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Amine-Promoted Synthesis of Vinyl Aziridines

Alan Armstrong,*[,†] Robert D. C. Pullin,[†] Chloe R. Jenner,[†] and James N. Scutt[‡]

[†]*Department of Chemistry, Imperial College London, South Kensington, London, SW7 2AZ, United Kingdom, and* [‡]*Syngenta Ltd., Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, United Kingdom*

a.armstrong@imperial.ac.uk

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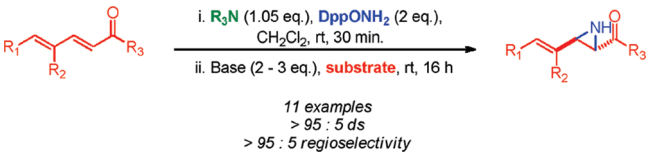

N-Unsubstituted vinyl aziridines were synthesized via an amine-promoted regioselective nucleophilic aziridination of α,*β*,*γ*,*δ*-unsaturated carbonyl compounds. The reaction is completely regioselective (>95: 5) for the α,*β*-alkene and completely diastereoselective, affording the *trans*-vinyl aziridine in moderate-to-good yields.

Aziridines are versatile building blocks for the synthesis of diverse nitrogen-containing products via ring-opening and ring-expansion reactions.[1−5] Vinyl aziridines are a particularly interesting class of aziridine that lend themselves to a host of highly useful synthetic transformations. They are versatile electrophiles and notably undergo regioselective ring-opening via addition at either the vinyl terminus[6] or directly at the aziridine depending on the reagents employed.[7] Moreover, vinyl aziridines can be exploited in a variety of ring-expansion reactions to afford a range of heterocyclic products, including piperidines,[8] pyrrolines,[9] imidazolidinones,[10] *β*-lactams,[11] and azepines.[12] Strategies for their synthesis include guanidinium ylide addition to α,*β*-unsaturated aldehydes,[13] nitrenoid additions to 1,3-dienes,[14] elimination from amino- or azido-alcohols,[15] and Wittig reactions of aziridine-2-carbaldehydes,[16] with the most common strategy involving allyl ylide addition to imines.[17] However, it is notable that few methods provide the desired vinyl aziridines with consistently high levels of cis/trans diastereoselectivity for a broad range of substrates.

We have previously reported[18] a diastereoselective aziridination of α,*β*-unsaturated carbonyl compounds to afford *trans*-aziridines in good to excellent yield (Scheme 1).[19] Our method involves the amination of a tertiary amine, which in the presence of base is presumed to form a reactive *N*-*N* ylide (referred to as an *aminimine* or *aminimide*), which subsequently undergoes conjugate addition to α,*β*-unsaturated carbonyl compounds, followed by ring-closure to afford the *NH*-aziridine. The tertiary amine mediator is regenerated in this step, and can in principle be used in substoichiometric quantities. The reaction proved broad in scope allowing the aziridination of α,*β*-unsaturated ketones bearing either *β*-alkyl, aromatic, or heterocyclic aromatic substituents, and significantly also allowed the aziridination of α,*β*-unsaturated esters, a challenge not possible via iminium ion organocatalytic aziridination methods.[20] We were also able to

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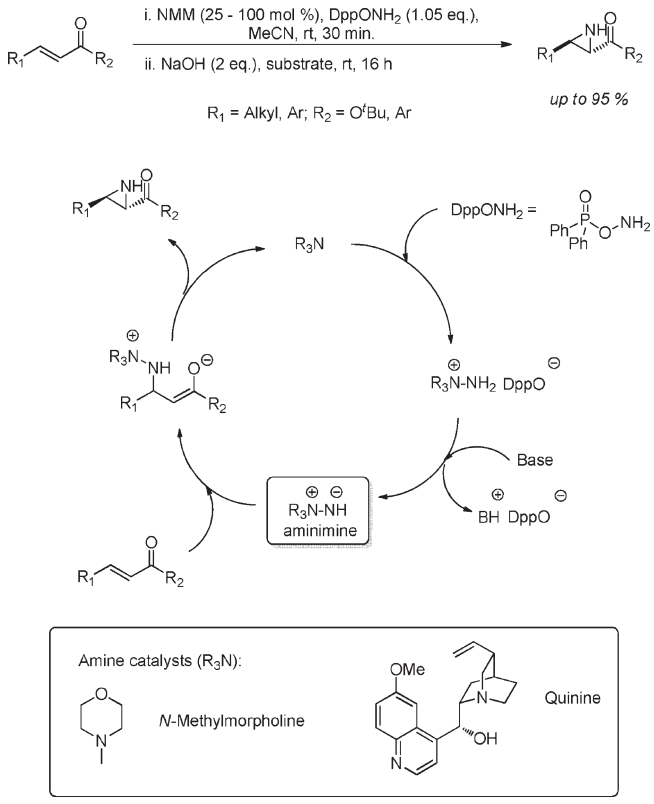
SCHEME 1. Approach to Organocatalytic Alkene Aziridination



