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Stereodivergent Synthesis of Complex *N*-Sulfonimidoyl Lactams via the Castagnoli–Cushman Reaction

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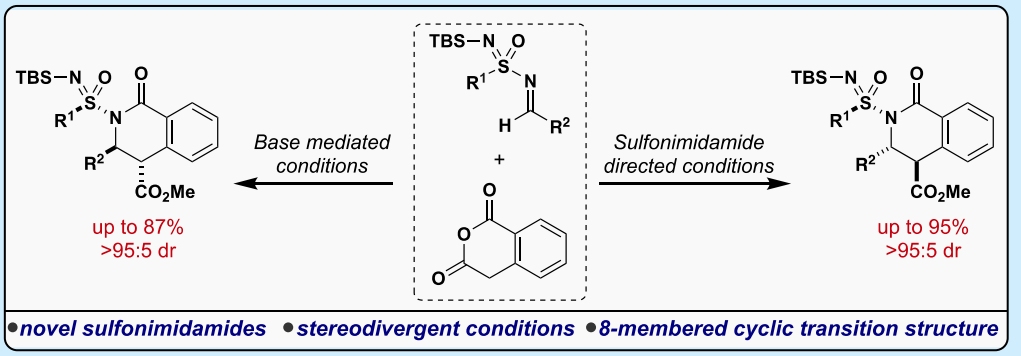

ABSTRACT: The reactivity between sulfonimidamide-derived imines and cyclic anhydrides has been investigated. Sulfonimidamide imines readily react with homophthalic anhydride under mild conditions in the presence of non-nucleophilic bases to yield complex lactam products with high diastereoselectivity. Furthermore, it was discovered that sulfonimidamide imines react with homophthalic anhydride in the absence of a base to yield distinct diastereomer products with high diastereoselectivity. Density functional theory calculations suggest the existence of an open transition state pathway in the presence of base and a novel cyclic eight-membered transition state in the absence of base.

Sulfonimidamides have gained popularity as useful substrates in medicinal chemistry due to their stereogenicity and ability to serve as isosteres for sulfonamides, carboxylic acids, and pseudopeptides along with an expanding list of functional group replacements.[1−10] Although applications of sulfonimidamides outside of therapeutic use are less common, they have been used as ligands in asymmetric catalysis, novel superacids, useful ionic polymer electrolytes, and chiral amine auxiliaries.[11−17] Recent methodology has focused on the preparation of enantiomerically enriched sulfonimidamides as well as the development of new reactions using them as substrates.[18−20] Many methods for the synthesis and functionalization of sulfonimidamides have been developed, but the ability of the stereogenic sulfur center to influence diastereoselective reactions remains largely unexplored. Although *N*-sulfinyl imines and *N*-sulfonyl imines are broadly employed, only a single report describing the synthesis of sulfonimidamide imines has been reported.[17,21,22]

Reactions of imines with cyclic anhydrides, initially pioneered by Castagnoli and Cushman, have been used in the synthesis of a diverse array of complex lactam products containing multiple stereogenic centers (Figure 1).[23,24] Castagnoli observed that succinic anhydride reacted with imines derived from aldehydes and primary amines at a high temperature. Cushman later described the reactivity of

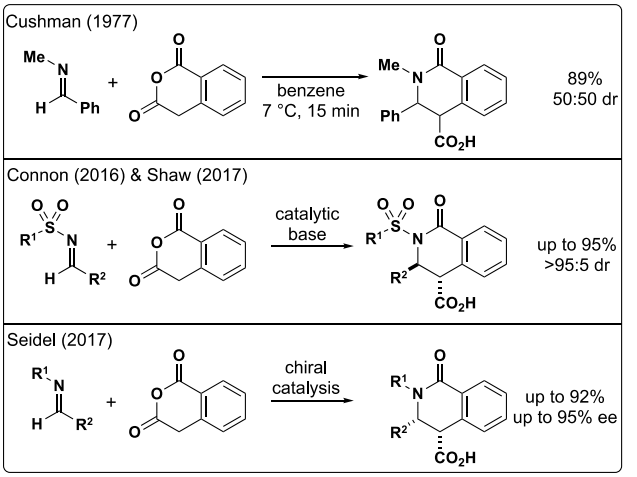

Figure 1. Known strategies to access substituted lactams via the Castagnoli–Cushman reaction (CCR).

