

Asymmetric Synthesis of 2*H*-Azirine
3-Carboxylates

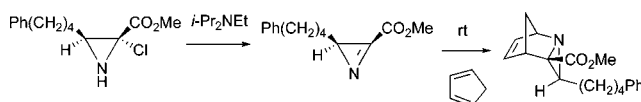
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Received February 12, 2007

ABSTRACT



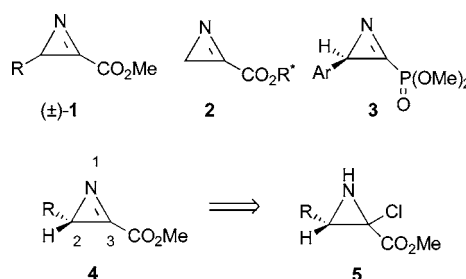
Dehydrochlorination of methyl 2-chloroaziridine 2-carboxylates generates the first examples of enantiopure 2-substituted 2*H*-azirine 3-carboxylates which undergo the aza Diels–Alder reaction with dienes to give bicyclic and tricyclic aziridines in good yields.

The chemistry of 2*H*-azirines, the smallest unsaturated nitrogen heterocycle, has been extensively explored.¹ The C=N π -bond and nitrogen lone pair, activated by the high ring strain, partake in a variety of reactions with nucleophiles. 2*H*-Azirines also undergo Diels–Alder reactions, but are generally poor dienophiles reacting only with highly reactive dienes. However, Gilchrist and co-workers have shown that 2*H*-azirine 3-carboxylates such as (\pm)-**1**, available only in racemic form, are effective aza dienophiles and participate in a variety of cycloaddition reactions (Scheme 1).² These additions are highly regio- and stereoselective and consistent with endo addition of the azirine to the diene. Unfortunately, attempts to control the absolute stereochemistry by installing chiral auxiliaries (chiral ester and amide) in **1** were unsuccessful.³ However, using the same approach, Somfai and co-workers later found that Diels–Alder reactions with unsubstituted chiral aziridine **2** and Lewis acids resulted in bi- and tricyclic aziridines in good yields and in high selectivity.⁴ In 2002 we disclosed the first asymmetric synthesis of 2*H*-azirine-3-phosphonates (+)-**3** by Swern oxidation of *NH*-aziridine-2-phosphonates and demonstrated their utility as

new chiral aza dienophiles.⁵ Here we describe a new method for the asymmetric synthesis of 2-substituted 2*H*-azirines 3-carboxylates **1**, where the chirality resides within the azirine ring, and their Diels–Alder reactions.

Methods currently available for the preparation of azirines, including the thermal decomposition of vinyl azides and elimination reactions of functionalized aziridine, are not suitable for the asymmetric synthesis of 2*H*-azirine 3-carboxylates.¹ Vinyl azides lack chirality¹ and Swern oxidation of *NH* aziridine esters⁶ and elimination of sulfenic acid from *N*-sulfinyl aziridine esters always produce 2*H*-azirine 2-carboxylates.⁷ Conceptually, dehydrochlorination of a chiral 2-chloroaziridine 2-carboxylate **5** would have to give the desired enantiopure 2*H*-azirine 3-carboxylate **4**. We describe here the realization of this concept resulting in the first asymmetric synthesis of **4** where the chirality resides only at the 2-position (Scheme 1).

Scheme 1



(1) For recent reviews on 2*H*-azirines see: (a) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon Press: Oxford, UK, 1966, Chapter 1. (b) Palacios, F.; Ochoa de Retana, A. M.; de Marigorta, Z. M.; Manuel de los Santos, J. *Eur. J. Org. Chem.* **2001**, 2401. (c) Pinho e Melo, T. M. V. D.; Rocha Gonsalves, A. D. D'a. *Curr. Org. Synth.* **2004**, 1, 275.

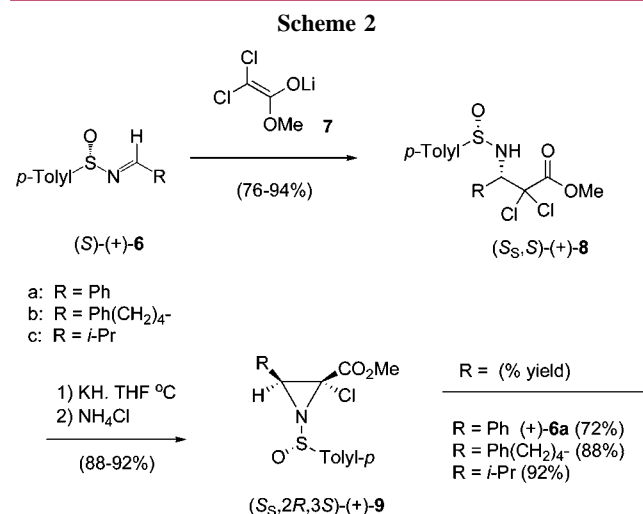
(2) Gilchrist, T. L. *Aldrichim. Acta* **2001**, 34, 51.

