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Synthetic Methods

Cycloadditions of Donor–Acceptor Cyclopropanes and -butanes using S=N-Containing Reagents: Access to Cyclic Sulfinamides, Sulfonamides, and Sulfinamidines

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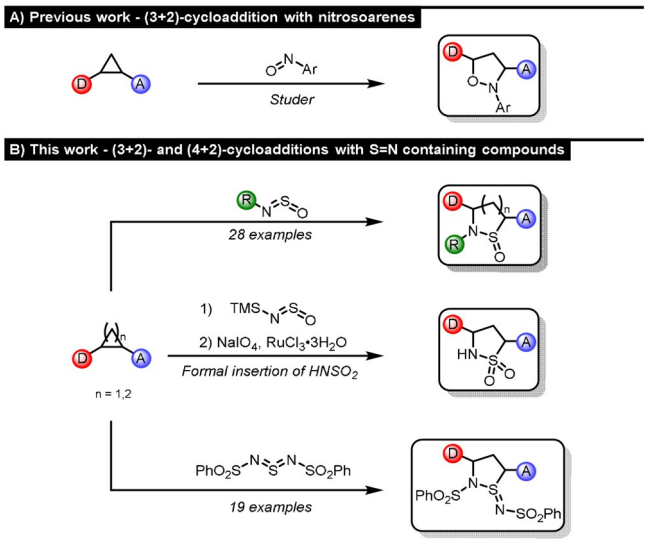
Abstract: *We present (3+2)- and (4+2)-cycloadditions of donor–acceptor (D–A) cyclopropanes and cyclobutanes with N-sulfinylamines and a sulfur diimide, along with a one-pot, two-step strategy for the formal insertion of $HNSO_2$ into D–A cyclopropanes. These are rare examples of cycloadditions with D–A cyclopropanes and cyclobutanes whereby the 2π component consists of two different heteroatoms, thus leading to five- and six-membered rings containing adjacent heteroatoms.*

Introduction

Donor–acceptor (D–A) cyclopropanes are versatile three-carbon building blocks. Their relatively high ring-strain ($\approx$115 kJ mol^{-1}),[1] together with the strongly polarized carbon-carbon bond, leads to their widespread use as 1,3-zwitterionic synthons in organic synthesis and methodology.[2] D–A cyclopropanes are known to undergo (3+2)-cycloaddition reactions with a variety of hetero-2π components,[3] such as aldehydes,[4] ketones,[5] imines,[6] and thiocarbonyl compounds.[7] To the best of our knowledge, there is only one example of a (3+2)-cycloaddition to D–A cyclopropanes where the 2π component consists of two different heteroatoms, namely the synthesis of isoxazolidines by reaction with nitrosoarenes as achieved by the Studer group (Scheme 1).[8]

Sulfur has been a popular choice of heteroatom for the reactions of D–A cyclopropanes,[9] not only because of its reactivity, but also its prevalence in important pharmaceutical compounds and natural products.[10] Sulfinylamines have recently been utilized heavily by Willis and co-workers[11] as stable starting materials for the synthesis of both sulfur(IV) and sulfur(VI) containing compounds including sulfilimines,[12] sulfonamides,[13] and sulfonimidamides.[14] Inspired by this, we decided to explore the use of the S=N double bond of sulfinylamines as a 2π component in the $(n+2)$-cycloaddition reactions of D–A cyclopropanes and D–A cyclobutanes. Ease of synthesis makes sulfinylamines an attractive choice of starting material, particularly because of the possibility of having a leaving group at the nitrogen atom, thus allowing formal insertion of $HNSO_2$ upon cleavage and oxidation. We further envisaged that a sulfur diimide would be able to undergo a similar cycloaddition reaction, resulting



Scheme 1. A) Previous (3+2)-cycloaddition of D–A cyclopropanes with two different heteroatoms as a 2π component. B) Our (3+2)- and (4+2)-cycloadditions utilizing S=N double bonds as 2π components.

