ChemPubSoc Europe

DOI: 10.1002/chem.201303699

CHEMISTRY
A European Journal
Full Paper

Organic Synthesis

Stereoselective Lewis Acid Mediated (3+2) Cycloadditions of *N*-H- and *N*-Sulfonylaziridines with Heterocumulenes

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Abstract: Alkyl and aryl isothiocyanates and carbodiimides are effective substrates in (3+2) cycloadditions with *N*-sulfonyl-2-substituted aziridines and 2-phenylaziridine for the synthesis of iminothiazolidines and iminoimidazolidines. Additionally, the stereoselective (3+2) cycloaddition of *N*-H- and *N*-sulfonylaziridines with isothiocyanates can be accomplished, allowing for the synthesis of highly enantioenriched iminothiazolidines. Evidence for an intimate ion-pair mechanism is presented herein in the context of these chemo-, regio-, and diastereoselective transformations. The demonstrated ability to remove the sulfonyl group from the heterocyclic products displays the utility of these compounds for further derivatization and application.

Introduction

Aziridines are versatile intermediates and reaction partners for the preparation of a structurally diverse assortment of nitrogen-containing architectures.[1] These heterocycles are characterized by a unique reactivity profile, in part due to the large strain energy (27 kcal mol^{-1}) contained within their three-membered ring structure,[2] rendering them susceptible to nucleophilic ring opening,[3] carbonylation,[4] and ring expansion.[5] Previous work has shown the utility of 2-arylaziridines in transition metal-mediated and -catalyzed (3+2) cycloadditions with heterocumulenes for the formation of imidazolines,[6a–e] oxazolidines,[6d–e] iminoazolidinones,[6f–i] iminothiazolidines,[6i–k] and iminoimidazolidines.[6f,i] Iminothiazolidines and iminoimidazolidines have enjoyed broad application as effective organic catalysts in asymmetric transformations including Strecker reactions,[7a] O- and N-acylations,[7b–c] and Michael additions,[7d] and as highly active pharmacophores for the treatment of a wide range of medical conditions including obesity, diabetes, cancer, and arthritis.[8]

The critical limitation of the majority of the existing (3+2) cycloaddition manifolds is the requirement that aziridine starting materials bear either alkyl or aryl N-substitution. The harsh conditions necessary for the removal of such robust groups severely limits the potential for derivatization and, thus, the utility of the products. Despite this, the use of *N*-sulfonyl-protected aziridines in (3+2) cycloadditions has been explored minimally.[6a–e,k] In fact, only the work of Nadir and co-workers has examined the (3+2) cycloadditions of *N*-sulfonyl-2-arylaziridines with heterocumulenes.[6k,9] Their reaction system has a narrow scope and is only able to accommodate aryl isocyanates and aryl isothiocyanates, resulting in similarly limited product derivatization options. This transformation depends on the use of an alkali metal iodide as a noninnocent reaction partner; Nadir and co-workers explicitly demonstrate the formation of the ring-opened iodide intermediate prior to product formation.

Additionally, only a single example is known for the synthesis of enantioenriched iminothiazolidines by a stereoselective (3+2) cycloaddition[6i] despite readily available enantioenriched aziridine starting materials.[1,2,6h] This method, however, has an extremely narrow substrate scope, requiring the use of *N*-alkyl- or *N*-arylaziridines and aryl heterocumulenes. There are no examples of this transformation with *N*-sulfonyl-protected aziridines or more synthetically versatile heterocumulenes.

From this foundation, we sought to develop the first stereoselective Lewis acid mediated (3+2) cycloaddition reaction of *N*-sulfonyl-2-substituted aziridines and alkyl heterocumulenes. The Lewis acid mediated conditions would likely enable the use of a broad variety of heterocumulenes and consequently furnish readily derivatizable, highly enantioenriched heterocyclic building blocks.

Results and Discussion

Optimization of reaction conditions

Initial reaction development focused on the cycloaddition of *N*-tosyl-2-phenylaziridine (**1a**) with allyl isothiocyanate (Table 1). In contrast to our previous work on (3+2) cycloadditions of donor–acceptor cyclopropanes with heterocumulenes,[10] tin(II) triflate was found to be an ineffective Lewis acid mediator for the desired transformation (Table 1, entry 1). Alter-

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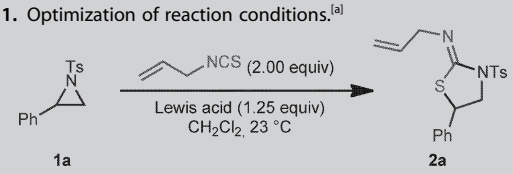
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201303699.

Table 1. Optimization of reaction conditions.[a]



Entry	Lewis acid	*t* [h]	Yield [%][b]
1	$Sn(OTf)_2$	1.0	0
2	$Zn(OTf)_2$	60.0	79
3	$ZnCl_2$	6.0	95
4	ZnI_2	3.0	95
5	$ZnBr_2$	1.3	99
6	LiBr[c]	72.0[d]	7
7	$ZnBr_2$[e]	72.0[d]	4

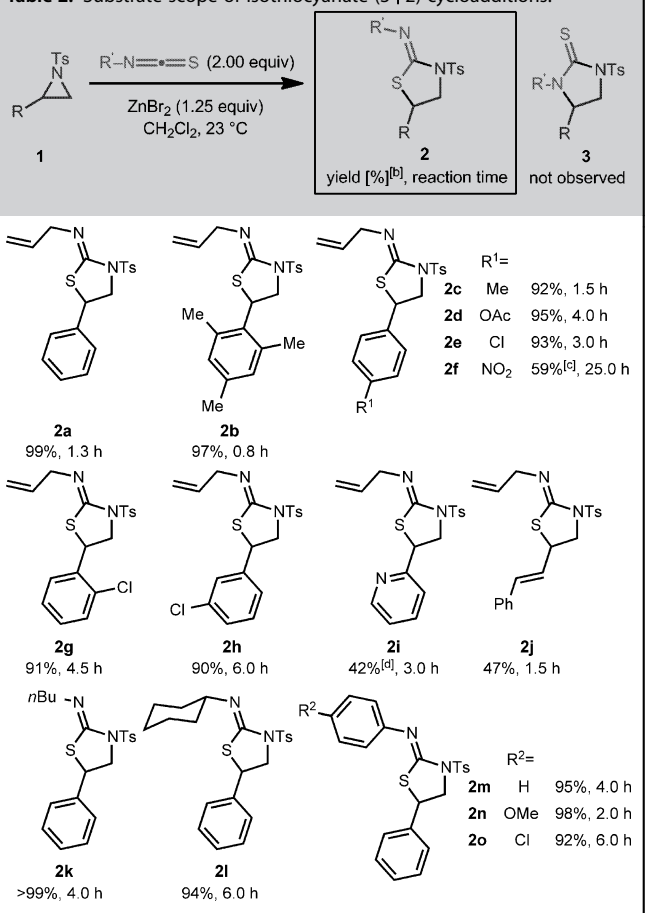
[a] Conditions: aziridine **1a** (0.40 mmol), isothiocyanate (0.80 mmol), Lewis acid (0.50 mmol), CH_2Cl_2 (0.80 mL). [b] Isolated yield. [c] 1.00 mmol of LiBr. [d] Starting material was not fully consumed. [e] 0.12 mmol of $ZnBr_2$ with 0.40 mmol of tetra(*n*-butyl)ammonium bromide.

