *116*, 4441.

(2) (a) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395. (b) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397.

(3) (a) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394. (b) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881. (c) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *Tetrahedron* **1988**, *44*, 5525. (d) Oppolzer, W.; Moretti, R. *Helv. Chim. Acta* **1986**, *69*, 1923. (e) Oppolzer, W.; Moretti, R. *Tetrahedron* **1988**, *44*, 5541. (f) Oppolzer, W.; Tamura, O. *Tetrahedron Lett.* **1990**, *31*, 991. (g) Oppolzer, W.; Tamura, O.; Deerberg, J. *Helv. Chim. Acta* **1992**, *75*, 1965. (h) Oppolzer, W.; Cintas-Moreno, P.; Tamura, O.; Cardinaux, F. *Helv. Chim. Acta* **1993**, *76*, 187. (i) Chao, C. S.; Cheng, C. K.; Li, S. H.; Chen, K. *Tetrahedron Lett.* **2009**, *50*, 333.

(4) For reviews, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831. (c) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162. (d) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600. (e) Dong, H.-Q.; Xu, M.-H.; Feng, C.-G.; Sun, X.-W.; Lin, G.-Q. *Org. Chem. Front.* **2015**, *2*, 73.

(5) (a) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 6518. (b) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276. (c) Peltier, H. M.; Ellman, J. A. *J. Org. Chem.* **2005**, *70*, 7342. (d) Lanter, J. C.; Chen, H. F.; Zhang, X. Q.; Sui, Z. H. *Org. Lett.* **2005**, *7*, 5905. (e) Zhao, C. H.; Liu, L.; Wang, D.; Chen, Y. J. *Eur. J. Org. Chem.* **2006**, *2006*, 2977. (f) Liu, Z.-J.; Mei, Y.-Q.; Liu, J.-T. *Tetrahedron* **2007**, *63*, 855. (g) Priede, M.; Kazak, M.; Kalnins, T.; Shubin, K.; Suna, E. *J. Org. Chem.* **2014**, *79*, 3715. (h) Foley, V. M.; McSweeney, C. M.; Eccles, K. S.; Lawrence, S. E.; McGlacken, G. P. *Org. Lett.* **2015**, *17*, 5642.

(6) Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 3621.

(7) (a) Colpaert, F.; Mangelinckx, S.; Verniest, G.; De Kimpe, N. *J. Org. Chem.* **2009**, *74*, 3792. (b) Colpaert, F.; Mangelinckx, S.; De Kimpe, N. *J.*

DOI: 10.1021/acs.orglett.6b03835
Org. Lett. XXXX, XXX, XXX−XXX

Org. Chem. **2011**, *76*, 234. (c) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652.
(8) (a) Colpaert, F.; Mangelinckx, S.; De Kimpe, N. *Org. Lett.* **2010**, *12*, 1904. (b) Colpaert, F.; Mangelinckx, S.; De Brabandere, S.; De Kimpe, N. *J. Org. Chem.* **2011**, *76*, 2204. (c) Semina, E.; Colpaert, F.; Van Hecke, K.; De Kimpe, N.; Mangelinckx, S. *Eur. J. Org. Chem.* **2015**, *2015*, 4847.
(9) (a) Wang, J. F.; Zhou, Y.; Zhang, L.; Li, Z.; Chen, X. J.; Liu, H. *Org. Lett.* **2013**, *15*, 1508. (b) Wang, H.-J.; Tang, P.; Zhou, Q.-L.; Zhang, D.; Chen, Z.-T.; Huang, H.-X.; Qin, Y. *J. Org. Chem.* **2015**, *80*, 2494. (c) Huang, H.-X.; Wang, H.-J.; Tan, L.; Wang, S.-Q.; Tang, P.; Song, H.; Liu, X.-Y.; Qin, Y. *J. Org. Chem.* **2016**, *81*, 10506.
(10) Bartrum, H. E.; Viceriat, A.; Carret, S.; Poisson, J.-F. *Org. Lett.* **2014**, *16*, 1972.
(11) For earlier examples of asymmetric hydroxyamination reactions using nitrosoarenes as nitrogen sources, see: (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360. (b) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080. (c) Guo, H.-M.; Cheng, L.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Chem. Commun.* **2006**, 429. (d) Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6046.
(12) For α-electrophilic amination of *N*-*t*BS ketimines with azodicarboxylates with moderate diastereoselectivity using manganese amides as base, see: Dessole, G.; Bernardi, L.; Bonini, B. F.; Capitò, E.; Fochi, M.; Herrera, R. P.; Ricci, A.; Cahiez, G. *J. Org. Chem.* **2004**, *69*, 8525.
(13) For earlier examples of asymmetric α-oxygenation reactions using nitrosoarenes as oxygen sources, see: (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (c) Zhong, G.-F. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (d) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112. (e) Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109.
(14) For example of dehydration of α-hydroxyamino ketone affording α-imino ketone under basic conditions, see: Lewis, J. W.; Myers, P. L.; Ormerod, J. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, *20*, 2521.
(15) Substantial degradation was observed for the α-hydroxyamino *N*-*t*BS imidate products **3c**, **3g**, **3q**, and **3v** when these samples were stored overnight at room temperature. Other products presented in Table 2 are much more stable to ensure easy operations for their characterization.
(16) For the crystal structure of compound **4**, which is generated from **3e** following N−O bond cleavage, see the Supporting Information.
(17) Huang, W.; Liu, H.; Lu, C.-D.; Xu, Y.-J. *Chem. Commun.* **2016**, *52*, 13592. See also refs 8c, 9b, 9c, and 10.
(18) For Mannich reaction of *N*-sulfonyl imidates in the presence of a catalytic amount of bases, see: Matsubara, R.; Berthiol, F.; Nguyen, H. V.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1083 and refs cited therein.

DOI: 10.1021/acs.orglett.6b03835
Org. Lett. XXXX, XXX, XXX−XXX