induce promising levels of asymmetric induction via the use of quinine and related cinchona alkaloid tertiary amines.[18a] We were keen to extend the application of our developed aziridination to the aziridination of dienones in order to provide the vinyl aziridine motif. To the best of our knowledge there exist only two isolated instances of the regioselective aziridination of α,β,γ,δ-unsaturated carbonyl compounds. Ito presented complementary conditions for either the cis- or trans-selective aziridination of an α,β,γ,δ-unsaturated amide at the α,β-position, with stereoselectivity governed by choice of lithiated diaziridine reagent.[21] Additionally Xu has reported two examples of the aziridination of α,β,γ,δ-unsaturated ketones, via a Cu-catalyzed nitrene addition in the presence of a bisoxazoline ligand, with the reaction selective for the γ,δ-alkene of the substrate and providing the *cis*-aziridine.[22] Herein, we describe the adaptation of our own nucleophilic aziridination chemistry to provide a novel method for the diastereoselective synthesis of unprotected-*NH*-vinyl aziridines.

Initially we attempted to extend our reported reaction conditions[18a] to the aziridination of the diphenyl-substituted dienone cinnamylideneacetophenone **1a** (Table 1, entry 1). Pleasingly we were able to isolate the vinyl aziridine **2a** in moderate yield (42%), although it appeared that the reactivity of the diene substrate was lower than that of the α,β-unsaturated carbonyl compounds studied earlier. The reaction was found to be selective for the α,β-alkene of the substrate, as determined by strong ^2J and ^3J HMBC correlations

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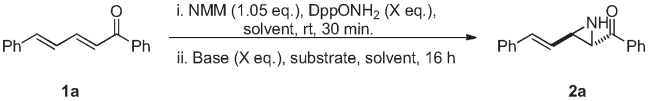
TABLE 1. Optimization of the Reaction Conditions for Aziridination of Dienone 1a



1a 2a

entry[a]	base	base (equiv)	solvent	$DppONH_2$ (equiv)	NMR yield[b] (%)
1	NaOH	2	MeCN	1	42[c]
2[d]	NaOH	2	MeCN	1	41
3	NaH/^{i}PrOH	2	CH_2Cl_2	1	45
4[d]	NaH/^{i}PrOH	2	CH_2Cl_2	1	37
5	NaH/^{i}PrOH	2	CH_2Cl_2	1.5	54
6	NaH/^{i}PrOH	3	CH_2Cl_2	1.5	62
7	NaH/^{i}PrOH	3	CH_2Cl_2	2	67
8	KO^{t}Bu/THF[e]	3	CH_2Cl_2	2	83

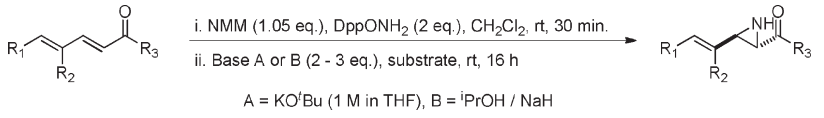
[a]Reactions performed at 0.06 M in substrate on a 0.12 mmol scale. [b]Yield determined by ^{1}H NMR with Bn_2O as the internal standard. [c]Isolated yield after flash column chromatography. [d]Reaction performed at 0.12 M in substrate on 0.12 mmol scale. [e]1 M solution of KO^{t}Bu in THF

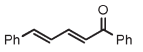
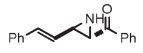
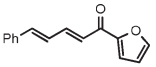
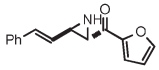
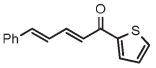
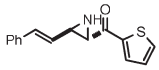
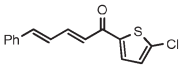
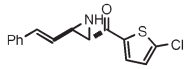
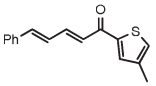
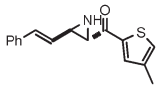
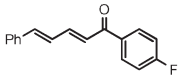
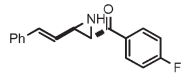
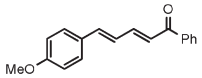
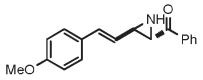
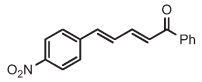
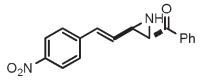
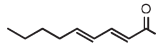
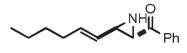
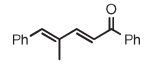
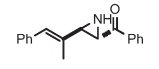
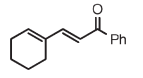
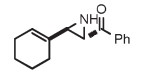
between the carbonyl carbon and the C*H* protons of the aziridine ring, and an absence of carbonyl carbon correlations to either vinylic proton. The reaction was also completely diastereoselective (>95: 5 by NMR spectroscopy) for the *trans*-aziridine as determined by $^3J_{2H-3H}$ coupling constants of the aziridine ring ($^3J_{2H-3H}$ = 2.6 Hz; generally the cis value is ca. 7−9 Hz and the trans value is ca. 2−4 Hz).[13−17]