natively, zinc(II) salts proved competent for the formation of iminothiazolidine **2a**. While zinc(II) triflate furnished the product in good yield, the reaction times were greatly reduced when zinc(II) halides were employed (entries 2–5). Lithium bromide mediated reaction conditions resulted in low conversion (entry 6). Attempts to develop a catalytic system with zinc(II) bromide proved unsuccessful, even in the presence of an additional bromide ion (entry 7). Ultimately, the use of 1.25 equivalents of zinc(II) bromide and 2.00 equivalents of allyl isothiocyanate in dichloromethane at ambient temperature proved optimal (entry 5).[11]

Exploration of 2-aziridine and heterocumulene substitution

With optimal conditions identified, we examined the substrate scope of the reaction. We found that a variety of *N*-tosyl-2-aryl-substituted aziridines participated effectively in the zinc(II) bromide mediated (3+2) cycloaddition with allyl isothiocyanate to yield the corresponding iminothiazolidine products with complete chemo- and regioselectivity (Table 2).[12,13] Altering the *C*-aryl substitution from phenyl to mesityl allowed for the formation of the corresponding heterocycle (**2b**) in a shorter reaction time despite the increased steric bulk.[14] Similarly, (*p*-tolyl)thiazolidine **2c** was successfully furnished with a slightly decreased yield. Acetoxy substitution was compatible with the reaction conditions as well, generating **2d** in excellent yield. Compared to the *p*-chlorophenyl- or *o*-chlorophenylthiazolidines (**2e** and **2g**, respectively), the more electronically deactivated *m*-chlorophenylthiazolidine **2h** was produced more slowly, albeit without any significant reduction in yield.[15] The highly electron-deficient *p*-nitrophenylthiazolidine **2f** was formed in modest yield, with a significant portion of starting material lost to nucleophilic ring opening of the aziridine by the bromide counterion.[16] Substrates bearing coordinating *C*-aryl substituents served to slow the rate of reaction (e.g., **2d**, **2f**) or require additional $ZnBr_2$ to drive the reaction to completion (**2i**). Styrenyl thiazolidine **2j** could

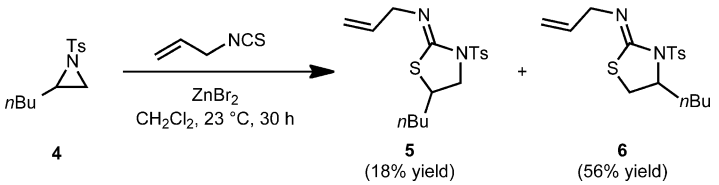
Table 2. Substrate scope of isothiocyanate (3+2) cycloadditions.[a]



[a] Conditions: aziridine **1** (0.40 mmol), isothiocyanate (0.80 mmol), $ZnBr_2$ (0.50 mmol), CH_2Cl_2 (0.80 mL). [b] Isolated yield. [c] The product of nucleophilic ring opening of the starting material by a bromide ion was isolated in 35% yield. [d] 0.90 mmol of $ZnBr_2$.

also be synthesized in approximately the same reaction time as phenyl product **2a**. Additionally, primary and secondary alkyl isothiocyanates were found to be highly compatible under the reaction conditions as were electron-neutral, -rich, and -deficient aryl isothiocyanates, all furnishing the desired iminothiazolidines in excellent yields (**2k**–**o**, respectively).

In contrast to the *C*-aryl-substituted aziridines, *C*-alkyl-substituted aziridine **4** reacted with allyl isothiocyanate under the reaction conditions to furnish two isomeric (3+2) adducts (Scheme 1). Formation of 5-alkyl-substituted iminothiazolidine **5** was accomplished in only 18% yield, whereas 4-alkyl-substituted product **6** was furnished in 56% yield. While *C*-alkyl-sub-



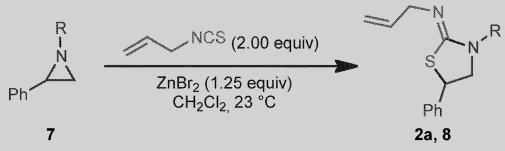
Scheme 1. (3+2) cycloaddition with 2-alkylaziridine **4**.

stituted aziridines are suitable reaction partners in the (3+2) cycloaddition and the heterocyclic products are formed with complete chemoselectivity, they are not formed with the regiofidelity exhibited by aziridines substituted at carbon with aryl groups or other conjugated systems.

Effect of aziridine N-substitution

As an extension of the substrate scope, we investigated the effect of N-substitution on the aziridine (Table 3). Aziridines protected with *N*-sulfonyl groups provided the desired iminothiazolidines (**2a**, **8a**–**c**) in excellent yields, generally showing

Table 3. N-Substitution scope of isothiocyanate (3+2) cycloaddition.[a]



7 2a, 8

Entry	R	Product	*t* [h]	Yield [%][b]
1	tosyl	**2a**	1.3	99
2	*p*-NO_2-C_6H_4-SO_2	**8a**	1.2	94
3	mesyl	**8b**	1.8	91
4	*p*-OMe-C_6H_4-SO_2	**8c**	2.0	90
5	H	**8d**	0.5	75
6	*n*-$C_{10}H_{21}$	**8e**	96.0[c]	0
7	pivaloyl	**8f**	96.0[c]	0
8	benzoyl	**8g**	96.0[c]	0