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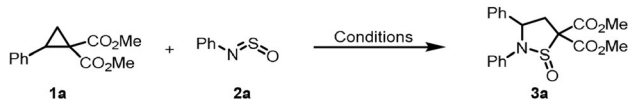
in *S*-imino isothiazolidines. These isothiazolidine products are potentially of great interest as bioactive compounds, with isothiazolidine dioxides and isothiazolidinones already known to be useful as antirheumatic and anticancer agents.[15] While syntheses for sultams are relatively common,[16] very few are known for *S*-oxo isothiazolidines, and the requirement for radical initiators such as AIBN, or lengthy starting material synthesis makes them a less attractive route.[17] To our knowledge, we present the first synthesis of *S*-imino isothiazolidines.

Results and Discussion

We initially chose cyclopropane **1a** and *N*-sulfinylamine **2a** as model substrates, and investigated the viability of this transformation using various reaction conditions and Lewis acids (Table 1). At room temperature in dichloromethane, we found $GaCl_3$ to be by far the most effective Lewis acid to afford the desired reactivity; however, the harshness of this reagent also afforded significant amounts of cyclopropane dimerization and lactonization products among other side reactions.[18] Choosing $GaCl_3$ meant that a stoichiometric amount of Lewis acid would be required, as binding to the sulfinyl group remains after the reaction has taken place, effectively removing the reagent from the system. A change of solvent to 1,2-dichloroethane saw a slight increase in yield (entry 7), and it was noted that chlorinated solvents are required for good reactivity, however the most crucial condition was the temperature at which the reaction was initiated. At temperatures below 0 °C it was possible to maximize product formation while shutting down other undesirable reactions. We found −20 °C to be the best temperature for combining the reagents (entry 10), while allowing the reaction to warm up slowly to room temperature over 22 h allowed for increased diastereoselectivity (entry 12). Because of the moisture sensitivity of $GaCl_3$, and of *N*-sulfinylamine **2a**, reaction mixtures and stock solutions of $GaCl_3$ were prepared in a glovebox and sealed before being removed and (where applicable) cooled. A slight excess of $GaCl_3$ was found to be beneficial for the yield of the reaction, probably because of its stronger ability to coordinate to the sulfinyl than to the carbonyl group. For the reaction to take place, an enhanced Lewis acidity, induced by dimerization or homolytic splitting of $GaCl_3$ (see below), appears to be required to afford the active chelated malonate species.

Table 1: Optimization of the reaction conditions[a] for formation of isothiazolidine *S*-oxides.