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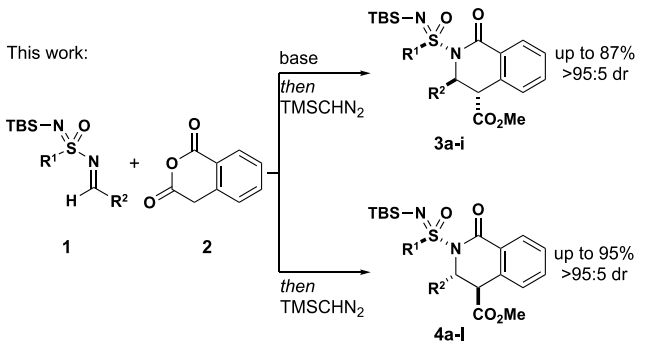
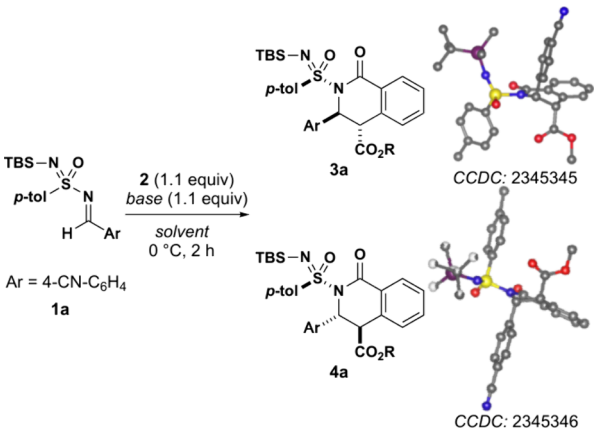


Figure 2. Stereodivergent synthesis of complex sulfonimidoyl lactams via the Castagnoli–Cushman reaction.

Table 1. Optimization and Discovery of the Base-Mediated Stereodivergent Conditions



entry	base	solvent	dr (3a:4a)	yield (%)
1	NEt_3	toluene	75:25	–
2	NEt_3	THF	86:14	–
3	NEt_3	CH_2Cl_2	77:23	–
4	NEt_3	EtOAc	85:15	–
5	NEt_3	$CHCl_3$	87:13	–
6	DBU	$CHCl_3$	62:38	–
7	TMG	$CHCl_3$	61:39	–
8	DABCO	$CHCl_3$	82:18	–
9	TMEDA	$CHCl_3$	62:38	–
10	n/a	$CHCl_3$	>5:95	91[a]
11	n/a	toluene	>5:95	93[b]
12	NEt_3[c]	$CHCl_3$	>95:5	87[a]

[a]Isolated yield (0.1 mmol scale) as the methyl ester after treatment of the crude material with (trimethylsilyl)diazomethane (1.5 equiv). [b]Isolated yield (1.0 mmol scale) as the free carboxylic acid. [c]**2** was prestirred in the presence of base.

