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Diastereoselective Synthesis of α-Quaternary Aziridine-2-carboxylates via Aza-Corey–Chaykovsky Aziridination of *N-tert*-Butanesulfinyl Ketimino Esters

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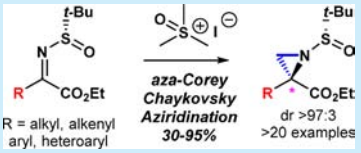
Supporting Information

ABSTRACT: A general, scalable, and highly diastereoselective aziridination of *N-tert*-butanesulfinyl ketimino esters is described. The methodology has been utilized to provide straightforward access to previously unobtainable, biologically relevant α-quaternary amino esters and derivatives starting from readily available precursors.



The asymmetric construction and application of α-quaternary amino acid derivatives has been an area of intense focus over the past several decades.[1] These privileged molecular entities are present in natural products,[1a,b] incorporated into useful chiral auxiliaries, and have been utilized to provide synthetic access to complex natural products and novel, tailor-made peptides that can impact protein folding, enzyme inhibition, and other biomimetic functions.[1d] Moreover, incorporation of these subunits into drug candidates allows medicinal chemists to fine-tune the activity of pharmacophores in question.

We recently required a concise, enantioselective synthesis of an unknown, heterocyclic dihydrobenzofuranyl amino ester (boxed, Figure 1). Initial synthetic efforts focused on utilizing a

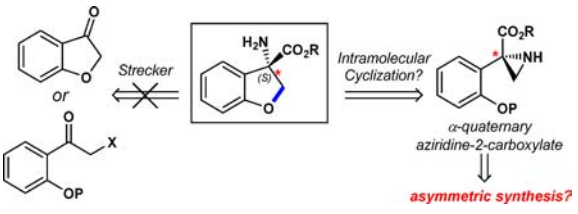


Figure 1. Strategies toward a heterocyclic amino ester.

Strecker cyanation strategy on a suitable benzofuranone or acyclic analog. Unfortunately, in contrast to the related dihydrobenzopyranyl system,[2] all Strecker-based strategies were unsuccessful in providing the desired product in a racemic or nonracemic manner. Instead, the inherent acidity of the benzofuranone substrate favors an unproductive intermolecular dimerization pathway.

Subsequently, we became intrigued by a strategy that utilized the intermediacy of an α-quaternary-substituted aziridine-2-carboxylate.[3] Tactically, we hypothesized a deprotection-induced intramolecular aziridine ring opening would allow us to forge the C–O bond.[4] However, this strategy required straightforward, enantioselective access to the desired aziridine-2-carboxylate substrate. These sought-after amino acid derivatives have been used as handles for peptide modification,[5] linchpins in the synthesis of natural products,[6] and intermediates en route to non-natural amino acids.[7] Accordingly, significant attention has been focused on the development of effective methods for their construction. Early reports focused on manipulation of suitably functionalized serine derivatives into simple, nonracemic unsubstituted aziridine-2-carboxylates.[8] An aza-Darzens strategy was first disclosed by Davis and further expanded by Jacobsen, Wulff, and others.[9] Auxiliary- and substrate-controlled addition to azirines has also been pursued with limited scope.[10] Metal-catalyzed nitrene–alkene additions, amine addition to vinyl triflates, and phase-transfer catalyzed alkylation/cyclization strategies have also been pursued.[11] Stereospecific α-alkylation of aziridines have also been exploited, though the methodology has limited scope and requires cryogenic conditions in order to obtain high stereospecificity.[7c,12] Additionally, Córdova and co-workers have developed an organocatalytic aziridination of acroleins utilizing prolinol-based catalysts and CbzNHOTs.[13] More recently, Gaunt et al. has disclosed a powerful, racemic strategy based on a novel C–H activation tactic.[14] However, most strategies afford limited access to α-quaternary aziridine-2-carboxylates.

Arguably, the most straightforward and well-established aziridine synthesis utilizes the addition of sulfur ylides to imines.[15] This aza-Corey–Chaykovsky aziridination strategy, first pioneered by Aggarwal and Dai[16] for simple aldimines, followed by Davis,[17] Garcia-Ruano,[18] and Stockman[19] in an asymmetric manifold, is general for *N-tert*-butanesulfinyl aldimines[20] and several sulfur ylide precursors (Scheme 1).