1a **2a** **3a**

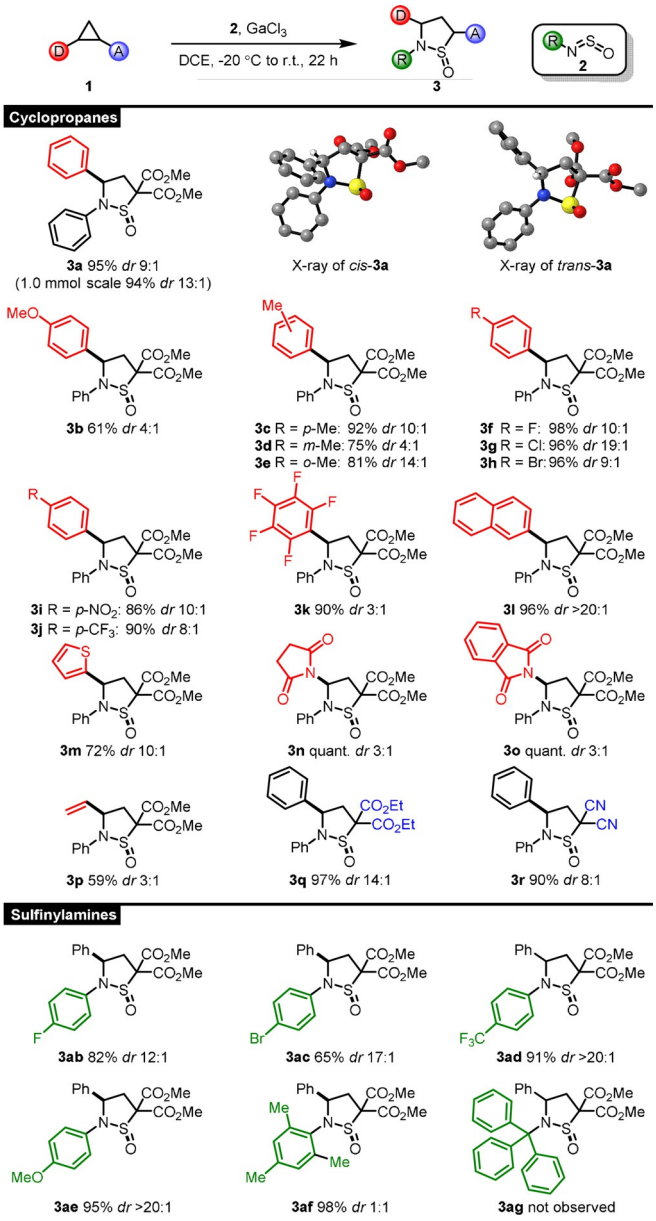
Entry	Lewis Acid	Solvent	*T* [°C]	Yield[b] [%]	dr[c]
1[d]	$AlCl_3$	DCM	r.t.	23	13:1
2[d]	$GaCl_3$	DCM	r.t.	60 (56)	9:1
3[d]	$InCl_3$	DCM	r.t.	n.d.	–
4[d]	$SbCl_5$	DCM	r.t.	37	9:1
5[d]	$SnCl_4$	DCM	r.t.	19	5:1
6	$GaCl_3$	DCM	r.t.	64	11:1
7	$GaCl_3$	DCE	r.t.	69	9:1
8	$GaCl_3$	$CHCl_3$	r.t.	38	12:1
9	$GaCl_3$	DCE	−10	89	5:1
10	$GaCl_3$	DCE	−20	94	5:1
11	$GaCl_3$	DCE	−30	93	4:1
12[e]	**$GaCl_3$**	**DCE**	**−20 to r.t.**	**(95)**	**9:1**

[a] Reaction conditions: **1a** (100 μmol), **2a** (200 μmol), Lewis acid (120 μmol), solvent (1 mL), setup in a glovebox under Ar, 16 h. [b] Yields refer to ^{1}H NMR yields; yields in parentheses refer to yields of isolated and purified products. [c] *dr* refers to *dr* calculated by ^{1}H NMR. [d] 100 μmol Lewis acid was used. [e] 22 h. DCE = 1,2-dichloroethane.

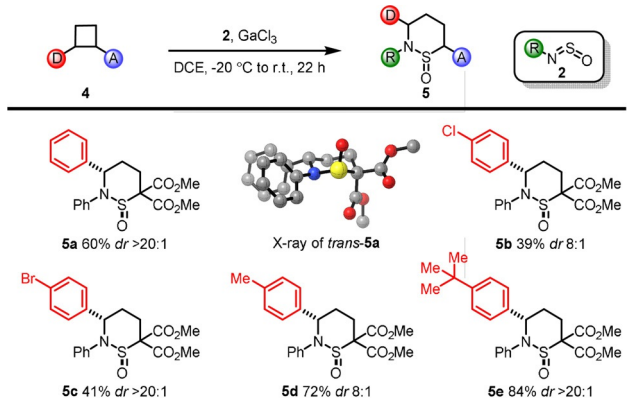
With optimized conditions in hand, we examined the scope of this (3+2)-cycloaddition (Scheme 2); a broad range of D–A cyclopropanes were tested using the reaction conditions. Methoxy substitution at the *para*-position somewhat lowered the yield; however, this was expected through coordination to the $GaCl_3$ by the methoxy group. Methyl substitution at the *ortho*-, *meta*-, and *para*-positions was well tolerated, giving the desired products **3c–e** in good to excellent yields and moderate to good diastereoselectivity. Compounds halogenated at the *para*-position **3f–h** gave 96–98% yield and *dr* ranging from 9:1 to 19:1, while decorating the aromatic ring with stronger electron-withdrawing groups also allowed very good yields (**3i**: 86%, *dr* 10:1; **3j**: 90%, *dr* 8:1), although in the case of the highly electron-withdrawing pentafluorophenyl group **3k** the *dr* fell to 3:1. The extended π-system of the naphthyl group led to an excellent yield and diastereoselectivity, and heteroaromatic system **3m** was found to give 72% yield and a *dr* of 10:1. Nitrogen-containing heterocyclic donors as introduced by Waser[19] allowed quantitative yields of the reaction, albeit with poor diastereoselectivity. Isothiazolidine **3p** bearing a vinyl substituent was obtained in a yield of 59% (*dr* 3:1). Changing the acceptor moieties to the ethyl ester **3q** or nitrile groups **3r** afforded the desired transformation in excellent yields and good diastereoselectivity. Scaling up the reaction (1.0 mmol) using cyclopropane **1a** as starting material gave an almost identical yield to our original small scale reaction, and enhanced the diastereoselectivity to 13:1.