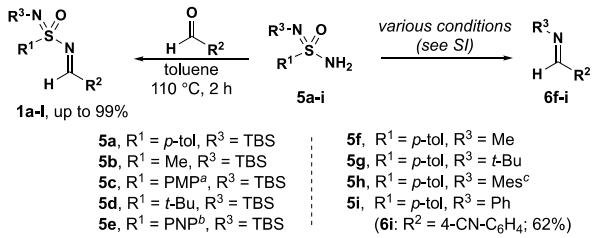
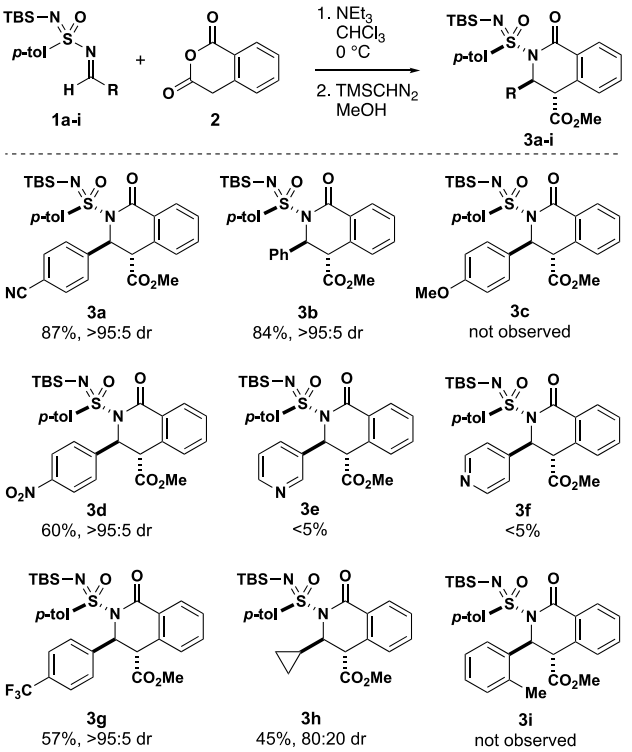


Figure 3. Synthesis of sulfonimidamide-derived imines. See the SI for details. [a]PMP = *p*-methoxyphenyl. [b]PNP = *p*-nitrophenyl. [c]Mes = 2,4,6-trimethylbenzene.

Table 2. Substrate Scope for the Anhydride Enolate Reaction Conditions[a]



[a]Reaction conditions: anhydride **2** (0.11 mmol) and triethylamine (0.11 mmol) with imine **1** (0.10 mmol) in $CHCl_3$ (0.5 mL) at 0 °C for 2 h. See the SI for details.

homophthalic anhydrides with similarly basic imines under mild conditions, a reaction that has been widely employed for natural product synthesis and drug discovery.[25−28]

Subsequent investigations into the mechanism of this reaction revealed that less enolizable anhydrides react by a Mannich-like mechanism through a closed transition state via the enol tautomer of the anhydride.[29,30] More readily enolizable anhydrides, including homophthalic anhydride, undergo proton transfer to form an iminium ion and anhydride enolate which reacts through an open transition state.[31] Imines substituted with electron-withdrawing groups, such as *N*-sulfonyl imines, participate in the Castagnoli–Cushman reaction (CCR) in the presence of base.[32] The addition of base allows the formation of an anhydride enolate that attacks the electron-deficient imine. Predictably, in the absence of base there is no enolate formation, and no reaction occurs. The recognition of base catalysis prompted many attempts to control the enantioselectivity.[33] Ultimately *N*-aryl and *N*-*tert*-butyl imines, which avoid the high background reaction rates of *N*-alkyl imines, proved to be optimal for the development of a highly enantioselective reaction using chiral hydrogen-bonding catalysts.[34]

We recognized that the CCR offered the dual opportunity to access *N*-sulfonimdoyl lactam products, a previously inaccessible motif, and to explore how sulfonimidamides influence the diastereoselectivity. Although sulfonimidamide imines have scarcely been reported as reaction substrates, we hypothesized their reactivity to be a hybrid between those of *N*-sulfonyl and *N*-alkyl imines. Additionally, the S chirality of sulfonimidamides suggests the possibility of diastereomeric control in the