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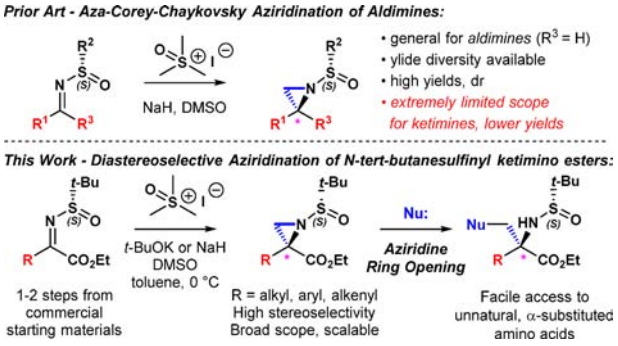
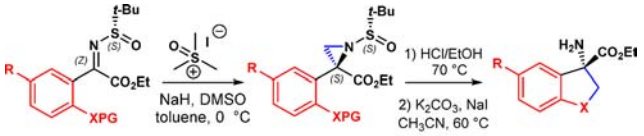
Scheme 1. Strategy for Synthesis of Aziridine-2-carboxylates



Nevertheless, *ketimine* aziridination is extremely limited in scope, especially for the traditional Corey−Chaykovsky methylide reagents.[21] We became intrigued by the idea of utilizing ketimino esters to potentially increase the reactivity of the imine carbon toward aziridination. Herein, we report our successful development of a general, highly diastereoselective synthesis of α-quaternary aziridine-2-carboxylates via aza-Corey−Chaykovsky aziridination of *N-tert*-butanesulfinyl ketimino esters and its application toward novel amino acid synthesis.

We began by developing a short synthesis of the desired imine substrates starting from the corresponding α-ketoesters via condensation with (*S*)-*tert*-butanesulfinamide and $Ti(OEt)_4$ in THF.[22] All ketimino esters were found to exist as single geometrical isomers, with the orientation of the *tert*-butanesulfinyl group about the imine bond assigned as (*Z*) with respect to the ester (confirmed by X-ray analysis of imino-ester **4h**; see Supporting Information). Dimethylsulfoxonium methylide was quickly found to be a highly competent ylide for effecting this transformation, forging the desired aziridine-2-carboxylates in short reaction times (<10 min at 0 °C), moderate to excellent yield, and high diastereoselectivity (Table 1).

Table 1. Aziridination−Cyclization Synthesis of Heterocyclic Amino Esters



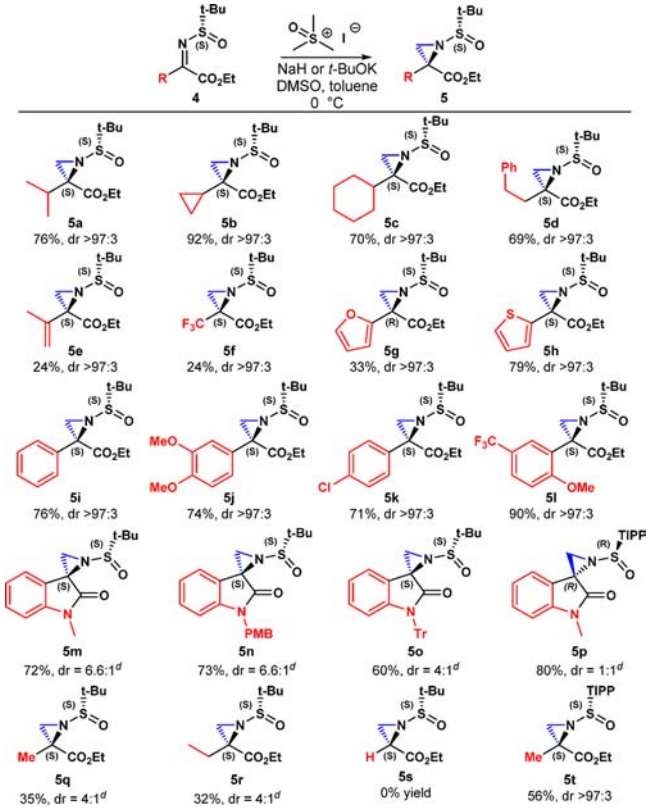
				aziridination		cyclization
entry	X	PG	R	**2** (yield %)	dr[a]	**3** (yield %)
1	O	MOM	H	**2a** (64)	>97:3	**3a** (53)
2	O	MOM	OMe	**2b** (73)	>97:3	**3b** (79)
3	O	MOM	CF_3	**2c** (87)	>97:3	**3c** (88)
4	S	PMB	H	**2d** (53)	>97:3	**3d** (51)

[a]Diastereoselectivity determined by crude ^{1}H NMR analysis.

Next, subjection of these aziridines to HCl in EtOH induces sulfinyl cleavage, phenol deprotection, and chloride ring opening. After concentration of the reaction mixture and redissolution in CH_3CN, addition of K_2CO_3/NaI and application of heat effect intramolecular cyclization to afford the desired heterocyclic amino ester in good yield for the two-step, one-pot protocol. As illustrated in Table 1, the strategy is applicable to the synthesis of O- and S-containing heterocyclic amino esters. Notably, these compounds have never been reported in the literature, presumably due to the lack of straightforward syntheses prior to our studies.