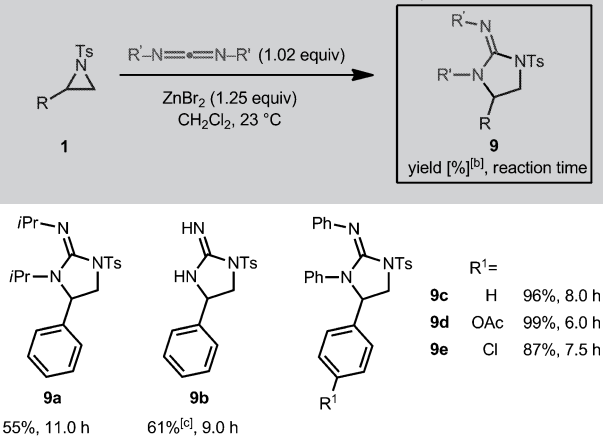
[a] Conditions: aziridine **7** (0.40 mmol), isothiocyanate (0.80 mmol), $ZnBr_2$ (0.50 mmol), CH_2Cl_2 (0.80 mL). [b] Isolated yield. [c] Starting material was not consumed.

reaction times that were slightly shorter for electron-deficient sulfonyl groups (Table 3, entry 2) and slightly longer for more electron-rich sulfonyl groups (entries 3–4) in comparison to the *N*-tosyl-substituted substrate (entry 1). Interestingly, unprotected 2-phenylaziridine showed an improved reaction time yet a partially decreased yield of the heterocyclic product **8d**, whereas *N*-(*n*-decyl)-substituted aziridine was unreactive under the reaction conditions (entries 5–6). *N*-Acyl aziridines also failed to furnish any of the desired heterocycles **8f** and **8g** (entries 7–8).

Extension of heterocumulene scope

Subsequently, we turned our attention to broadening the scope of competent heterocumulenes and found that while isocyanates gave only trace yields of the (3+2) cycloaddition adducts,[17] carbodiimides were compatible with the conditions, furnishing iminoimidazolidines (Table 4).[18] Our unique zinc-mediated conditions enabled the (3+2) cycloadditions of *N*-sulfonylaziridines with dialkyl- and disilyl-carbodiimides, unlike any previously published systems,[6,9] furnishing diisopropyliminoimidazolidine **9a** and secondary

Table 4. Substrate scope of carbodiimide (3+2) cycloaddition.[a]



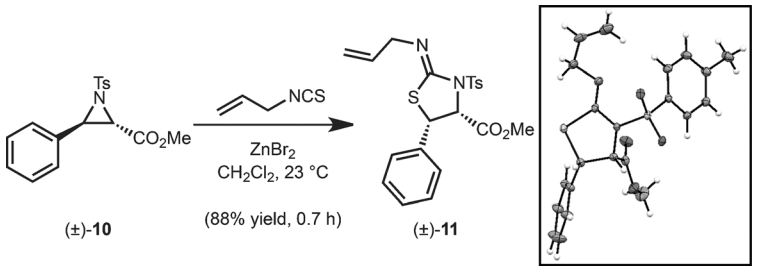
[a] Conditions: aziridine **1** (0.40 mmol), carbodiimide (0.41 mmol), $ZnBr_2$ (0.50 mmol), CH_2Cl_2 (0.80 mL). [b] Isolated yield. [c] Bis(trimethylsilyl)carbodiimide was used.

imidazolidine **9b**. In accordance with our observations in the isothiocyanate (3+2) cycloadditions, a variety of 2-arylaziridines were suitable reaction partners with diphenylcarbodiimide (**9c**–**e**).

Cycloaddition of disubstituted *N*-sulfonylaziridines

During our investigation of the substrate scope of the (3+2) cycloaddition of *N*-sulfonylaziridines with isothiocyanates, we discovered that *trans*-2,3-disubstituted aziridine **10** was an acceptable reaction partner, furnishing *cis*-thiazolidine **11** in high yield in the shortest reaction time observed for any *N*-tosyl-substituted substrate (Scheme 2). Iminothiazolidine **11** was formed as a single diastereomer, and the relative stereochemistry was confirmed by single-crystal X-ray diffraction. The *cis* configuration of product **11** led to the hypothesis that the mechanism of the reaction involves inversion at the benzylic position of the aziridine starting material.[19]

To confirm that the chemo-, regio-, and diastereoselective formation of *cis*-thiazolidine **11** was not substrate dependent, we exposed *trans*-2,3-disubstituted acroylaziridine **12** to identical reaction conditions and were pleased to find that *cis*-acroylthiazolidine **13** was similarly formed as the sole product and as a single diastereomer (Scheme 3).



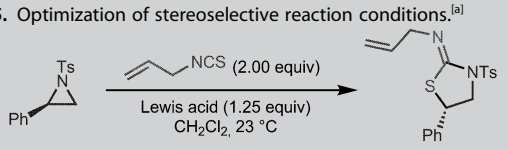
Scheme 2. Diastereoselective (3+2) cycloaddition with aziridine **10**.

Contrastingly, the (3+2) cycloaddition of allyl isothiocyanate with *cis*-2,3-disubstituted aziridine **15** resulted in the nondiastereoselective formation of both *trans*-thiazolidine **16** and the *cis* isomer **17** (Scheme 4a). Interestingly, exposure of *cis*-aziridine **15** to the reaction conditions in the absence of heterocumulene resulted in the rapid formation of pyrrolines **18** and **19** (Scheme 4b).[20] Finally, we found that geminally disubstituted *N*-tosyl-2-methyl-2-phenylaziridine failed to provide any (3+2) cycloaddition product.[21]

Stereoselective (3+2) cycloaddition

The formation of *cis*-thiazolidines **11** and **13** with excellent chemo-, regio-, and diastereoselectivity intimated the potential to develop a stereoselective reaction manifold. Initial development focused on the (3+2) cycloaddition of (*R*)-*N*-tosyl-2-phenylaziridine ((*R*)-**1a**) with allyl isothiocyanate (Table 5).[22] The optimized zinc(II) bromide mediated reaction conditions furnished (*S*)-**2a** in excellent yield and with 42% enantiomeric excess (*ee*) (Table 5, entry 1). Other zinc(II) halide salts furnished the desired product in similar yield with increased *ee* when zinc(II) chloride was employed (entries 2–3). Zinc(II) triflate provided no improvement in the *ee* of (*S*)-**2a** (entry 4). Lithium bromide mediated and catalytic zinc(II) bromide conditions both exhibited incomplete conversion of (*R*)-**1a** (entries 5–6). Interestingly, while the lithium bromide conditions furnished the opposite enantiomer (*R*)-**2a**, the catalytic zinc(II) bromide conditions produced (*S*)-**2a** with an improved 69% *ee*. Inspired by this result, we were pleased to find that increasing the equivalents of isothiocyanate in the presence of stoichiometric zinc(II) bromide could provide a similar boost in *ee* while maintaining full conversion of the starting material (entry 7). Ultimately, the use of 1.25 equivalents of zinc(II) chloride and 10.0 equivalents of allyl isothiocyanate in dichloromethane at ambient temperature proved optimal, furnishing (*S*)-**2a** in 99% yield and with 94% *ee* (entry 8).