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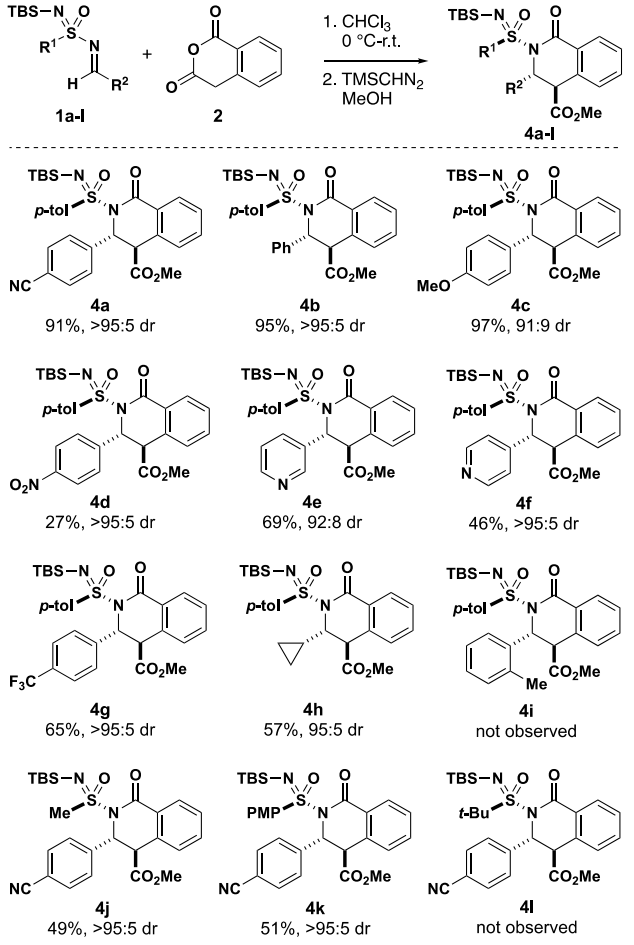
Table 3. Substrate Scope for Base-Free Anhydride Enol Reaction Conditions[a]



[a]Reaction conditions: imine **1** (0.10 mmol) and anhydride **2** (0.11 mmol) in $CHCl_3$ (0.5 mL) at 0 °C for 2 h. See the SI for details.

CCR. Herein we further develop the synthesis of sulfonimidamide imines and describe the divergent reactivity of sulfonimidoyl imines in the CCR. We report the unprecedented stereochemical control of sulfonimidamide imines in the CCR and demonstrate reactivity in both base-mediated enolate and base-free enol conditions with complementary stereochemical outcomes (Figure 2). We further disclose density functional theory (DFT) calculations for each observed pathway that support a novel eight-membered cyclic transition structure for the base-free pathway.

Initial investigation into the CCR of sulfonimidamide-derived imines examined the reactivity of homophthalic anhydride (**2**) under basic conditions, as has been previously reported with *N*-sulfonyl-derived imines (Table 1). Non-nucleophilic bases were carefully chosen based on previously reported use as well as taking into account that **2** has a reported pK_a of 8.15.[35] Initial success was observed when imine **1a** was reacted with **2** under a mild excess of triethylamine in several different solvents. These conditions yielded the respective sulfonimidamide lactams **3a** and **4a** with modest to good diastereoselectivity. Exploration of various amine bases in chloroform initially showed no improvement in yield or stereoselectivity. Surprisingly, in the absence of any base or additional additives, a complete reversal of diastereoselectivity was observed, and lactam **4a** was produced