Next, we investigated the scope with respect to the *N*-sulfinylamine. Simple changes to the system such as addition of a halogen at the *para*-position were tolerated in good yields (**3ab** and **3ac**). Electron-withdrawing (**3ad**) and electron-donating (**3ae**) groups both resulted in excellent yield and *dr*. The more sterically bulky mesitylene derived system gave excellent yield, albeit with no diastereoselectivity (**3af**). In all cases the *cis*-diastereomer was obtained as the major component. Application of more specialized systems, such as those pioneered by the Willis group (TrNSO, *t*OctNSO, *t*BuONSO) was unsuccessful. We suggest that the steric bulk of TrNSO and *t*OctNSO caused the lack of reactivity, while the electronic properties of *t*BuONSO were almost certainly too different from those required for our optimized system.

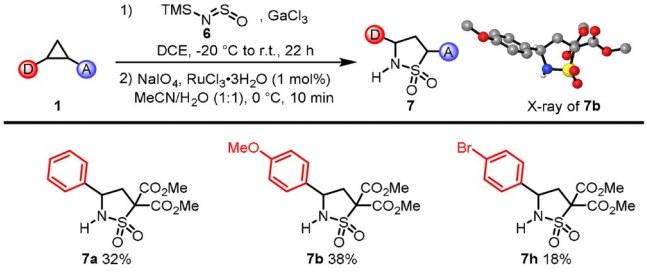
Because of previous reports of D–A cyclobutanes displaying similar reactivity to D–A cyclopropanes,[21] we investigated the potential (4+2)-cycloaddition to produce 1,2-thiazenanes using the same conditions (Scheme 3). Interestingly, we observed that the diastereoselectivity in this case favored the *trans*-products. Use of phenyl cyclobutane gave



Scheme 2. Scope of the (3+2)-cycloaddition of D–A cyclopropanes with *N*-sulfinylamines, the *cis*-diastereomer (shown) is the major product in all cases.[20]



Scheme 3. Scope of the (4+2)-cycloaddition of D–A cyclobutanes with *N*-sulfinylamines, the *trans*-diastereomer (shown) is the major product in all cases.[20]



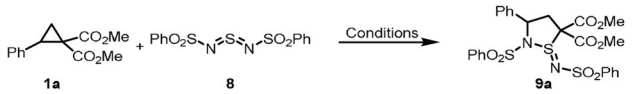
Scheme 4. Formal insertion of $HNSO_2$.

moderate yield and excellent *dr* (**5a**), while halogenation decreased the yield to 39 and 41% (**5b** and **5c**). Alkyl substitutents at the *para*-position provided very good yields, with the *tert*-butyl example also displaying a *dr* of >20:1.