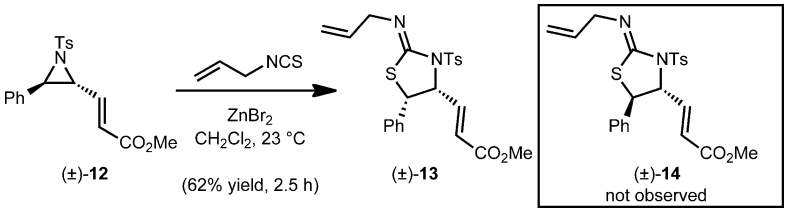
Table 5. Optimization of stereoselective reaction conditions.[a]



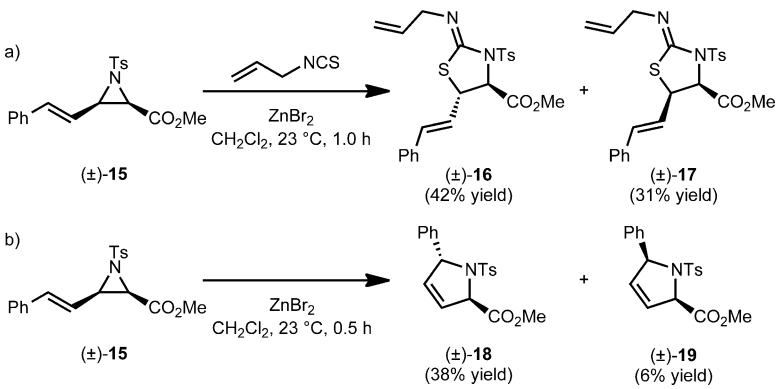
(*R*)-**1a** 99% *ee* → (*S*)-**2a**

Entry	Lewis acid	*t* [h]	Yield [%][b]	*ee* [%][c]
1	$ZnBr_2$	1.3	99	42
2	ZnI_2	3.0	95	32
3	$ZnCl_2$	6.0	95	63
4	$Zn(OTf)_2$	60.0	79	31
5	LiBr	96[d]	10	−76
6	$ZnBr_2$[e]	72[d]	67	69
7	$ZnBr_2$[f]	1.3	98	65
8	$ZnCl_2$[g]	2.0	99	94

[a] Conditions: aziridine (*R*)-**1a** (0.40 mmol, 99% *ee*), isothiocyanate (0.80 mmol), Lewis acid (0.50 mmol), CH_2Cl_2 (0.80 mL). [b] Isolated yield. [c] Determined by analytical chiral SFC. [d] Starting material was not fully consumed. [e] 0.12 mmol of $ZnBr_2$. [f] 6.00 equiv allyl isothiocyanate. [g] 10.0 equiv allyl isothiocyanate.



Scheme 3. Diastereoselective (3+2) cycloaddition with aziridine **12**.

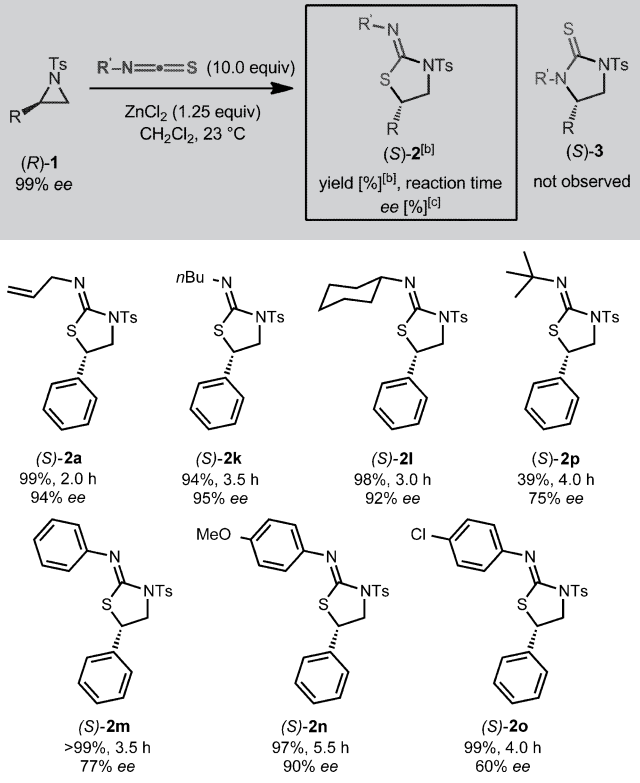


Scheme 4. (3+2) cycloaddition with aziridine **15**.

Exploration of isothiocyanate substitution

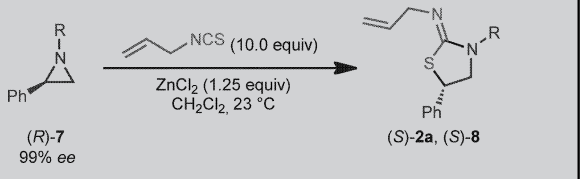
With optimal conditions identified, we examined the scope of heterocumulene substitution in the reaction.[23] We found that, along with allyl isothiocyanate, primary and secondary alkyl isothiocyanates were all highly compatible under the reaction conditions, furnishing desired enantioenriched iminothiazolidines (*S*)-**2a**, (*S*)-**2k**, and (*S*)-**2l** in uniformly excellent yields and *ee* (Table 6).[13] The use of a tertiary isothiocyanate, however, extended the reaction time and provided thiazolidine (*S*)-**2p** in decreased yield and *ee*. Additionally, aryl isothiocyanates were competent cycloaddition reaction partners under the zinc(II) chloride mediated conditions, providing thiazolidine products (*S*)-**2m**, (*S*)-**2n**, and (*S*)-**2o** in ex-

Table 6. Substrate scope of stereoselective isothiocyanate (3+2) cycloaddition.[a]



[a] Conditions: aziridine (*R*)-**1** (0.40 mmol, 99% *ee*), isothiocyanate (4.00 mmol), $ZnCl_2$ (0.50 mmol), CH_2Cl_2 (0.80 mL). [b] Isolated yield. [c] Determined by analytical chiral SFC.

