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Three-Component Reactions of Sulfonylimidates, Silyl Glyoxylates and *N-tert*-Butanesulfinyl Aldimines: An Efficient, Diastereoselective, and Enantioselective Synthesis of Cyclic *N*-Sulfonylamidines

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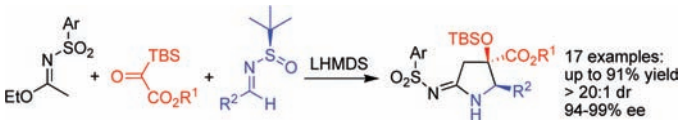
ABSTRACT



Three-component coupling reactions of sulfonylimidates, silyl glyoxylates and *N-tert*-butanesulfinyl aldimines efficiently provide cyclic *N*-sulfonylamidines containing free endocyclic N–H. The formation of two C–C bonds (contiguous stereogenic carbons), one O–Si bond, and one C–N bond, together with the cleavage of the chiral auxiliary (*tert*-butanesulfinyl group), occurs with excellent chemoselectivity, diastereoselectivity, and enantioselectivity in this one-pot cascade transformation.

Amidines have been identified as an important class of compounds with applications in medicinal chemistry,[1] coordination chemistry,[2] and supramolecular chemistry[3] due to their structural characteristics. Traditional protocols for the synthesis of the amidines rely on transforming the functional groups of amides, nitriles, aldoximes, and amines, among others.[4] In addition, several methods involving convergent direct couplings of sulfonyl azides,[5] isocyanides,[6] or carbodiimides[7] with the suitable coupling partners have been developed in recent years, allowing easy access to several types of amidines. However, the applicability of these methods is restricted by intrinsic limitations in the reaction scope and generality.[8] Meeting the demand for the efficient construction of the structurally diverse group of amidines necessitates further synthetic explorations toward efficient methods for their synthesis.

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(3) Katagiri, H.; Tanaka, Y.; Furusho, Y.; Yashima, E. *Angew. Chem., Int. Ed.* 2007, *46*, 2435 and references therein.

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(5) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038. (b) Chang, S.; Lee, M.; Jung, D. Y.; Yoo, E. J.; Han, S. K. *J. Am. Chem. Soc.* **2006**, *128*, 12366. (c) Yoo, E. J.; Chang, S. *Curr. Org. Chem.* **2009**, *13*, 1766. (d) Xu, X.; Li, X.; Ma, L.; Ye, N.; Weng, B. *J. Am. Chem. Soc.* **2008**, *130*, 14048. (e) Xu, X.; Ge, Z.; Cheng, D.; Ma, L.; Lu, C.; Zhang, Q.; Yao, N.; Li, X. *Org. Lett.* **2010**, *12*, 897. (f) Wang, S.; Wang, Z.; Zheng, X. *Chem. Commun.* **2009**, 7372.

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(8) For example, only cyclic *N*-sulfonylamidines with a protected nitrogen at the *N*-amino position can be accessed by the direct-coupling methods in refs 5b and 5e. The analogues provided in refs 6 and 7 are *N*-alkyl amidines.

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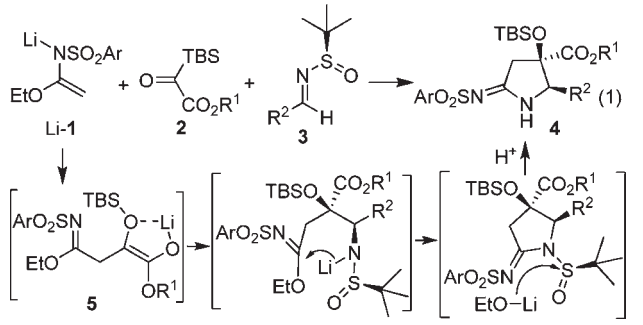
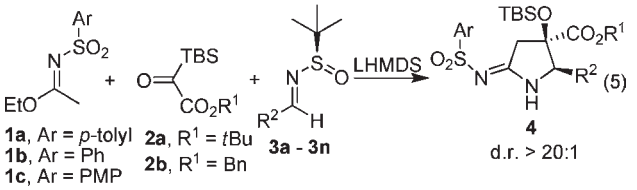
Herein, we report a three-component coupling reaction of sulfonylimidates, silyl glyoxylates[9] and *N*-*tert*-butanesulfinyl aldimines for an efficient, convergent, asymmetric synthesis of substituted cyclic *N*-sulfonylamidines possessing free N−H at the cyclic nitrogen atom (Scheme 1). In this reaction, the nucleophilic addition of lithium aza-enolates Li-**1** to silyl glyoxylates **2** triggers a Brook rearrangement,[10] and the generated enolates **5** undergo addition to (R_S)-*N*-*tert*-butanesulfinyl aldimines **3**, in which the Ellman imines[11] participate as the second electrophile. The anionic nitrogen-induced cyclization and subsequent desulfinylation by nucleophilic attack by the extruding ethoxide give enantioenriched cyclic *N*-sulfonylamidines **4**. To the best of our knowledge, this is the first report that explores the use of lithium aza-enolates as nucleophiles to initiate a Brook rearrangement and the first report that azomethines serve as the second electrophile in silyl glyoxylate-mediated cascades.[12]