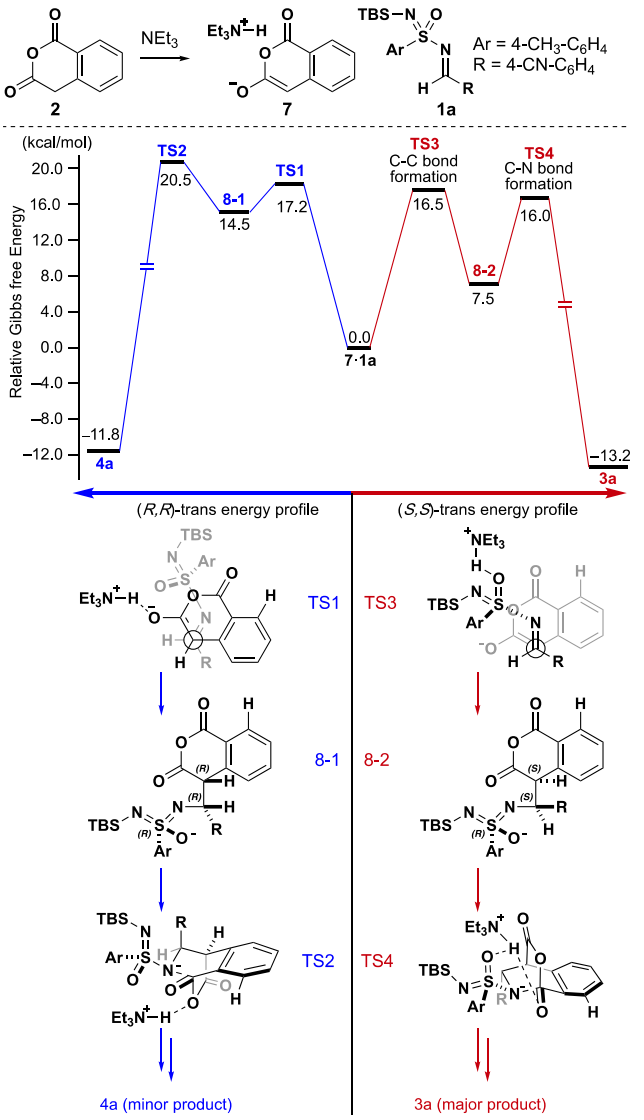


Figure 4. Potential energy profile at 25 °C and transition structures for the anhydride enolate pathway with imine **1a**. For computational details, see the SI.

in a good yield with excellent diastereoselectivity within 2 h (Table 1, entries 10 and 11). These results suggested that two pathways were present: one that was base-dependent and one that was base-free, each leading to a different major diastereomer. A further series of experiments led to the discovery that conversion of **2** to its enolate form by premixing it in a solution of solvent with base prior to the addition of imine **1a** maximized the diastereoselectivity to favor the formation of lactam **3a** (Table 1, entry 12). The diastereoselectivity of this process was measured by comparing the integration of lactam ring signals in the ^{1}H NMR spectra of the crude reaction mixtures. The pure diastereomers were isolated after conversion to their methyl esters with (trimethylsilyl)diazomethane. The relative stereochemistry of these products was assigned by X-ray crystallography, which shows each product to have an *anti* configuration between the two ring substituents and complementary relationships to the sulfonimidamide configuration.

A series of imines were prepared from accessible sulfonimidamides to investigate the scope of this CCR

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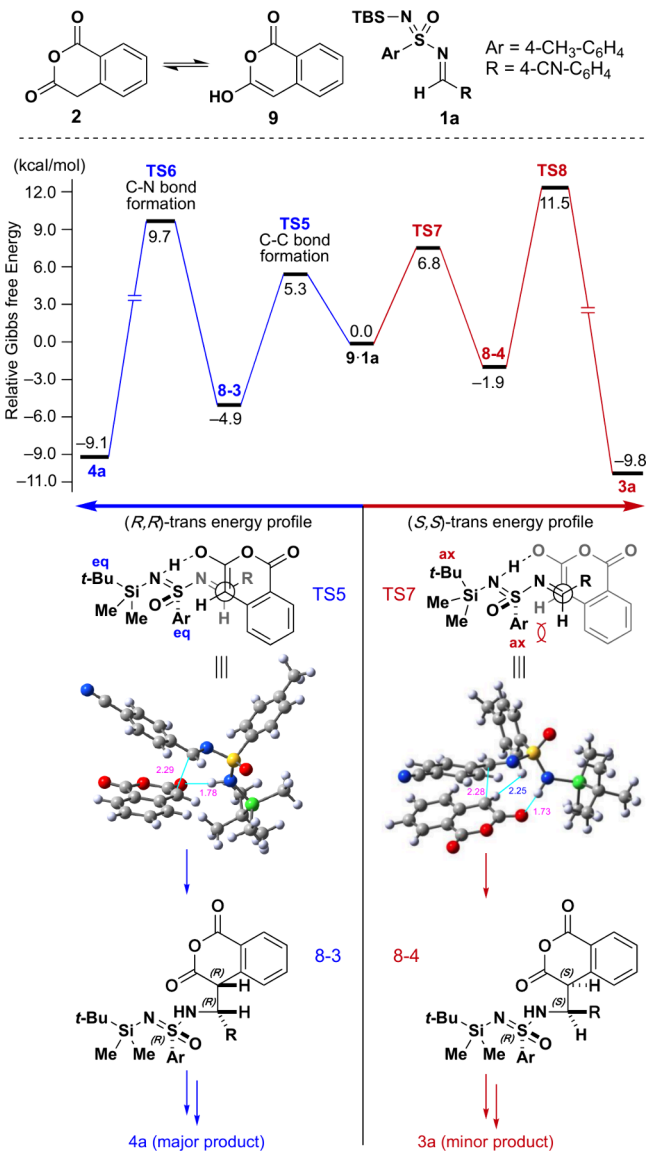