(3) (a) Alves, M. J.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 229. (b) Alvares, Y. S. P.; Alves, M. J.; Azoia, N. G.; Bickley, J. F.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1911.

(4) Timen, A. S.; Somfai, P. *J. Org. Chem.* **2003**, 68, 9958.

Although 2-halo 2*H*-azirines are known^{1d} methods for the synthesis of 2-haloaziridines usually result in low yields and mixtures of *cis* and *trans* isomers.⁸ Recently, De Kimpe and co-workers described the selective synthesis of *N*-tosyl 2-chloro-2-imidoylaziridines via the addition of dichloroaza-allylic anions to *N*-sulfonyl imines.⁸ However, there are no reports of the asymmetric syntheses of 2-haloaziridines.

Earlier studies from our laboratory demonstrated that the one-pot, highly diastereoselective aza-Darzens reaction of lithium α -bromo enolates with enantiopure sulfinimines (*N*-sulfinyl imines) is an important method for the asymmetric construction of aziridine 2-carboxylates.^{9,10} For the asymmetric synthesis of methyl 2-chloroaziridine 2-carboxylates **9**, we examined the addition of the lithium enolate of methyl dichloroacetate **7** to sulfinimines (*S*)-(+)-**6** (Scheme 2). The



dichloro enolate **7** was generated at -78°C by treatment of methyl dichloroacetate with LiHMDS.

The enolate was added to the appropriate sulfinimines (*S*)-(+)-**6**, affording the corresponding 2,2-dichloro- β -amino esters (*S*_S,*S*)-(+)-**8** in good to excellent yield as single enantiomers. The (*S*)-stereochemistry was assigned to the stereocenter at C-3 in **8** based on our earlier proposed six-membered chairlike transition state model for the addition of enolates to sulfinimines.¹¹

(5) Davis, F. A.; Wu, Y.; Yan, H.; Prasad, K. R.; McCoull, W. *Org. Lett.* **2002**, *4*, 655.

(6) Gentilucci, L.; Grijzen, Y.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, *36*, 4665.

(7) (a) Davis, F. A.; Reddy, G. V.; Liu, H. *J. Am. Chem. Soc.* **1995**, *117*, 3651. (b) Davis, F. A.; Liang, C.-H.; Liu, H. *J. Org. Chem.* **1997**, *62*, 3796. (c) Davis, F. A.; Liu, H.; Liang, C.-H.; Reddy, G. V.; Zhang, Y.; Fang, T.; Titus, D. D. *J. Org. Chem.* **1999**, *64*, 8929.

(8) For leading references to 2-haloaziridines see: Giubellina, N.; Mangelinckx, S.; Tornroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 5881.

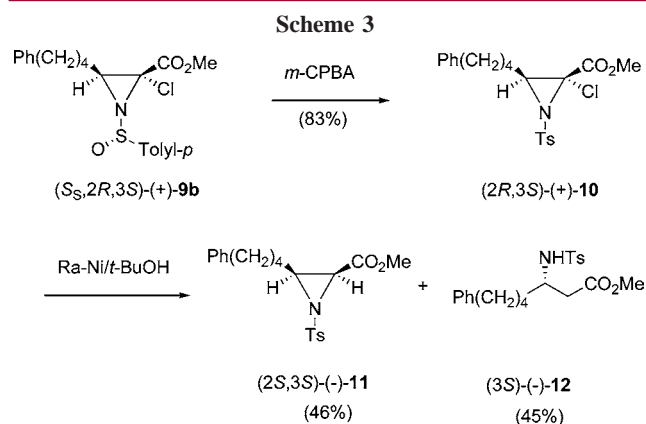
(9) (a) Davis, F. A.; Liu, H.; Zhou, P.; Fang, T.; Reddy, G. V.; Zhang, Y. *J. Org. Chem.* **1999**, *64*, 7559. (b) Davis, F. A.; Zhang, Y.; Rao, A.; Zhang, Z. *Tetrahedron* **2001**, *57*, 6345. (c) Davis, F. A.; Deng, J.; Zhang, Y.; Haltiwanger, R. C. *Tetrahedron* **2002**, *58*, 7135.