Table 7. N-substitution scope of stereoselective isothiocyanate (3+2) cycloaddition.[a]



Entry	R	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	tosyl	(*S*)-**2a**	2.0	99	94
2	*p*-NO_2-C_6H_4-SO_2	(*S*)-**8a**	1.8	>99	95
3	mesyl	(*S*)-**8b**	4.0	95	90
4	*p*-OMe-C_6H_4-SO_2	(*S*)-**8c**	5.0	94	91
5	H	(*S*)-**8d**	0.5	31	34

[a] Conditions: aziridine (*R*)-**7** (0.40 mmol, 99% *ee*), isothiocyanate (4.00 mmol), $ZnCl_2$ (0.50 mmol), CH_2Cl_2 (0.80 mL). [b] Isolated yield. [c] Determined by analytical chiral SFC.

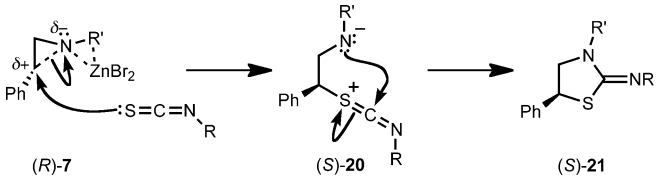
cellent yields. While phenyliminothiazolidine (*S*)-**2m** was isolated with good *ee*, the use of a more electron-rich isothiocyanate resulted in the formation of a thiazolidine product ((*S*)-**2n**) with an excellent 90% *ee*, whereas the use of a more electron-deficient isothiocyanate provided a product with a significantly lower *ee* ((*S*)-**2o**).

Effect of aziridine N-substitution on the transfer of chiral information

We subsequently investigated the effect of N-substitution on the aziridine in the stereoselective (3+2) cycloaddition. Aziridines with *N*-sulfonyl substitutions were extremely well tolerated under the reaction conditions, furnishing the desired thiazolidines ((*S*)-**2a**, (*S*)-**8a**–**c**) in excellent yield with uniformly high *ee*'s, exhibiting reaction times that increased slightly moving from more electron-deficient (Table 7, entry 2) to more electron-rich (entry 4) sulfonyl groups. While unprotected 2-phenylaziridine showed an improved reaction time, unfortunately both the yield and *ee* of thiazolidine (*S*)-**8d** were reduced (entry 5).

Proposed mechanism of stereoselective (3+2) cycloaddition

We hypothesize that the mechanism of the (3+2) cycloadditions presented herein proceeds through a stereoselective intimate-ion-pair mechanism similar to that invoked in our previous work[10] and by Johnson[24] and Kerr[25] in related work on the cycloadditions of donor–acceptor cyclopropanes (Scheme 5). Our observations including lack of reactivity in the

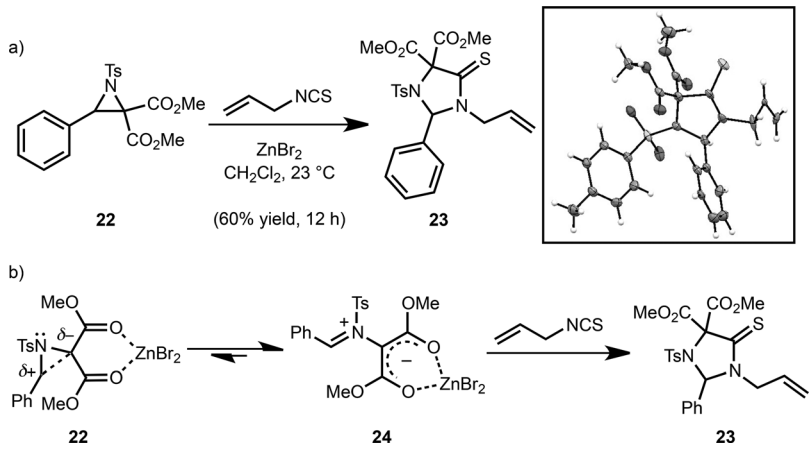


Scheme 5. Proposed general mechanism for stereoselective (3+2) cycloaddition.

absence of Lewis acid,[11,26] inversion at the benzylic position, greater reactivity of aziridines with electron-rich aryl substituents, and shorter reaction times of *N*-substituted aziridines with more electron-withdrawing groups are all consistent with this mechanistic hypothesis. The formation of (*R*)-**2a** under lithium bromide mediated conditions strongly suggests we have developed a Lewis acid mediated process in contrast to the related alkali metal halide mediated system reported by Nadir and co-workers,[6k,9] who observe overall stereoretention as a result of a double inversion pathway, which proceeds through an iodinated intermediate, and the palladium(II)-catalyzed reaction conditions of Alper and co-workers[6i] who also observe the stereoretentive product as the major enantiomer. This hypothesis also accounts for the observed nondiastereoselective formation of thiazolidines **16** and **17** and pyrrolines **18** and **19**, considering the fully separated ion-pair intermediate that likely results from destabilization of the polarized C–N bond by the steric interaction between the *cis* substituents on aziridine **15** (see Scheme 4).

Cycloaddition of a diester aziridine

Noting the apparent mechanistic similarities with our previous work,[10] we synthesized diester aziridine **22** to assess the potential for selective activation of the C–C or C–N bond under either our tin(II)- or zinc(II)-mediated conditions, respectively.[27] Unfortunately, $Sn(OTf)_2$ failed to provide any cycloaddition product.[28] Alternatively, use of $ZnBr_2$ provided thiolactam **23** as the sole (3+2) adduct (Scheme 6a). This is the only thiolactam (3+2) cycloaddition product observed during our studies.[13] The ability of the malonate group to stabilize the negative charge and the nitrogen to further stabilize the benzylic positive charge allows for the formation of zwitterion **24**, likely resulting in the observed divergent reactivity (Scheme 6b).[29]



Scheme 6. (3+2) cycloaddition with diester aziridine **22**.