Having established that our procedure was effective for the formation of *N*-aryl isothiazolidines and thiazinanes, we were keen to apply a similar system for the formal insertion of $HNSO_2$ into a D–A cyclopropane. Pleasingly, application of the trimethylsilyl sulfinylamine **6** synthesized by Parkes and Woollins in 1989,[22] followed by a modified Ley oxidation[23] gave these γ-sultams **7** in mediocre yields (Scheme 4), providing proof of concept. The intermediate TMS-substituted isothiazolidine was not isolable; however, it was observed by LC-MS, and therefore we can state that cleavage occurs during the oxidation step. TMSNSO is a rather unstable molecule, and therefore we propose that the more activated *para*-methoxy substituted compound **7b** gave the best yield (38%) by virtue of the reaction taking place more quickly, therefore minimizing decomposition and unwanted side reactions.

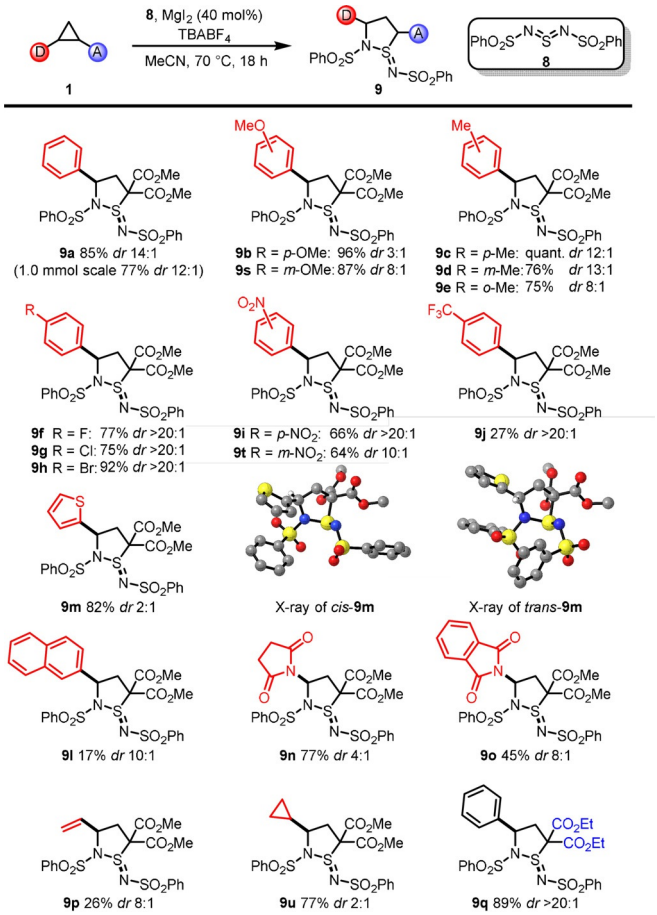
With the successful cycloadditions of *S*-oxo reagents to D–A cyclopropanes in hand, we turned our attention to *S*-imino systems. For this, we employed a sulfur diimide reagent **8** that has recently been the focus of several studies in the Tambar group.[24] For this transformation, a new catalytic system was required; therefore, we began a thorough screening and optimization procedure (Table 2). It was found that only MgI_2 and $AlCl_3$ gave any appreciable yield of the desired product. Further reactions established that 40 mol% was the optimal catalyst loading, and a temperature of 70 °C (entry 5) was required for efficient conversion of the starting material. Increasing the sulfur diimide equivalents to 2.5 (entry 6) and changing the solvent to MeCN (entry 7) delivered significant increases in yield; however no further increase was possible beyond 75% until we investigated the effect of additives on the reaction. $TBABF_4$ was found to be effective in increasing the yield, although some diastereoselectivity was lost. The mode of action of this additive is not clear to us, and we abstain from speculation. The choice of cation appeared to make very little difference to the reactivity (entries 10 and 11), BF_4^- was however far more effective than other anions. A 2:1 ratio of additive to Lewis acid was found to be optimal (entry 12), and further attempts to reduce catalyst and additive loading were found to decrease the yield.

Table 2: Optimization of the reaction conditions[a] for formation of *S*-imino isothiazolidines.