Figure 5. Potential energy profile at 25 °C and transition structures for the anhydride enol pathway with imine **1a**. For computational details, see the SI.

variant.[36] These substrates were accessed by refluxing the primary *N*-silyl sulfonimidamides **5a**–**e** with each respective aldehyde in toluene to yield the respective imines **1a**–**l** in excellent yield (Figure 3). Aromatic and non-enolizable alkyl imine substituents were well-tolerated and isolable. Attempts to form imines with enolizable side chains led to complex mixtures and no isolable imine products. In addition, attempts to synthesize the corresponding *N*-alkyl or *N*-aryl sulfonimidoyl imine products by condensing **5f**–**i** with various aldehydes proved to be unsuccessful under a wide variety of conditions. The major products of these reactions were imines **6f**–**i**, which were formed between the aldehyde and the alkyl or aryl imines. Although this is poorly understood, liberation of amines from sulfonimidamides has been previously reported.[37]

A series of imine substrates were examined in base-mediated reactions with homophthalic anhydride (**3a**–**h**, Table 2). In each case, a solution of **2** that had been pretreated with triethylamine was added to a solution of imine at 0 °C. Substrates derived from benzaldehyde and analogs with *para* electron-withdrawing substituents formed the expected lactam products with high diastereoselectivity. Conversely, imines derived from heteroaryl aldehydes showed trace lactam products as well as the formation of byproducts in the ^{1}H NMR spectrum. Although most aliphatic aldehydes could not be used to form imines, the sulfonimidoyl imine of cyclopropane carboxaldehyde formed the lactam product in modest yield and diastereoselectivity. Imines **1j**–**l** derived from variations to the S substituents failed to react with **2** to form any discernible lactam products. The stark contrast in reactivity observed suggests that the base-mediated reaction depends on close alignment of the enolate nucleophilicity and the electronic character of the imine.

The base-free reactions of **2** exhibited a broad substrate scope leading to lactams with excellent diastereoselectivity observed (Table 3). In the absence of a base, **2** readily reacted with electron-deficient as well as electron-rich aryl substituents. Unlike the base-mediated reaction, pyridyl substrates formed lactams **4e** and **4f** with high diastereoselectivity. Imines derived from variations in the S substituents formed lactams **4j** and **4k**, albeit in moderate yield. Several electron-deficient imines derived from sulfonimidamide **5e**, in which the *p*-tolyl group is replaced by *p*-nitrophenyl, formed lactam products as detectable by ^{1}H NMR spectroscopy but seemed to be chemically unstable and could not be isolated.

To better understand the role of the sulfonimidamide and how the substituents influence the diastereoselectivity in these two reaction conditions, we performed DFT calculations at the B3LYP-D3/6-31+G(d),SCRF($CHCl_3$)//B3LYP-D3/6-31+G(d) level. It was hypothesized that the observed stereochemistry originates from the addition of anhydride **2** to the respective imine, of which there are four possible diastereomer lactam products. The speculative (*R*,*S*)-*cis* and (*S*,*R*)-*cis* lactams were not observed under either reaction condition regardless of the presence of a base. This selectivity is explained by a steric clash between the S substituent and the imine aryl ring (see the Supporting Information (SI)).