Scheme 1. Silyl Glyoxylates-Mediated Cascade Reaction for the Synthesis of Chiral Cyclic *N*-Sulfonylamidines



We began our investigation with the coupling reaction of **1a** (Ar = 4-MeC_6H_4), **2a** (R^1 = *t*Bu), and **3a** (R^2 = Ph) in the presence of several readily available metal amides.[13] After some pilot studies, the optimized reaction conditions were found to be the metalation of sulfonylimidate **1a** with LHMDS at −78 °C, followed by the sequential addition of (R_S)-*tert*-butanesulfinyl aldimine **3a** and silyl glyoxylate **2a**. The reaction mixture was stirred at −78 °C for 5 h and warmed gradually to −5 °C. The three-component product **4a** was obtained in 82% isolated yield with excellent diastereoselectivity and enantioselectivity (Table 1, entry 1).

Table 1. Scope of Cyclic Sulfonyl Amidines **4a**−**4q**[a]



1a, Ar = *p*-tolyl; **1b**, Ar = Ph; **1c**, Ar = PMP; **2a**, R^1 = *t*Bu; **2b**, R^1 = Bn; **3a** - **3n**; **4**; d.r. > 20:1

entry	1, 2	imine **3** (R^2)	4	yield [%][b]	*ee* [%][c]
1[f]	**1a, 2a**	**3a** (Ph)	**4a**	82 (76)[d]	98 (−99)[d]
2[f]	**1a, 2a**	**3b** (4-ClC_6H_4)	**4b**	72	95
3[f]	**1a, 2a**	**3c** (4-BrC_6H_4))	**4c**	72	94
4[f]	**1a, 2a**	**3d** (4-MeC_6H_4)	**4d**	80	98
5[g]	**1a, 2a**	**3e** (4-MeOC_6H_4)	**4e**	85	99
6[g]	**1a, 2a**	**3f** (3-MeOC_6H_4	**4f**	89	97
7[g]	**1a, 2a**	**3g** (2-MeOC_6H_4)	**4g**	82	99
8[g]	**1a, 2a**	**3h** (piperonyl)	**4h**	91	99
9[f]	**1a, 2a**	**3i** (1-naphthyl)	**4i**	69	97
10[g]	**1a, 2a**	**3j** (2-furyl)	**4j**	86	98
11[g]	**1a, 2a**	**3k** (2-thienyl)	**4k**	90 (83)[h]	99.3 (99)
12[g]	**1a, 2a**	**3l** (Et)	**4l**	80	98
13[g]	**1a, 2a**	**3m** ($PhCH_2CH_2$)	**4m**	70	96
14[e,g]	**1a, 2a**	**3n** (*trans*-PhCH=CH)	**4n**	76	99
15[g]	**1a, 2b**	**3k** (2-thienyl)	**4o**	59	99
16[g]	**1b, 2a**	**3k** (2-thienyl)	**4p**	82	99
17[g]	**1c, 2a**	**3k** (2-thienyl)	**4q**	86	99

[a] Imine **3** and silyl glyoxylate **2** were added sequentially to a 0.1 M enolate solution in THF at −78 °C (see the Supporting Information for the detailed procedures). The diastereoselectivity (dr) was determined from ^{1}H NMR spectra of crude reaction mixtures. [b] Isolated yields after silica gel chromatography. [c] Determined by HPLC with a Chiralcel OD-H column. [d] Using (S_S)-**3a** as a substrate in place of (R_S)-**3a**. [e] Amidines of *tert*-butanesulfinyl-**4n** and **4n** were obtained in 63 and 13% yields, respectively. [f] Substrate ratio: sulfonylimidate **1** (2.5 equiv), silylglyoxylate **2** (2.5 equiv), imine **3** (1.0 equiv). [g] Substrate ratio: sulfonylimidate **1** (2.0 equiv), silylglyoxylate **2** (2.0 equiv), imine **3** (1.0 equiv). [h] One-gram scale reaction.

