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Carbamoyl Anion Addition to Azirines

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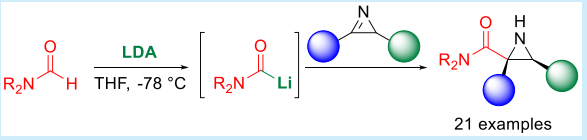
ABSTRACT: The addition of carbamoyl anions to azirines affords synthetically useful 2-aziridinyl amide building blocks. The reaction scope was explored with respect to both formamide and azirine, and the addition was found to be highly diastereoselective. A one-pot conversion of a ketoxime to an aziridinyl amide was demonstrated. The method was employed to incorporate an aziridine residue into a dipeptide segment.



Among the carbonyl anions, carbamoyl anions have demonstrated considerable practical utility due to their relatively high stability and ease of generation from readily available *N*,*N*-disubstituted formamides and strong bases such as LDA or *t*-BuLi.[1] Since the first report of these anions by Schöllkopf in 1967, they have been added to electrophiles including aldehydes, ketones, esters, alkyl halides, Bu_3SnCl, and trialkylsilyl chlorides.[2] Enders subsequently reported the addition of chiral prolinol-derived carbamoyl anions to ketones in diastereomeric excess of up to 30%.[3] In 2013, we reported the first reaction of carbamoyl anions with imine electrophiles, using the diastereoselective addition to *N*-sulfinyl imines to obtain α-amino amides (Figure 1A).[4] Subsequently we reported the addition of these anions to nitrones to provide α-(*N*-hydroxy)amino amides (Figure 1B).[5] Li and co-workers further extended the reactivity of carbamoyl anions to a diastereoselective reaction with chiral *N*-phosphinyl aldimines (Figure 1C).[6] The addition of nucleophiles to the C=N double bond of azirines serves as a convenient entry to C-substituted N−H aziridines.[7] A plethora of nucleophiles have been reported to add to azirines, including organolithiums,[8] Grignard reagents,[9] N−H compounds,[9c,10] phosphites,[11] thiols,[12] $TMSCF_3$,[13] TMSCN,[13,14] and hydride.[15] Given this excellent demonstrated reactivity of azirines, we reasoned that carbamoyl anions should also add readily to the strained heterocycles to provide 2-aziridinyl amides (Figure 1D). Aziridines are present in natural products and pharmaceuticals, and can serve as useful precursors to diverse functionalities.[16] Aziridinyl carboxylates and their derivatives are valuable precursors to unnatural amino acids.[17] When incorporated into peptides, they provide a convenient handle for site-selective ligation with thiol containing molecules.[18] Thus, new routes to these valuable building blocks are desirable. Herein, we report the scope of the addition of carbamoyl anions to azirines and its application to the synthesis of an aziridinyl peptide.

Initial feasibility studies were performed using 2,3-diphenyl-2*H*-azirine **1** and *N*,*N*-diisopropylformamide (Scheme 1). We

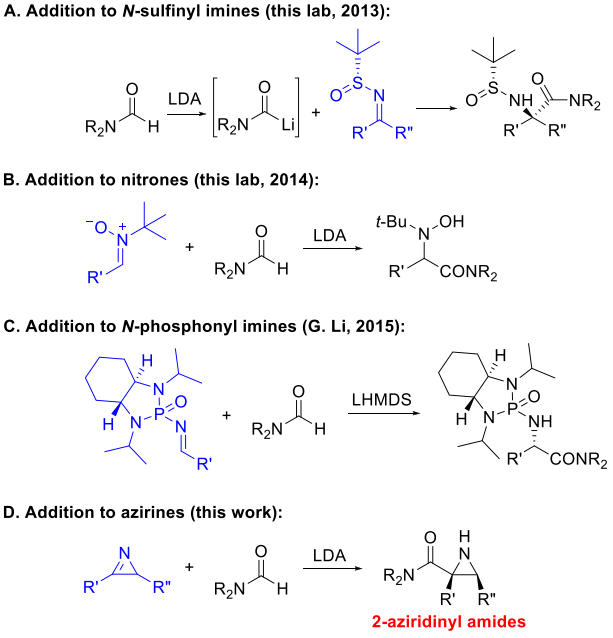


Figure 1. Previously reported reactions of carbamoyl anions with *N*-sulfinyl imines (A), nitrones (B), and *N*-phosphonyl imines (C), and the extension to azirines (D) reported herein.