Deprotection of *N*-sulfonyl heterocycles

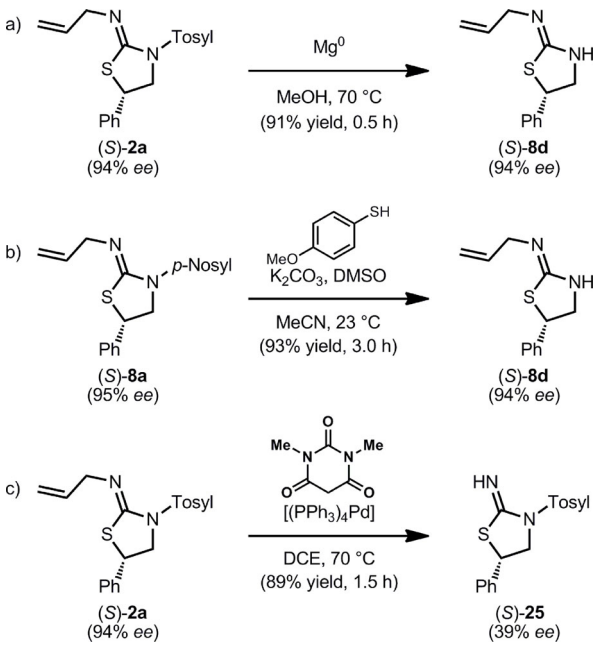
Having explored a range of substrates, heterocumulenes, and N-protecting groups, we next sought to assess the potential to derivatize our heterocyclic products. As expected, the *N*-sulfonyl protecting group removal was trivial. Secondary iminothiazolidine (*S*)-**8d** could be accessed rapidly in an excellent 91% yield without any loss of enantiomeric excess through detosylation of thiazolidine (*S*)-**2a** (Scheme 7a)[30] or through the desulfonylation of *p*-nosyl-protected thiazolidine (*S*)-**8a** with slightly increased yield (Scheme 7b), furnishing thiazolidine (*S*)-**8d** in 87% yield and with 94% *ee* over two steps from (*R*)-*N*-(*p*-nitrobenzenesulfonyl)-2-phenylaziridine.[31]

Alternatively, cleavage of the allyl imine C–N bond of heterocycle (*S*)-**2a** in the presence of palladium(0) enabled access to secondary iminothiazolidine (*S*)-**25** with some loss of enantiomeric excess (Scheme 7c). While the cleavage of *N*-allyl bonds has been shown in the literature for functional groups including amines[32] and amides,[33] this is the first known example of the cleavage of an imino *N*-allyl bond.

Iminothiazolidines (*S*)-**8d** and (*S*)-**25** are extremely versatile heterocycles. Derivatization and synthetic manipulations of the imine, allyl group, and secondary nitrogen could be envisioned to provide rapid access to highly enantioenriched oxothiazolidines, thiazoles, and a variety of polyclic scaffolds.[34] Critically, access to the enantioenriched secondary thiazolidine and imidazolidine products enabled by our (3+2) cycloaddition allows for their use as asymmetric organic catalysts, as the free secondary nitrogen functions as a necessary hydrogen bond donor for the majority of these applications.[7a–d]

Conclusion

We have disclosed the first stereoselective Lewis acid mediated (3+2) cycloaddition of *N*-H- and *N*-sulfonylaziridines with alkyl heterocumulenes. These zinc(II)-mediated conditions offer broad tolerance of alkyl, silyl, and aryl heterocumulenes, as well as aziridine substitution, enabling the formation of iminoimidazolidines and enantioenriched iminothiazolidines in overall excellent yields from enantioenriched aziridines, which are easily accessible from their amino acid precursors. Combined with the exhibited ability to simply and orthogonally remove the sulfonyl and allyl protecting groups, this reaction system enables the installation of a broad number of functional group handles for further derivatization of these biologically and catalytically important heterocyclic scaffolds.



Scheme 7. Desulfonylation and deallylation of iminothiazolidine products.

Experimental Section

Representative general procedure for the (3+2) cycloaddition of *N*-H- and *N*-sulfonylaziridines with heterocumulenes

To an oven-dried 1-dram vial equipped with a magnetic stir bar was added zinc(II) bromide (113 mg, 0.50 mmol, 1.25 equiv), freshly powdered with a mortar and pestle, in an inert atmosphere glovebox. The vial was sealed with a screw cap fitted with a Teflon septum, removed from the glovebox, and placed under an inert atmosphere. To a separate, oven-dried 1-dram vial was added *N*-tosyl-2-phenylaziridine (**1a**, 109 mg, 0.40 mmol, 1.00 equiv). The vial was then sealed with a screw-cap fitted with a Teflon septum and anhydrous CH_2Cl_2 (0.60 mL) and allyl isothiocyanate (79 μL, 0.80 mmol, 2.00 equiv) were added. The mixture was transferred to the first vial with a rinse of anhydrous CH_2Cl_2 (0.20 mL). The heterogeneous reaction mixture was then allowed to stir at ambient temperature. Upon consumption of the aziridine (determined by TLC analysis), the reaction solution was diluted with CH_2Cl_2 (3 mL) and CH_3OH (1 mL), adsorbed onto Celite, and purified by silica gel column chromatography (20% acetone in hexanes eluent) to furnish thiazolidine **2a** (147 mg, 99% yield) as an amorphous white solid.

Acknowledgements

The authors wish to thank NIH-NIGMS (R01M080269—01), Amgen, and Caltech for financial support. R.A.C. gratefully acknowledges the support of this work provided by a fellowship from the National Cancer Institute of the National Institutes of Health under Award Number F31A174359. A.F.G.G. thanks the Natural Sciences and Engineering Research Council (NSERC) of Canada for a PGS D scholarship. L. Henling (Caltech) and Dr. M. Takase (Caltech) are gratefully acknowledged for X-ray crystallographic structural determination. The Bruker KAPPA APEXII X-ray diffractometer was purchased via an NSF CRIF:MU award to the California Institute of Technology, CHE-0639094.

Keywords: cycloadditions · heterocumulenes · heterocycles · Lewis acids · stereoselectivity

[1] a) A. Padwa, in *Comprehensive Heterocyclic Chemistry III*, Vol. 1 (Eds: A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor), Elsevier, Oxford, **2008**, pp. 1–105; b) W. McCoull, F. A. Davis, *Synthesis* **2000**, 1347–1365; c) D. Tanner, *Angew. Chem.* **1994**, *106*, 625–646; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599–619.

[2] a) W. H. Pearson, B. W. Lian, S. C. Bergmeier, in *Comprehensive Heterocyclic Chemistry II*, Vol. 1 A (Eds: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Elsevier, Oxford, **1996**, p. 1; b) T. L. Gilchrist, *Heterocyclic Chemistry*, 2nd ed., Longman, Essex, **1992**, p. 38.