We then proceeded to expand the generality of this methodology by performing the aziridination on a diverse set of *N-tert*-butanesulfinyl ketimino esters (Scheme 2). Except for

Scheme 2. Diastereoselective Aziridination of *N-tert*-Butanesulfinyl Ketimino Esters: Substrate Scope[a,b,c]



[a]Typical reaction conditions: 1 equiv of ketimino ester in toluene (1 M), 2 equiv NaH or KO*t*Bu, 2 equiv of trimethylsulfoxonium iodide in DMSO (0.8 M), 0 °C. [b]Yields are for isolated products via column chromatography. [c]Diastereoselectivity determined by crude ^{1}H NMR analysis. [d]dr based on isolated yield of individual diastereomers.

the noted entries, only a single diastereomer was detected via crude ^{1}H NMR analysis (dr >97:3). Regarding scope, alkyl (**5a−d**), alkenyl (**5e**), trifluoromethyl (**5f**), heteroaryl (**5g−h**), and aryl (**5i−k**) functionality is tolerated. Extension to *N*-protected isatins **5m−o** was also successful, albeit with lower-than-expected diastereoselectivity. The methyl and ethyl analogs **5q−r** were obtained in low yield and dr, and the glyoxalate-derived **5s** could not be obtained due to decomposition under the reaction conditions. In an attempt to obtain a higher dr for lower alkyl substrates, the triisopropylphenylsulfinyl auxiliary (TIPPS)[23] was investigated. While ineffective for the isatin scaffold **5p**, TIPPS aziridine **5t** was obtained in higher yield than the *N-tert*-butanesulfinyl derivative as a single diastereomer.

Next, intermolecular aziridine ring opening was investigated. Although ring opening of aziridine-2-carboxylates containing an *N*-tosyl, Bus, or related protecting groups is well established,[7] the *N-tert*-butanesulfinyl group was found to be an ineffective activator for selective aziridine ring opening; most attempted reactions resulted in low (<10%) conversion. However, we subsequently found that, after oxidation of the *N-tert*-butanesulfinyl of **5i** to the corresponding Bus group,[24] the

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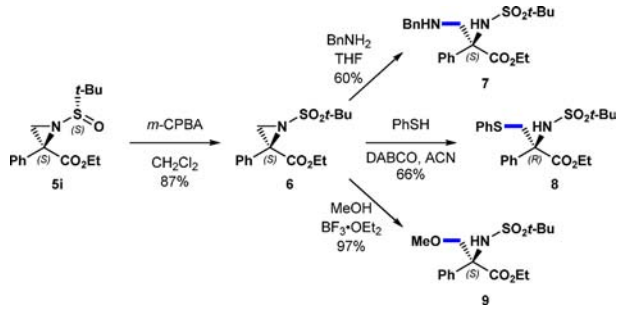
resulting aziridine **6** could be engaged by nucleophiles resulting in cleavage at the terminal aziridinyl carbon (Scheme 3). Amine,

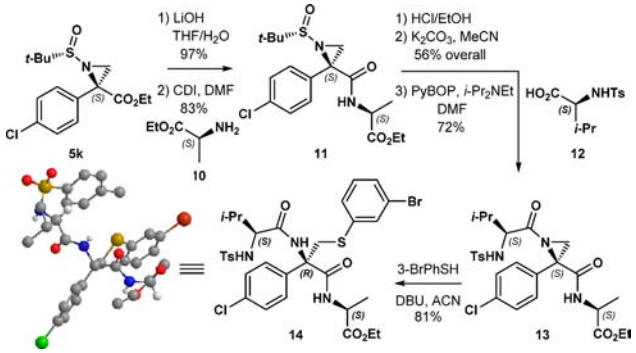
Scheme 3. Oxidation and Nucleophilic Ring Opening of Aziridine-2-carboxylate 6



sulfide, and alcohol nucleophiles were found to react in a facile manner to afford the ring-opened amino esters. Notably, the syntheses of α-phenyl threonine **7**, cysteine **8**, and serine **9** analogs takes place in 4 steps from commercially available ethyl benzoylformate and compare favorably to other literature methods for the preparation of similar compounds.[25]

As a final application in a biological context, incorporation of a quaternary aziridine-2-carboxylate into a peptide was investigated. Yudin[5a] and Gin[5b] have illustrated the utility of serine-derived aziridine-2-carboxylates ("Azy" units) when built into peptides for chemoselective amide hydrolysis and ring opening, respectively. However, all prior studies have focused on Azy units lacking α-substitution. With ready access to "α-Azy" units, we felt that substantial expansion of Azy substrate diversity would be possible. To this end, 4-chlorophenyl aziridine-2-carboxylate **5k** was subjected to ester hydrolysis and CDI-mediated amide coupling with L-alanine ethyl ester **10** to afford peptide **11** (Scheme 4).