Entry	Lewis Acid	Additive	Solvent	*T* [°C]	Yield[b] [%]	dr[c]
1[d,e]	$AlCl_3$	None	DCE	r.t.	7	>20:1
2[d,e]	$GaCl_3$	None	DCE	r.t.	n.d	–
3[d,e]	MgI_2	None	DCE	r.t.	14	>20:1
4[e]	MgI_2	None	DCE	r.t.	40	>20:1
5[e]	MgI_2	None	DCE	70	62	>20:1
6	MgI_2	None	DCE	70	64	>20:1
7	MgI_2	None	MeCN	70	71	>20:1
8[f]	MgI_2	None	MeCN	70	75	>20:1
9[f]	MgI_2	$TBABF_4$	MeCN	70	79 (76)	12:1
10[f]	MgI_2	$TBAPF_6$	MeCN	70	67	10:1
11[f]	MgI_2	KPF_6	MeCN	70	65	12:1
12[f,g]	**MgI_2**	**$TBABF_4$**	**MeCN**	**70**	**90 (85)**	**12:1**

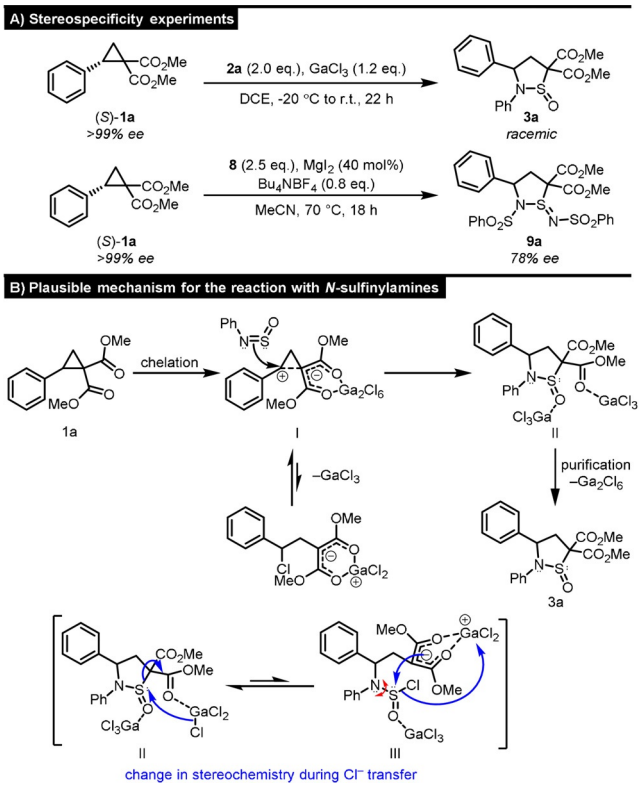
[a] Reaction conditions: **1a** (100 µmol), **8** (250 µmol), Lewis acid (40 µmol), additive (40 µmol), solvent (1.5 mL), setup in a glovebox under Ar, 18 h. [b] Yields refer to ^{1}H NMR yields; yields in parentheses refer to yields of isolated and purified products. [c] *dr* refers to *dr* calculated by ^{1}H NMR. [d] 10 µmol Lewis acid. e] 150 µmol **8**. [f] 1 mL solvent. [g] 80 µmol additive. DCE = 1,2-dichloroethane. TBA = tetra-*n*-butylammonium.



Scheme 5. Scope of the (3+2)-cycloaddition forming *S*-imino isothiazolidines, the *cis*-diastereomer (shown) is the major product in all cases.[20]

A broad range of D–A cyclopropanes were then exposed to the optimized conditions in order to investigate the scope of this reaction (Scheme 5). *para*- and *meta*-methoxy-substituted compounds **9b** and **9s** were obtained in excellent yields, albeit with low *dr*. A methyl substitutent at the *para*-position **9c** gave a quantitative yield (*dr* 12:1), and the *meta*- and *ortho*-methyl products **9d** and **9e** were available in good yields. *para*-Halogenated cyclopropanes furnished the corresponding isothiazolidines **9f–9h** in yields of 75–92% with *dr* >20:1. The electron-withdrawing nitro substituent was tolerated in both *para*- and *meta*-position, a *para*-trifluoromethyl group, however, considerably decreased the yield to 27% (*dr* >20:1). The extended π-system of the naphthyl group was also only poorly tolerated. Heterocycles **9m**, **9n** and **9o** showed varying levels of success, with yields ranging from 45–82% and poor diastereoselectivity. Vinyl **9p** and cyclopropyl **9u** substituents showed drastically different reactivity, with the former giving 26% yield and 8:1 *dr*, and the latter providing a 77% yield with poor diastereoselectivity. Ethyl esters as the acceptor moiety **9q** were well tolerated giving very good yield and *dr*. Overall, we noticed a tendency for electron-poor aromatic systems and larger donor groups to give poorer yields, whereas electron-rich aromatic systems were higher yielding.