Keen to optimize the yield of the vinyl aziridine, we screened alternative base and solvent combinations that had afforded high product yields in our previous work with amine-promoted aziridination (entries 3 and 4). Only a minimal improvement in the yield of vinyl aziridine was observed, including at a doubled concentration, but the majority of remaining material was returned as unreacted starting material. It was found the combination of NaH/^{i}PrOH in CH_2Cl_2 at a concentration of 0.06 M in substrate gave the best combined yield of product (45%) and return of starting material (entry 3) and optimization continued with these conditions. We decided to investigate the effect of varying the equivalents of aminating agent, $DppONH_2$. Pleasingly, it was found that an increase from 1.0 to 1.5 equiv, still with 2 equiv of base, increased the yield of vinyl aziridine to 54% and this could be improved further to 62% by using 3.0 equiv of base (entries 5 and 6). The yield could further be enhanced (to 67%) utilizing 2.0 equiv of $DppONH_2$ with 3.0 equiv of base (entry 7). In earlier work, we had found KO^{t}Bu in DMSO to be an effective base for aziridination using stoichiometric hydrazinium salts.[18b] Preliminary attempts to aziridinate **1a** by using this base/solvent combination with NMM and $DppONH_2$ led only to very low yields of aziridine. However, use of a commercial THF solution of KO^{t}Bu in CH_2Cl_2 was more successful, and pleasingly gave an increase to 83% (entry 8).

With two effective sets of reaction conditions in hand (entries 7 and 8) we then sought to apply the conditions to a range of different diene substrates, synthesized via either an aldol condensation or a Wittig reaction (see the Supporting Information) (Table 2). The reaction proved applicable to a range of diene substrates providing the vinyl aziridines in moderate to good yield. While either NaH/^{i}PrOH or KO^{t}Bu

TABLE 2. Investigation into the Substrate Tolerance of the Dienone Aziridination



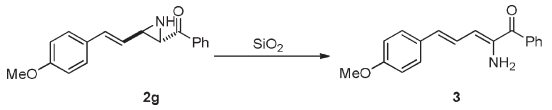
entry[a]	substrate		product		base (eq.)	isolated yield (%)[b]
1		**1a**		**2a**	A (3)	79
2		**1b**		**2b**	B (3)	64
3		**1c**		**2c**	B (3)	69
4		**1d**		**2d**	B (3)	70
5		**1e**		**2e**	A (3)	67
6		**1f**		**2f**	A (3)	46
7		**1g**		**2g**	B (3)	78[c]
8		**1h**		**2h**	A (2)	30
9		**1i**		**2i**	A (2)	62
10		**1j**		**2j**	B (3)	67
11		**1k**		**2k**	A (2)	60

[a]Reactions performed at 0.06 M in substrate on a 0.12−0.24 mmol scale. [b]Isolated yield after flash column chromatography. [c]Yield determined by ^{1}H NMR spectroscopy, using Bn_2O as the internal standard. This product underwent decomposition on attempted purification (see Scheme 2).

was generally effective as a base, KO^{t}Bu gave slightly better results with electron-deficient substrates and also those possessing alkyl groups. Cinnamylideneacetophenone **1a** afforded the diphenyl-substituted vinyl aziridine **2a** in very good yield (79%) (entry 1), and a variety of heterocyclic aromatics, including furyl **1b** (entry 2) and thiophenyl-C1 substituents **1c**−**e** (entries 3−5) also performed well (64−70%). The reaction was also tolerant of electron-deficient aromatics at C1, with *p*-F-substituted diene **1f** affording vinyl aziridine **2f**, albeit with a slight drop in yield (46%) (entry 6). Various substituents at C5 were also tolerated. The strongly electron-rich 4-methoxyphenyl diene **1g** gave very good conversion to vinyl aziridine **2g** (78%) (entry 7). Interestingly the product was found to rearrange to diene **3** upon attempted flash column chromatography purification, using either silica gel or neutral alumina, presumably via either a Bronsted or Lewis acid-promoted ring-opening via a stabilized allyl cation (Scheme 2).