This high yield suggested that the lithium enamide of sulfonylimidate **1a** reacts as a discriminating nucleophile with a strong preference for the silylglyoxylate **2a** over *N*-*tert*-butanesulfinyl aldimine **3a** (Scheme 2). To verify this, several control experiments were conducted. The aldimine **3a** was added to the solution of the lithium enamide of sulfonylimidate **1a** at −78 °C, and no product was observed. Even when the reaction mixture was warmed to room temperature, only the starting materials were recovered (eq 2). Furthermore, when *N*-Ts phenyl aldimine **6** was used instead of the sulfinyl aldimine **3a** as an electrophile under the standard three-component coupling conditions, the major product appeared to be the two-component adduct **7** derived from the sulfonylimidate **1a** and the *N*-Ts imine **6** (eq 3).[14] Studies of the nucleophilic

(9) The synthetic applications of silyl glyoxylates are growing in prominence. For related examples see: (a) Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 6170. (b) Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. S.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 17281. (c) Greszler, S. N.; Johnson, J. S. *Org. Lett.* **2009**, *11*, 827. (d) Greszler, S. N.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3689. (e) Greszler, S. N.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 17393. (f) Boyce, G. R.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8930. (g) Schmitt, D. C.; Johnson, J. S. *Org. Lett.* **2010**, *12*, 944.

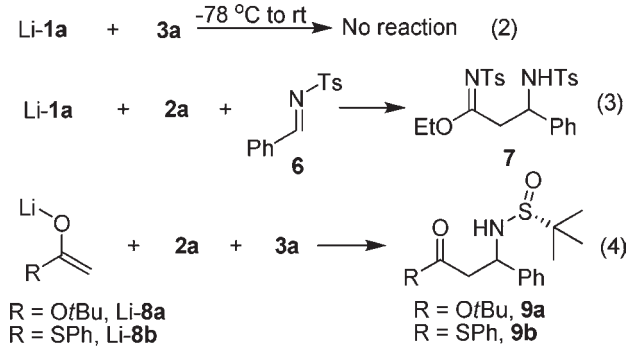
(10) (a) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77. (b) Bulman Page, P. C.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147. (c) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065.

(11) For reviews of *tert*-butanesulfinamide: (a) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162. (b) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.

(12) For examples of aryl acylsilanes acting as conjunctive reagents for the union of lithium amide enolates and *N*-diphenylphosphinyl imines, see: (a) Lettan, R. B.; Woodward, C. C.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2294. (b) Lettan, R. B.; Galliford, C. V.; Woodward, C. C.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 8805. It is noteworthy that the aryl acylsilanes failed to enable the three-component coupling reaction described here; see ref 17.

(13) See the Supporting Information for details.

Scheme 2. Control Experiments

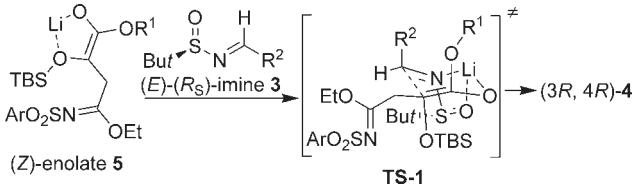


behaviors of lithium ester enolates (Li-**8a** and Li-**8b**) toward the mixture of **2a** and **3a** indicated that the predominant reaction pathway is addition to sulfinylimine **3a**, rather than the addition to the silylglyoxylate **2a** (eq 4). These results reveal that the three-component reaction described here exhibits unusual and exquisite chemoselectivity.

The scope and limitations of this method were investigated, and are summarized in Table 1. The reactions provided the desired products in good isolated yields (59−91%) with excellent diastereoselectivity (>20:1 dr) and enantioselectivity (94−99.3% *ee*). The enantiomer of the cyclic sulfonylamidine **4a** could be obtained by employing (S_S)-*tert*-butanesulfinyl phenyl aldimines (entry 1). The crystalline compound of the (*R*)-mandelic acid derivative from **4j** was prepared, which allowed us to determine the absolute stereochemistry of the newly formed contiguous stereogenic carbons by single-crystal X-ray diffraction.[15]