To shed some light on the mechanisms of these reactions, we subjected enantioenriched cyclopropane (*S*)-**1a** (>99% *ee*) to the reaction conditions (Scheme 6A). In the case of the reaction with N-sulfinylamines no baseline separation of the enantiomers was possible by chiral HPLC; however, upon oxidation to product **10** it was possible to observe baseline separation of the enantiomers. Complete loss of stereoinformation is observed in this reaction, giving a racemic mixture of sultam **10**. This observation is in agreement with the literature regarding $GaCl_3$ mediated reactions of D–A cyclopropanes.[18] Further reactions to determine which reaction conditions facilitate the change in *dr* were then completed (see SI for details). Our quantum chemical investigation employing density functional theory (DFT) calculations show a metastable ring-opened zwitterionic intermediate (see SI for details).[25] Here, malonate chelation by a $GaCl_2^+$ cation coincides with the binding of the chloride anion to the carbon stereocenter. Given the relative stability of this intermediate ($\Delta G = +21$ kJ mol^{-1}) and availability of additional Lewis acid in the mixture, further chloride anion transfers are possible which then cause the change of the stereoinformation. Therefore, we propose the mechanism shown in Scheme 6B. Via chloride transfer in **I**, chelation becomes possible in the zwitterion. Here, a nucleophilic attack by the lone pair of the sulfinylamine nitrogen is possible. In this step, the chloride anion is transferred back to the $GaCl_2^+$, chelation is lifted and cyclization is completed by attack from the negatively charged acceptor end of the molecule to the sulfur atom. Alternatively, the sulfur atom of the sulfinylamine may perform an electrophilic attack of the central malonate carbon atom with subsequent cyclization. We find that, thermodynamically, the *cis* form of **3a** is more stable by 10 kJ mol^{-1}. However, before quenching, $GaCl_3$ remains bound to the molecule, preferentially to the sulfinyl

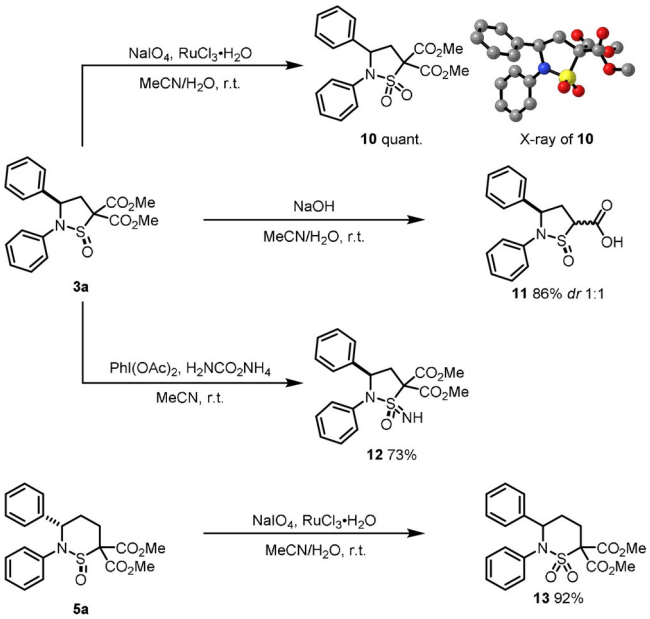


Scheme 6. A) Stereospecificity experiments. B) Plausible mechanism for the reaction of D–A cyclopropanes with *N*-sulfinylamines.