(10) For a review on the synthesis of chiral aziridines see: McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347.

(11) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387.

Cyclization of the β -amino esters **8** to the 2-chloroaziridines **9** was next explored. Treatment of **8** with NaH in THF gave low yields, ca. 20% of the corresponding aziridines **9b** and **9c** along with recovered starting material and decomposition products. Attempts to improve the yields by increasing the amount of hydride and increasing the reaction temperature were unsuccessful. With 2 equiv of KH at 0°C in THF, (+)-**8b** and (+)-**8c** gave (*S*_S,2*R*,3*S*)-(+)-**9b** and (*S*_S,2*R*,3*S*)-(+)-**9c** in 88% and 92% yields, respectively (Scheme 2). Under similar conditions, (+)-**8a** (R = Ph) gave the retro-Mannich product sulfinimine (*S*)-(+)-**6a** in 72% isolated yield. Retro-Mannich fragmentations of sulfinimine-derived sulfinamide products are usually rare because the *N*-sulfinyl group stabilizes anions at nitrogen.¹² However, in **8a** the combination of steric inhibition to chloride displacement and the stability of the dichloro enolate **7** apparently favors the retro-Mannich fragmentation.¹³

The absolute stereochemistry of methyl 2-chloroaziridine 2-carboxylate (+)-**9b** was assigned by transforming it into products of known absolute configuration as shown in Scheme 3. Oxidation of (+)-**9b** with *m*-CPBA gave the



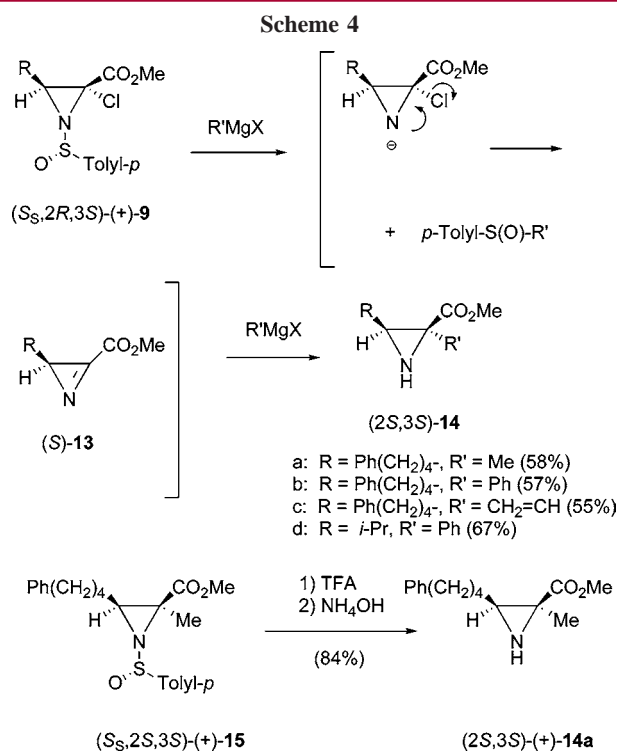
N-tosyl 2-chloroaziridine (+)-**10** in 83% isolated yield. When (+)-**10** was subjected to catalytic ring opening with Raney-Nickel in *t*-BuOH two products, aziridine (2*S*,3*S*)-(-)-**11** and β -amino ester (*S*)-(-)-**12**, were isolated in 45% and 46% yields, respectively. Under these conditions the C-2 chloro group is stereoselectivity replaced with a hydrogen atom, and aziridine ring opening gives the β -amino ester. Both (-)-**11** and (-)-**12** have previously been prepared,^{9c} which confirms the stereochemistry at C-3 in (+)-**8** as (*S*) and two stereocenters at C-2 and C-3 in the 2-chloroaziridines (+)-**9** as (2*R*) and (3*S*).

To induce dehydrochlorination in (+)-**9** it is necessary to first remove the *N*-sulfinyl group. Not unexpectedly, attempts to eliminate this group in the usual manner with TFA–MeOH or HCl–Et₂O resulted in decomposition. 2*H*-Azirine

(12) For leading references see: (a) Zhou, P.; Chen, B. C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (b) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.

(13) For a recent example of the sulfinimine retro-Mannich fragmentation see: Davis, F. A.; Zhang, Y.; Qiu, H. *Org. Lett.* **2007**, *9*, 833.