The aryl aldimines bearing electron-donating groups were more reactive than those bearing electron-withdrawing groups. Higher yields were obtained, and an excess of more than 2.0 equiv of the sulfonylimidates and silylglyoxylates was unnecessary: yields of 80−91% were obtained with 2.0 equiv, compared to the 72% with 2.5 equiv (Table 1, entrie 4−8, 10, and 11 vs entries 2−3). Good yields and excellent enantioselectivities were achieved using the following compounds: phenyl aldimines with a methoxy substituent in the *ortho*, *meta*, and *para* positions; heteroaromatic aldimines; and unbranched aliphatic aldimines (Table 1, entries 5−7, 10−13). Unfortunately, sulfinylimine derived from bulky pivaldehyde was inert. When the α,β-unsaturated aldimine **3n** was used in the reaction (Table 1, entry 14), two products were observed: the N−H sulfonylamidine **4n** and the *N*-sulfinyl sulfonylamidine *tert*-butanesulfinyl-**4n**. The latter compound was the product without cleavage of the sulfinyl auxiliary. Warming the reaction mixture to −5 °C resulted in an intractable mixture of products. Notably, the enantioselectivity for **4k** (99.3% *ee*, entry 11) is consistent with the enantiopurity of (R_S)-*tert*-butanesulfinamide (99.3% *ee*) used to prepare imine **3k**.[16] This implies that a complete chirality transfer from the chiral auxiliary occurred in this example. One-gram scale preparation of **3k** gave comparable *ee* and a slightly lower yield compared to a small scale process because the desulfinylation in the larger scale reaction is slower, and prolonging the reaction time led to partial decomposition (entry 11). The cyclic arylsulfonyl amidines incorporating a benzyl ester or other arylsulfonyl groups (Ar = Ph, PMP) can be prepared using the corresponding starting materials (Table 1, entries 15−17). Aryl acylsilanes such as PhCOTBS (**10**) did not function as useful reagents to enable the three-component coupling reaction because the intramolecular electrophilic trapping is more efficient.[17]

Scheme 3. Rationale of Stereochemistry



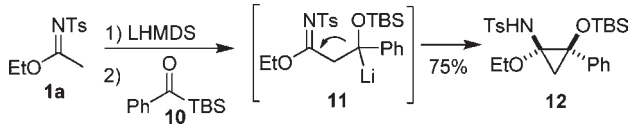
To rationalize the stereochemistry of this transformation, a transition state **TS-1** was proposed (Scheme 3) according to Ellman's six/four-membered bicyclic transition state with a preferred chair conformation.[18] It has been well established by Johnson and co-workers that (*Z*)-glycolate enolates were preferentially formed over (*E*)-isomer in the lithium enolate-initiated Brook rearrangements of silyl glyoxylates.[9g] The intermediate glycolate enolates (*Z*)-**5** approach the imines (*E*)-(R_s)-**3** from the

(14) For studies on the addition of sulfonylimidates to *N*-Ts imines in the presence of catalytic amounts of base or alkaline earth metal complexes, see: (a) Matsubara, R.; Berthiol, F.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 1804. (b) Nguyen, H. V.; Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 5927. (c) Matsubara, R.; Nguyen, H. V.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1083.

(15) The absolute stereochemistry of the product **4j** was determined by X-ray crystallography of the (*R*)-mandelic acid derivative of the enantiopure **4j**, with **4a**−**4i** and **4k**−**4q** assigned by analogy. Single crystal structure of racemic **4q** were also provided to determine the relative configuration. See the Supporting Information for details.

(16) The enantioselectivity of *tert*-butanesulfinamide was determined by HPLC with a Chiralcel OD column. See the Supporting Information for details.

(17) The cyclopropane derivative **12** was predominantly formed with excellent diastereoselectivity by intramolecular nucleophilic trapping of the α-silyloxy carbanion **11** (intermediate of Brook rearrangement). The stereochemistry of the product **12** was determined from 2D ROESY spectrum. For details, see the Supporting Information. For similar reaction behavior in the addition of lithium ketone enolates to acylsilanes, see: Takeda, K.; Nakatani, J.; Nakamura, H.; Sako, K.; Yoshii, E.; Yamaguchi, K. *Synlett* **1993**, 841.



(18) For the addition of lithium (or titanium) ester enolates to sulfinylimines rationalized by a six/four-membered bicyclic transition state, see: (a) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387. (b) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819.

opposite direction of the sterically hindered *tert*-butyl group (the *Si* face of imines **3**). Nucleophilic attack by the *Re* face of the lithium enolates **5** is facilitated and favored by the complexation of the lithium and gives the products with the observed stereochemistry.

In summary, we have devoloped a Brook rearrangement-mediated, three-component coupling reaction of sulfonylimidates, silyl glyoxylates and *N*-*tert*-butanesulfinyl aldimines for efficient asymmetric synthesis of substituted cyclic sulfonyl amidines. The cascade promotes the formation of two C−C bonds (contiguous stereogenic carbons), one C−N bond, and one O−Si bond, together with cleavage of the chiral auxiliary (*tert*-butanesulfinyl group) in a one-pot operation. The reaction occurs with exquisite chemoselectivity, excellent diastereoselectivity, and excellent enantioselective induction.

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Supporting Information Available. Experimental details, characterization data, and crystal structure data of the racemic **4q** and the (*R*)-mandelic acid derivative of the enantiopure **4j**. This material is available free of charge via the Internet at http://pubs.acs.org.