group. For this adduct, the *trans* form becomes more stable than the corresponding *cis* adduct by 4 kJ mol^{-1}. Hence, the observed behavior at elevated temperature (entry 12 in Table 1) indicates a shift of the *dr* due to other effects than just the thermodynamic equilibrium. Via a second $GaCl_3$ molecule and subsequent chloride transfer, chelation can again take place and, therefore, cleave the C–S bond. This time, it is the partially positively charged sulfur atom that functions as the chloride acceptor. Upon warming to room temperature an equilibrium exists between the closed (II) and opened (III) configurations. Due to the S–Cl bond in the open form, the S–N linkage allows an almost free rotation and chloride back transfer can then lead to the change of the chirality of the sulfinyl moiety. The free energy difference for the equilibrium between the open and closed form is lower for the *trans*-configuration than for *cis* by about 11 kJ mol^{-1}. This is in line with the observed increase in the *dr* at elevated temperature. At lower temperatures, this process appears to be hindered, presumably because of an insufficient concentration of the active open species. The lower energy of the *cis*-form appears to be because of a tendency for the S=O to occupy the axial position on the flap of the envelope conformation. This means that the C-aryl group is in a more pseudoequatorial position, whereas the *trans*-form has a more pseudoaxial C-aryl group, which is forced to be close to the axial ester group on the same face of the ring. The extra CH_2 unit in the six-membered ring means that no such interaction can occur, and a simple preference for the aryl group to be in the equatorial position explains the *trans*-selectivity. The inverted stability in the adducts appears to be attributable to repulsion of the $GaCl_3$ and the proximate phenyl ring in the *cis* configuration.

For the reaction with a sulfur diimide, baseline separation was indeed possible, and it was observed that only partial loss of stereoinformation occurred, giving the product with 78% *ee*. To understand this better, we stirred the enantioenriched cyclopropane (*S*)-**1a** (>99% *ee*) under the reaction conditions while excluding first the sulfur diimide, and secondly both the sulfur diimide and $TBABF_4$; in both cases we observed that complete racemization of the cyclopropane occurs, and therefore we propose that the reaction taking place does so without loss of stereoinformation, but that this is in competition with racemization induced by MgI_2. The reaction takes place too slowly to completely avoid this racemization, and therefore some loss of stereoinformation is seen in the products.

Finally, we demonstrated the utility of the reaction with *N*-sulfinylamines by subjecting products **3a** and **5a** to further selected transformations (Scheme 7). Pleasingly, both the (3+2)- and (4+2)-products were oxidized in excellent yields to the corresponding sultams by a modified Ley oxidation.[23] Hydrolysis and concomitant decarboxylation was realized using NaOH in a very good yield of 86%, although no diastereoselectivity was observed in this reaction. Cyclic sulfonimidamide **12** was provided in 73% yield when **3a** was stirred with excesses of PIDA and ammonium carbamate.[26]



Scheme 7. Follow-up chemistry. Single diastereomers of **3a** and **5a** used.[20]

Conclusion

In summary, we have developed a successful strategy for (3+2)- and (4+2)-cycloadditions of D–A cyclopropanes and D–A cyclobutanes with *N*-sulfinylamines, leading to a broad scope of five- and six-membered cyclic sulfinamides. Formal insertion of $HNSO_2$ into a D–A cyclopropane was achieved using a similar procedure, with a two-step one-pot approach

consisting of cycloaddition followed by oxidation and concomitant TMS cleavage. Furthermore, we were able to extend this chemistry to (3+2)-cycloadditions using a sulfur diimide as the S=N component. Mechanistic experiments showed complete racemization during the reaction with *N*-sulfinylamines, whereas the reaction with sulfur diimides occurs without loss of stereoinformation, although this process is in competition with scrambling of the stereocenter by the Lewis acid catalyst. Supported by DFT calculations, these results allowed us to tentatively propose a mechanism involving ring-opening induced by the Lewis acid and chloride transfer, which explains the observed diastereoselectivity.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: cycloadditions · cyclopropanes · donor–acceptor systems · sulfinylamines · sulfur diimide

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