[3] a) R. Chawla, A. K. Singh, L. D. S. Yadav, *RSC Adv.* **2013**, *3*, 11385–11403; b) M. K. Ghorai, D. P. Tiwari, N. Jain, *J. Org. Chem.* **2013**, *78*, 7121–7130; c) X. E. Hu, *Tetrahedron* **2004**, *60*, 2701–2743.

[4] a) P. Davoli, I. Moretti, F. Prati, H. Alper, *J. Org. Chem.* **1999**, *64*, 518–521; b) S. V. Ley, B. Middleton, *Chem. Commun.* **1998**, 1995–1996; c) K. Khumtaveeporn, H. Alper, *Acc. Chem. Res.* **1995**, *28*, 414–422.

[5] a) A. L. Cardoso, T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.* **2012**, 6479–6501; b) D. M. Hodgson, P. G. Humphreys, J. G. Ward, *Org. Lett.* **2006**, *8*, 995–998; c) W. Zhu, G. Cai, D. Ma, *Org. Lett.* **2005**, *7*, 5545–5548; d) J. Huang, P. O'Brien, *Chem. Commun.* **2005**, 5696–5698; e) E. A. Acar, F. Glarner, U. Burger, *Helv. Chim. Acta* **1998**, *81*, 1095–1104; f) G. Cardillo, L. Gentilucci, A. Tolomelli, C. Tomasini, *Tetrahedron Lett.* **1997**, *38*, 6953–6956.

[6] a) M. K. Ghorai, K. Ghosh, K. Das, *Tetrahedron Lett.* **2006**, *47*, 5399–5403; b) M. K. Ghorai, K. Das, A. Kumar, K. Ghosh, *Tetrahedron Lett.* **2005**, *46*, 4103–4106; c) B. A. B. Prasad, G. Pandey, V. K. Singh, *Tetrahedron Lett.* **2004**, *45*, 1137–1141; d) S. Gandhi, A. Bisai, B. A. B. Prasad, V. K. Singh, *J. Org. Chem.* **2007**, *72*, 2133–2142; e) V. K. Yadav, V. Sriramurthy, *J. Am. Chem. Soc.* **2005**, *127*, 16366–16367; f) M. Sengoden, T. Punniyamurthy, *Angew. Chem.* **2013**, *125*, 600–603; *Angew. Chem. Int. Ed.* **2013**, *52*, 572–575; g) T. Munegumi, I. Azumaya, T. Kato, H. Masu, S. Saito, *Org. Lett.* **2006**, *8*, 379–382; h) M. S. Kim, Y.-W. Kim, H. S. Hahm, J. W. Jang, W. K. Lee, H.-J. Ha, *Chem. Commun.* **2005**, 3062–3064; i) J.-O. Baeg, C. Bensimon, H. Alper, *J. Am. Chem. Soc.* **1995**, *117*, 4700–4701; j) J.-Y. Wu, Z.-B. Luo, L.-X. Dai, X.-L. Hou, *J. Org. Chem.* **2008**, *73*, 9137–9139; k) U. K. Nadir, S. Joshi, *Indian J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.* **2003**, *42B*, 1760–1764.

[7] a) E. J. Corey, M. J. Grogan, *Org Lett.* **1999**, *1*, 157–160; b) V. B. Birman, X. Li, *Org. Lett.* **2006**, *8*, 1351–1354; c) V. B. Birman, H. Jiang, X. Li, L. Guo, E. W. Uffman, *J. Am. Chem. Soc.* **2006**, *128*, 6536–6537; d) W. Ye, D. Leow, S. L. M. Goh, C.-T. Tan, C.-H. Chian, C.-H. Tan, *Tetrahedron Lett.* **2006**, *47*, 1007–1010.

[8] a) V. S. Jain, D. K. Vora, C. S. Ramaa, *Bioorg. Med. Chem.* **2013**, *21*, 1599–1620; b) Y. Pandey, P. K. Sharma, N. Kumar, A. Singh, *Int. J. PharmTech Res.* **2011**, *3*, 980–985; c) M. D'hooghe, N. De Kimpe, *Tetrahedron* **2006**, *62*, 513–535; d) E. H. Schweizer, F. Märki, C. Lehmann, H. Dietrich, *J. Med. Chem.* **1983**, *26*, 964–970.

[9] a) U. K. Nadir, N. Basu, *Tetrahedron* **1993**, *49*, 7787–7792; b) U. K. Nadir, N. Basu, *Tetrahedron Lett.* **1992**, *33*, 7949–7952.

[10] A. F. G. Goldberg, N. R. O'Connor, R. A. Craig, II, B. M. Stoltz, *Org. Lett.* **2012**, *14*, 5314–5317.

[11] No reaction was observed in the absence of Lewis acid. For full details, see the Supporting Information.

[12] The *Z*-imino stereochemistry of the iminothiazolidine products was assigned by analogy to the structure of thiazolidine **11**, which was unambiguously established by single-crystal X-ray diffraction. For full details, see the Supporting Information.

[13] Thiourea product **3** was not observed in any case during this study. Similarly, the analogous thiolactam product was not observed during our previous studies of (3+2) cycloadditions of donor–acceptor cyclopropanes with heterocumulenes, see ref. [10].

[14] This observation is in stark contrast to our previous studies of (3+2) cycloadditions of donor–acceptor cyclopropanes with heterocumulenes, in which increased steric bulk on the ring caused a large increase in reaction time, see ref. [10].

[15] a) C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195; b) L. P. Hammett, *J. Am. Chem. Soc.* **1937**, *59*, 96–103.

[16] This was the only substrate found to be susceptible to nucleophilic ring opening by the zinc(II) counterion during our studies. For full details, see the Supporting Information.

[17] A variety of isocyanates were tested under zinc(II) bromide mediated conditions, including trimethylsilyl, phenyl, and allyl isocyanates.

[18] The assignment of the *E*-imino-stereochemistry of the iminoimidazolidine products was assigned by analogy to a structure related to imidazolidine **9a**, which was unambiguously established by single-crystal X-ray diffraction of the corresponding imidazolidinium ion. For full details, see the Supporting Information.

[19] Inversion at the benzylic position was observed in our previous studies of stereoselective (3+2) cycloadditions of donor–acceptor cyclopropanes with heterocumulenes, see ref. [10].