In the presence of a base, anhydride **2** is deprotonated to form enolate **7**, which reacts with imine **1a** in an open transition state (Figure 4). C–C bond formation is facilitated by hydrogen bonding of the protonated triethylammonium and the sulfoxide of the sulfonimidamide (**TS3**, Figure 4). This interaction lowers the energy of the transition structure relative to **TS1** and allows the addition into the imine. With the newly formed stereocenters set in intermediate **8-2**, C–N bond formation occurs while the triethylammonium facilitates addition into the carbonyl with hydrogen bonding to the anhydride carbonyl oxygen via **TS4**. C–N bond formation is followed by cleavage of the C–O bond promoted by the triethylammonium ion to ultimately yield the lower-energy (*S*,*S*)-*trans* lactam product **3a.**

In transition structure **TS1**, which leads to the formation of lactam **4a**, hydrogen-bonding interactions between the triethylammonium ion and the carbonyl of the anhydride lower the nucleophilicity of the enolate. Additionally, nucleophilic addition to the carbonyl of the anhydride via **TS2** occurs with higher energy due to steric congestion provided by the imine substituent, which limits hydrogen-bonding interactions to the anhydride. C–O bond cleavage ultimately occurs to form the lactam, leading to **4a**.

In the absence of a base, anhydride **2** reacts as the neutral enol tautomer (**9**, Figure 5). This nucleophile will undergo proton transfer from the enol oxygen to the sulfur imide

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nitrogen in a novel eight-membered cyclic closed transition structure **TS5**, in which C−C bond formation yields intermediate **8-3**. Upon rotation around the newly formed C−C bond, C−N bond formation occurs simultaneously with the transfer of the N−H proton to the carbonyl oxygen to yield a tetrahedral intermediate. C−O bond cleavage is mediated by a proton transfer assisted by water and ultimately forms the observed (*R*,*R*)-*trans* lactam **4a**.

Formation of the minor (*S*,*S*)-*trans* lactam **3a** was found to have a higher energy in the respective eight-membered cyclic transition structure **TS7**. This arises from the significant steric clash between the axial aryl S substituent and the anhydride, while the large TBS group is in a less favorable axial position. C−N bond formation occurs with a higher-energy transition structure, **TS8**, but ultimately leads to the lower energy (*S*,*S*)-*trans* lactam product, **3a**. Both pathways shown in Figure 5 are governed by C−N bond formation as the rate-determining step. **TS6** and **TS8** are separated by 1.77 kcal/mol at 25 °C, and ultimately, the formation of the major lactam product, **4a**, is favored (see the SI).

In summary, we have demonstrated that sulfonimidoyl imines undergo highly diastereoselective CCR reactions with homophthalic anhydride. In the presence of a non-nucleophilic base, homophthalic anhydride is deprotonated to the enolate form and reacts with sulfonimidamide imines to yield one major diastereomer out of the four that are possible. In the absence of base, completely complementary reactivity is observed, as homophthalic anhydride reacts via its enol form in a closed cyclic transition state to yield the corresponding *trans* diastereomer.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c04648.

Experimental procedures, X-ray crystallography data, computational data, and NMR spectra (PDF)

Accession Codes

Deposition numbers 2345345 and 2345346 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Author Contributions

M.S.: Writing—original draft, Writing—review and editing, Validation, Methodology, Investigation, Formal analysis, Visualization, Data curation, Conceptualization. J.C.F.: X-ray crystal structure analysis. K.A.: Software, Resources, Methodology, Validation. J.T.S.: Writing—review and editing, Supervision, Funding acquisition.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

THF, tetrahydrofuran; TEA, triethylamine; DBU, 1,8-diazobicyclo[5.4.0]undec-7-ene; TMG, tetramethylguanidine; DABCO, 1,4-diazabicyclo[2.2.2]octane; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; PMP, *p*-methoxyphenyl; PNP, *p*-nitrophenyl

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