previously reported that addition of LDA to a solution of an *N*-sulfinyl imine and an *N*,*N*-disubstituted formamide proved optimal.[4] This protocol minimizes carbamoyl anion decomposition since the electrophile is present in the reaction mixture and able to immediately react with the anion. We

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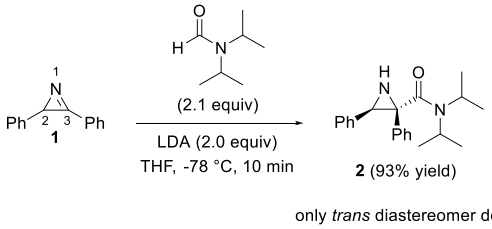
Scheme 1. Reaction Optimization of Addition to 2*H*-Azirine 1



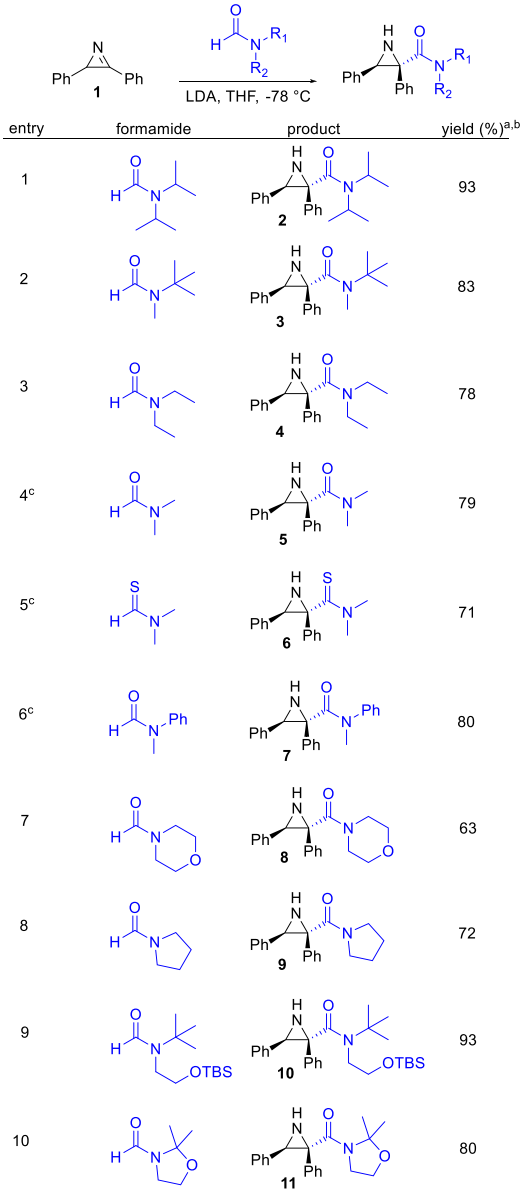
reasoned that potential competitive deprotonation of the azirine **1** by LDA should be disfavored since the resulting anion would be antiaromatic.[19] Thus, addition of LDA (2.0 equiv) to a cold (−78 °C) THF solution of **1** and *N*,*N*-diisopropylformamide (2.1 equiv) gave full conversion to adduct **2** after 10 min. ^{1}H NMR analysis of the crude product after workup showed the presence of a single diastereomer, with the expected *trans* relationship of the carboxamide and adjacent phenyl group. The aziridinyl amide **2** was isolated in 93% yield after chromatographic purification.

With the reaction conditions defined, the scope of the addition with respect to formamides was explored (Table 1). The reaction worked well for sterically demanding (entries 1 and 2) as well as smaller (entries 3 and 4) *N*,*N*-dialkylformamides. The addition of a thioformamide was possible (entry 5). For generation of small carbamoyl and thiocarbamoyl anions (entries 4 and 5) as well as *N*-aryl carbamoyl anions (entry 6), the bulkier base LiTMP was employed instead of LDA to avoid transformylation from the formamides to LDA.[5] Cyclic formamides were compatible with the reaction conditions (entries 7 and 8). Finally, the use of formamides bearing silyl ether (entry 9) or aminal (entry 10) moieties was feasible.