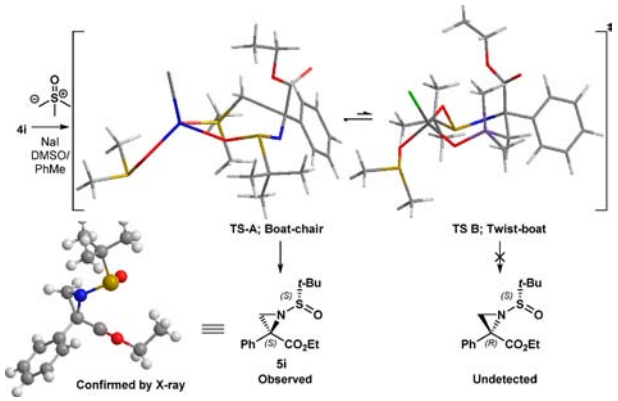
Scheme 4. Synthesis of α-Quaternary Conjugated Peptide 14



The sulfinyl group was then cleaved (with concomitant chloride-induced ring opening and subsequent base-mediated ring closure), after which a second peptide bond was forged between the resulting aziridine and *N*-tosyl valine **12** to provide α-Azy dipeptide **13**. Ring opening was then accomplished with 3-bromothiophenol to afford the thiol-conjugated dipeptide **14**, whose X-ray crystal structure was obtained to unambiguously confirm the absolute stereochemistry. This sequence demonstrates the potential use of α-Azy peptides for incorporation into biological scaffolds and subsequent conjugation to fluorescent tags or sugars.

To determine the absolute configuration of the aziridine-2-carboxylate products, phenyl aziridine **5i** was recrystallized from heptane and subjected to X-ray crystallographic analysis (Scheme 5). Starting from (*S*)-*tert*-butanesulfinamide and the

Scheme 5. X-ray Crystal Structure of Phenyl Aziridine 5i and Proposed Transition State Based on Computational Analysis



resulting (*Z*)-ketimino ester **4i**, the obtained crystal structure unambiguously defines the stereochemical configuration as (*S*,*S*). Initially, we attempted to rationalize the observed stereoselectivity by invoking a six-membered ring chairlike transition state[18] where the sodium cation coordinates the ylide oxygen and imine nitrogen. Since the final ring closure is fast and irreversible, the observed stereoselectivity was assumed to arise from the energy difference between the two diastereomeric betaine transition states.[26] However, we felt this proposal did not adequately consider the electronic influence of the pendant α-ester on the transition state.

In order to probe the origin of the observed stereoselectivity, a preliminary computational analysis was conducted (see Supporting Information for full details). Although several pathways were investigated invoking a six-membered ring transition state, a viable explanation for the observed stereoselectivity could not be rationalized. However, an energetically favorable pathway arose involving a cyclic, eight-membered ring transition state invoking chelation of sodium with the ylide and sulfinyl oxygens. The computed diastereomeric transition structures for ylide addition leading to two diastereomeric betaine intermediates are shown.

The cyclic transition state occurring from attack on the Si face of the imine (TS-A) has a boat-chair conformation that minimizes eclipsing transannular interactions in eight-membered rings. TS-B, which leads to the unobserved α-(*R*)-aziridine product, adopts a strained twist-boat conformation in order to overcome repulsive interactions between the phenyl ring of the iminyl carbon and sulfinyl-methyl substituents. Additionally, there are unfavorable gauche interactions between the dimethylsulfinyl group of the ylide and both the phenyl ring and the *N*-*tert*-butanesulfinyl group. As a result of this additional torsional strain that must be overcome in TS-B, TS-A is favored by >5 kcal/mol [$\Delta\Delta G^{\ddagger}$ @ 0 °C], which corresponds quite well with the observed diastereoselectivity.

In conclusion, a general method for the diastereoselective synthesis of α-quaternary aziridine-2-carboxylates via aziridination of readily available *N*-*tert*-butanesulfinyl ketimino esters has been developed. The methodology is scalable, has broad scope, and affords aziridines in good yield and high stereoselectivity. Several applications of the synthesis of amino acid derivatives based on both inter- and intramolecular aziridine ring opening

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have been demonstrated, and a stereochemical model has been proposed based on preliminary computational analysis. Application of this tactic using complex sulfur ylide reagents for entry to aziridine carboxylates containing vicinal stereocenters is underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02838.

Experimental procedures (PDF)
X-ray structure of **4h** (CIF)
X-ray structure of **5i** (CIF)
X-ray structure of **14** (CIF)

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Notes

The authors declare no competing financial interest.

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