Strongly electron-withdrawing C5 substitution was also permitted although the 4-nitrophenyl-substituted dienone **1h** did afford a lower yield of the aziridine and the reaction appeared to benefit from a reduced amount of base (entry 8). It seems the aziridination reaction appears to be less tolerant of electron-deficient substrates (entries 6 and 8), which is in contrast to the previously observed reactivity of α,β-unsaturated carbonyl compounds.[18] In most cases it was possible to recover unreacted starting material although this was not possible with substrates **1f** and **1h** and we believe the lower yields for these reactions are the result of partial decomposition of the more electron-deficient substrates. We were pleased to extend the scope of the reaction to δ-alkyl-substituted dienes, with optimal yields achieved by utilizing 2 equiv of base. Indeed primary butyl C5-substituted diene **1i** and cyclic derivative **1k** both underwent reaction to afford vinyl aziridines **2i** and **2k** in good yield (60−62%) (entries 9 and 11). The reaction was also found to be tolerant of branching at the C4-position with aziridines **2j** and **2k** isolated in respectable yield (60−67%) (entries 10 and 11).

SCHEME 2. Rearrangement of Aziridine 2g to Diene 3



In all cases the aziridination was completely regioselective for the α,β-alkene and also completely diastereoselective for

the *trans*-aziridine. In no case was the *cis*-aziridine observed. The complete control of diastereoselectivity observed is in contrast with many of the current methods used to prepare vinyl aziridines, where consistently high levels of diastereocontrol are rare.[16,17b−d,17f] We are currently investigating the utility of the aziridine products to provide diastereocontrolled access to functional amine building blocks.

In summary, we have developed a method for the synthesis of *trans*-*N*-unprotected-vinyl aziridines utilizing an amine-promoted nucleophilic aziridination of α,β,γ,δ-unsaturated carbonyl compounds. The reaction was observed to be completely regio- and diastereoselective and the scope tolerant of a range of diene substrates. Current studies are focused on the development of an asymmetric version of the reaction and also applications of the methodology to total synthesis. Further results will be reported in due course.

Experimental Section

General Procedures for the Aziridination of Dienes 1a−k: Synthesis of Vinyl Aziridines 2a−k: (*E*)-(2*R,3*S**)-Phenyl[3-(styryl)-aziridin-2-yl]methanone, 2a.** *N*-Methylmorpholine (NMM) (27.7 μL, 0.25 mmol) was added dropwise over 1 min to a solution of *O*-diphenylphosphinyl hydroxylamine ($DppONH_2$) (112 mg, 0.48 mmol) and dibenzyl ether (11.4 μL, 0.06 mmol) in CH_2Cl_2 (4 mL) at room temperature and the mixture was stirred for 0.5 h. Either KO^{t}Bu (0.36 mL, 1 M in THF, 0.36 mmol) or ^{i}PrOH (27.6 μL, 0.36 mmol) and NaH (60% in mineral oil) (14.4 mg, 0.36 mmol) were then added followed by cinnamylideneacetophenone (56 mg, 0.24 mmol) and the mixture was allowed to stir at room temperature overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (4 mL) and the aqueous layer was separated and extracted with CH_2Cl_2, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc/^{i}hexane) afforded **2a** (49.3 mg, 79%) as a yellow oil; R_f (20% EtOAc/^{i}hexane) 0.40; ν_{max} (ATR) 3267, 1671, 1602, 1582, 1255, 966 cm^{-1}; δ_H (400 MHz, CD_3OD) 8.05−8.10 (2H, m, Ar*H*), 7.63−7.69 (1H, m, Ar*H*), 7.52−7.57 (2H, m, Ar*H*), 7.40−7.45 (2H, m, Ar*H*), 7.28−7.34 (2H, m, Ar*H*), 7.21−7.26 (1H, m Ar*H*), 6.81 (1H, d, J = 16.0 Hz, PhC*H*═), 6.05 (1H, dd, J = 16.0 and 8.2 Hz, PhCH═C*H*−), 3.76 (1H, d, J = 2.6 Hz, 2-C*H*N), 2.86 (1H, dd, J = 8.2 and 2.6 Hz, 3-C*H*N); δ_C (100 MHz, CD_3OD) 197.1, 137.9, 137.4, 135.3, 135.2, 130.2, 129.8, 129.5, 129.2, 128.7, 127.6, 44.4, 42.1; m/z (ES^+) 250 (MH^+, 100%), 272 (MNa^+, 30); m/z HRMS (ES^+) MH^+ calcd for $C_{17}H_{16}NO$ 250.1232, observed 250.1241.

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Supporting Information Available: Experimental procedures, including full optimization studies, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.