The reaction scope for a set of structurally diverse azirines was examined next (Table 2). The incorporation of a pyridyl group into the azirine was tolerated (entry 1), and the corresponding aziridine **13** was obtained in good yield. Vinyl azirine **14** reacted smoothly, providing the adduct **15** in high yield (entry 2). Notably, vinyl aziridines have been demonstrated to be versatile substrates for derivatization to a wide array of acyclic and heterocyclic compounds.[20] Azirines possessing geminal disubstitution on the 3-carbon were also compatible and gave tetrasubstituted aziridine products in good yields (entries 3−5). The azirines bearing gem-disubstitution in the form of a spirocycle, as in entries 4 and 5, furnished novel spirocyclic aziridinyl amides. Notably, the highly strained spirocyclopropane in azirine **18** remained intact and the azaspirocyclopentane **19** was obtained in good yield (entry 4). Azirines bearing alkyl groups at the 2-position were amenable to the reaction (entries 6−8), although in these cases the carbamoyl anion was generated prior to introduction of the azirine. This protocol, which we originally employed for additions of carbamoyl anions to enolizable *N*-sulfinyl imines,[4] avoided side reactions due to deprotonation of the α-protons of the alkyl group by LDA.[21] The cyclooctane fused azirine **26** reacted smoothly to give the bicyclic aziridine product **27** in high yield (entry 8). Finally, the incorporation of a trifluoromethyl group in azirine **28** provided the corresponding aziridine **29** in good yield (entry 9).

Azirines lacking substituents in the 2-position are generally less stable than their more substituted counterparts.[7] This

Table 1. Formamide Scope in the Reaction with Azirine 1



[a]Typical reaction conditions: **1** (1.0 equiv), formamide (2.1 equiv), THF, −78 °C; add LDA solution (2.0 equiv, 2.0 M). [b]The diastereoselectivity as measured by ^{1}H NMR of the crude product was >97:3 in all cases. [c]Lithium 2,2,6,6-tetramethylpiperidide (3.0 equiv) and formamide (3.1 equiv) used for these examples.

lower stability can make their isolation and purification challenging. Furthermore, these compounds are generally prepared by thermal or photochemical decomposition of high energy vinyl azides.[22] To avoid the safety concerns of vinyl azides and to bypass isolation, we developed an *in situ* *O*-tosylation, Neber-type azirine formation, and subsequent carbamoyl anion addition, all in the same pot (Scheme 2). Treatment of acetophenone oxime **30** with NaH followed by TsCl resulted in formation of *O*-tosyl oxime **31**. Addition of *N*,*N*-diisopropylformamide followed by LDA to the reaction mixture at −78 °C provided the aziridine **33** in 54% isolated yield. The reaction presumably occurs via deprotonation of the *O*-tosyl oxime **31** and subsequent cyclization to azirine **32**,[23] which reacted with the concurrently generated carbamoyl-

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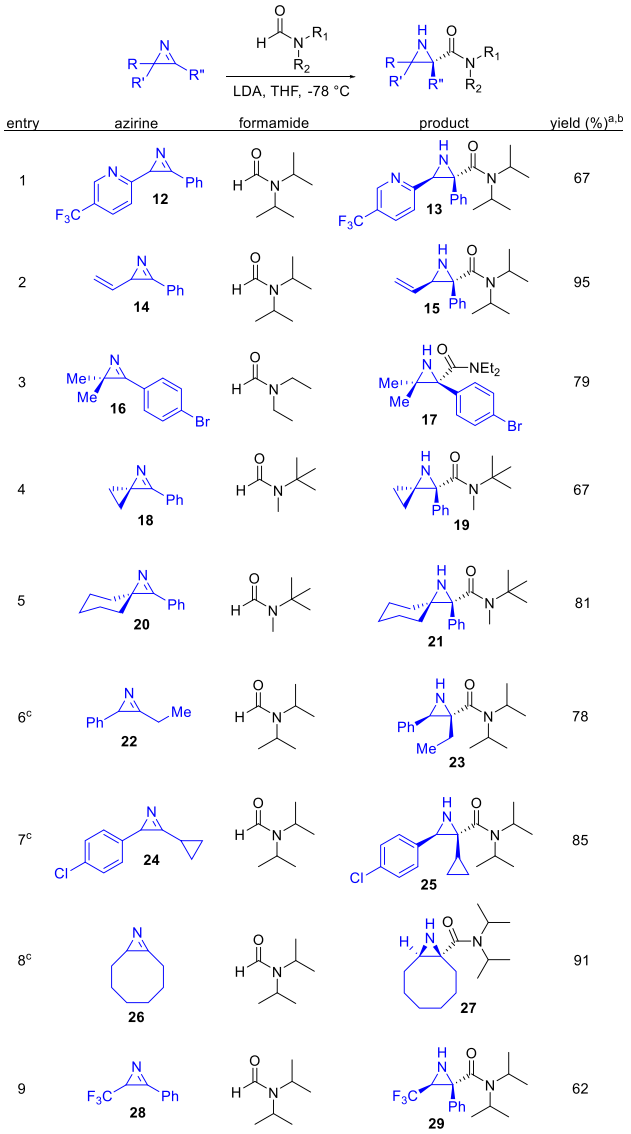
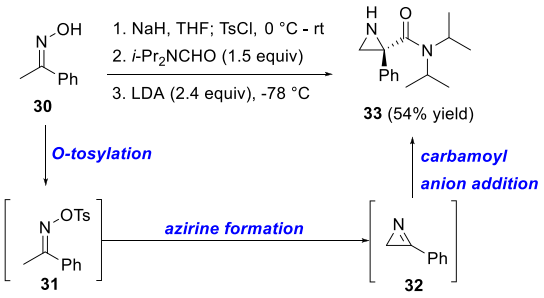
Table 2. Scope of Azirine in Carbamoyl Anion Addition