[20] Alternatively, *trans*-aziridine **12** did not undergo this transformation under the same conditions, although both styryl- and acroylaziridines are known to isomerize to pyrrolines, see: a) M. Brichacek, M. N. Villalobos, A. Plichta, J. T. Njardarson, *Org. Lett.* **2011**, *13*, 1110–1113; b) A.-H. Li, L.-X. Dai, X.-L. Hou, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2725–2729; c) R. S. Atkinson, C. W. Rees, *J. Chem. Soc. Chem. Commun. (London)* **1967**, 1232.

[21] *N*-Tosyl-2-methyl-2-phenylaziridine (**26**) proved susceptible to isomerization under the reaction conditions, furnishing no (3+2) adduct, but rather enamine **27** as a mixture of *E* and *Z* isomers. For full details, see the Supporting Information.

[22] Absolute stereochemistry of the iminothiazolidine products were assigned by analogy to the structure of thiazolidine (*S*)-**8a**, which was un-

ambiguously established by single-crystal X-ray diffraction. For full details, see the Supporting Information.

[23] As with the zinc(II) bromide mediated conditions, isocyanates were not suitable cycloaddition partners under our stereospecific reaction conditions. Diphenylcarbodiimide was compatible with the zinc(II) chloride mediated conditions, furnishing the iminoimidazolidine product in excellent yield, but with comparatively reduced *ee*. For full details, see the Supporting Information.

[24] a) P. D. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li, J. S. Johnson, *J. Am. Chem. Soc.* **2008**, *130*, 8642 – 8650; b) P. D. Pohlhaus, J. S. Johnson, *J. Am. Chem. Soc.* **2005**, *127*, 16014 – 16015.

[25] a) A. Karadeolian, M. A. Kerr, *J. Org. Chem.* **2007**, *72*, 10251 – 10253; b) K. Sapeta, M. A. Kerr, *J. Org. Chem.* **2007**, *72*, 8597 – 8599; c) D. Wanapun, K. A. Van Gorp, N. J. Mosey, M. A. Kerr, T. K. Woo, *Can. J. Chem.* **2005**, *83*, 1752 – 1767.

[26] In the absence of heterocumulene, aziridine (*R*)-**1a** was completely racemized in 10 min. Concurrently, no reduction in *ee* of (*S*)-**2a** was observed upon re-exposure to the reaction conditions. For full details, see the Supporting Information.

[27] The selective C–C bond cleavage of *N*-tosyl-3-arylaziridine-2,2-dicarboxylates has been explored previously in the literature, see: a) L. Li, J. Zhang, *Org. Lett.* **2011**, *13*, 5940 – 5943; b) Z. Jiang, J. Wang, P. Lu, Y. Wang, *Tetrahedron* **2011**, *67*, 9609 – 9617; c) P. D. Pohlhaus, R. K. Bowman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 2294 – 2295.

[28] Conditions: aziridine **22** (0.40 mmol), allyl isothiocyanate (0.80 mmol), $Sn(OTf)_2$ (0.44 mmol), CH_2Cl_2 (1.3 mL). See reference [10] and general procedure D in the associated Supporting Information.

[29] The same mode of reactivity has been previously observed in (3+2) cycloadditions with the *N*-alkylated and *N*-arylated derivatives of aziridine **22** under thermolysis conditions with isothiocyanates, see: H. Benhaoua, F. Texier, *Tetrahedron* **1978**, *34*, 1153 – 1161.

[30] D. A. Alonso, P. G. Andersson, *J. Org. Chem.* **1998**, *63*, 9455 – 9461.

[31] a) R. S. Narayan, M. S. VanNieuwenhze, *Org. Lett.* **2005**, *7*, 2655 – 2658; b) T. Kan, T. Fukuyama, *Chem. Commun.* **2004**, 353 – 359; c) T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373 – 6374.

[32] a) S. Chandrasekhar, C. R. Reddy, R. J. Rao, *Tetrahedron* **2001**, *57*, 3435 – 3438; b) M. Honda, H. Morita, I. Nagakura, *J. Org. Chem.* **1997**, *62*, 8932 – 8936; c) F. Garro-Helion, A. Merzouk, F. Guibe, *J. Org. Chem.* **1993**, *58*, 6109 – 6113.

[33] a) T. Matsumura, M. Akiba, S. Arai, M. Nakagawa, A. Nishida, *Tetrahedron Lett.* **2007**, *48*, 1265 – 1268; b) T. Koch, M. Hesse, *Synthesis* **1992**, 931 – 932.

[34] a) M. Jasinski, G. Mloston, H. Heimgartner, *J. Heterocycl. Chem.* **2010**, *47*, 1287 – 1293; b) K. Keiji, K. Takanobu, K. Masaki, S. Hiroki, Thiazoline Derivative and Use of the Same. Eur. Pat. Appl. 1669352, 2006; c) P. Pecorari, M. Rinaldi, L. Costantino, A. Provvisionato, C. Cermelli, M. Portolani, *Farmaco* **1991**, *46*, 899 – 911; d) R. Crossley, 2,3-Dihydro- Thiazolo- and Thiazino- Benzimidazoles as Anti-Hyper Secretion Agents. U. S. Patent 4,873,237, October 10, 1989; e) V. Skaric, D. Skaric, A. Cizmek, *J. Chem. Soc. Perkin Trans. 1* **1984**, 2221 – 2225; f) G. R. Brown, *J. Chem. Soc. Perkin Trans. 1* **1973**, 2022 – 2024.

Received: September 21, 2013
Published online on ■■ ■■, 0000

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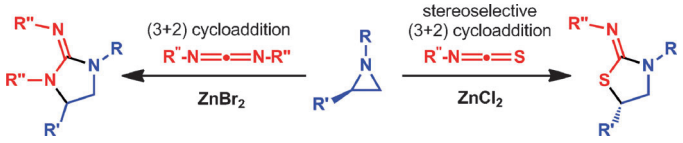

Coordinate, release, and expand: A Lewis acid coordinated process by which the release of strain energy drives the ring expansion of aziridines to five-membered heterocycles through a stereoselective (3+2) cycloaddition with alkyl and aryl isothiocyanates and carbodiimides is presented. These zinc(II)-mediated reactions exhibit broad substrate scope, high yields, and well-defined chemo- and regioselectivity.

Organic Synthesis

*R. A. Craig, II, N. R. O'Connor, A. F. G. Goldberg, B. M. Stoltz**

■■ – ■■

Stereoselective Lewis Acid Mediated (3+2) Cycloadditions of *N*-H- and *N*-Sulfonylaziridines with Heterocumulenes