[a]Typical reaction conditions: azirine (1.0 equiv), formamide (2.1 equiv), THF, −78 °C; add LDA solution (2.0 equiv, 2.0 M). [b]The diastereoselectivity for entries 1−2 and 6−9 as measured by ^{1}H NMR of the crude product was >97:3 in all cases. [c]The carbamoyl anion was generated first and the azirine added immediately thereafter.

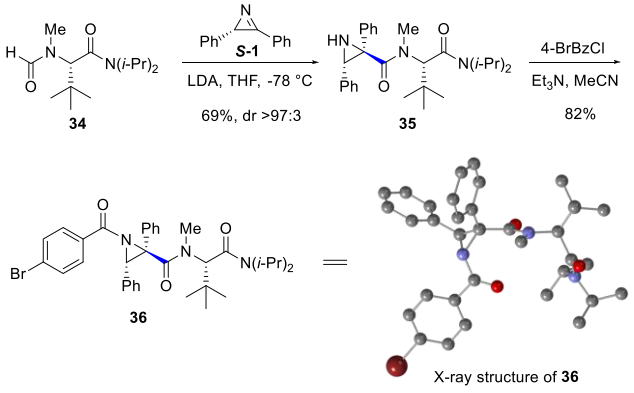
Scheme 2. One-Pot Azirine Formation/Carbamoyl Anion Addition



lithium reagent to give the aziridine **33**. This one-pot process conveniently avoids potentially dangerous azide chemistry for the formation of azirine **32** and the need to isolate and purify an unstable azirine.

The methodology was applied to the synthesis of an aziridinyl peptide (Scheme 3).[24] We previously reported the

Scheme 3. Synthesis of a Peptidyl Aziridine



synthesis of formamide **34** by the addition of *N*,*N*-diisopropyl carbamoyllithium to an *N*-sulfinyl imine, and subsequent sulfinyl deprotection, *N*-formylation, and *N*-methylation.[4] Treatment of **34** with LDA in the presence of enantiopure azirine *S*-**1**[25] resulted in the formation of the aziridinyl peptide **35** with >97:3 diastereoselectivity and a 69% yield after isolation by crystallization. Acylation of **35** with 4-bromobenzoyl chloride gave the dipeptidyl aziridine **36** in 82% yield. Single crystal X-ray structure analysis confirmed the stereochemistry at the newly formed quaternary aziridine carbon.

In summary, azirines have been shown to be competent electrophiles for the addition of carbamoyl anions. The reaction is amenable to a wide variety of formamides as well as significant structural diversity of the azirine. The product aziridines are formed with high *trans* diastereoselectivity from 2,3-disubstituted azirines. A one-pot conversion of a ketoxime to a 2,2-disubstituted aziridinyl amide was demonstrated. The reaction could be employed for the synthesis of an aziridine containing peptide.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01334.

Experimental procedures, spectroscopic data, and NMR spectra (PDF)

Accession Codes

CCDC 2077072 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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