3-carboxylates are very reactive toward nucleophilic addition^{2,3} and would not be expected to survive these conditions. When we employed our MeMgBr tactic for selective removal of aziridine *N*-sulfinyl groups with (+)-**9b**, 2-methylaziridine 2-carboxylate (2*S*,3*S*)-**14a** was isolated as a single isomer in 58% yield (Scheme 4).^{7c} This result provides strong

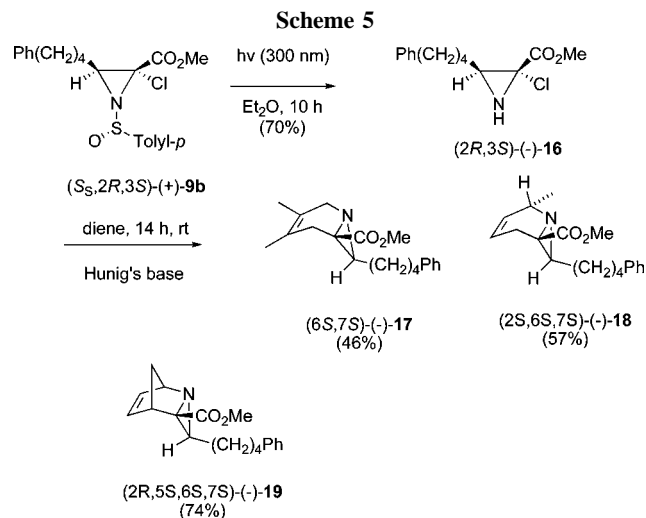


evidence for the formation of 2*H*-azirine 3-carboxylate (*S*)-**13** as an intermediate where the nitrogen anion induces the loss of the chloride anion (Scheme 4). The stereochemistry of the product results from addition of the Grignard reagent from the least hindered direction. The stereochemistry of **14** was determined by removal of the *N*-sulfinyl group in aziridine (+)-**15**,^{9c} a known compound, as shown in Scheme 4. Similar results were observed for the addition of phenylmagnesium bromide and vinylmagnesium chloride to **9b** and **9c**. This procedure represents a new way of preparing 2-substituted aziridine 2-carboxylates which are valuable precursors of enantiopure quaternary α -amino acids.^{7b}

It is not possible to carry out aza Diels–Alder reactions with 2*H*-azirine (*S*)-**13** because this highly reactive azirine does not survive the conditions currently employed for removal of the *N*-sulfinyl group. A new method, that does not require acids, bases, or protic solvents, is needed for elimination of the *N*-sulfinyl group in **9**. Photodesulfinylation is a solution to this problem. Although the selective photocleavage of the *N*-tosyl protecting group is well-known,¹⁴ related photocleavage of the *N*-sulfinyl groups has not been described.

(14) (a) Hamada, T.; Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140. (b) Art, J. F.; Kestemont, J. P.; Soumillon, J. P. *Tetrahedron Lett.* **1991**, 32, 1425. (c) Abad, A.; Mellier, D.; Pete, J. P.; Portella, C. *Tetrahedron Lett.* **1971**, 47, 4555.

Photolysis of (+)-**9b** in ether degassed with argon in a Pyrex vial at 3000 Å in a Rayonet photochemical reactor for 10 h gave 2-chloroaziridine (–)-**16** in 70% yield following chromatography (Scheme 5). Significantly, (–)-



16 is the first stable example of an *N*-unprotected α -halo- α -amino ester.¹⁵ The reluctance of (–)-**16** to eliminate HCl is likely due to the added strain energy that results in formation of the C–N double bond in the three-membered aziridine ring. Attempts at chromatographic isolation of azirine (*S*)-**13** by reaction of **16** with Et₃N or Hunig's base were unsuccessful, resulting in decomposition.

It was found to be more efficient to conduct the aza Diels–Alder reaction with crude (–)-**16**. Following the photodesulfinylation of (+)-**9b**, the crude reaction mixture was treated with 100 equiv of the appropriate diene, 2,3-dimethyl-1,3-butadiene, *trans*-piperylene, or cyclopentadiene, and a few drops of Hunig's base. After the solution was stirred for 8 h at rt, the enantiopure bicyclic and tricyclic aziridine carboxylates (–)-**17**, (–)-**18**, and (–)-**19** were isolated as single isomers in 46% to 74% yield for the two steps by chromatography (Scheme 5). The structures assigned to these aziridines are based on endo addition of the 2*H*-azirine 3-carboxylated aza dienophile (*S*)-**13** as previously reported.^{2,3,5}

In summary, the first asymmetric synthesis of 2-substituted 2*H*-azirine 3-carboxylates has been accomplished by dehydrochlorination of 2-chloroaziridine 2-carboxylates. These azirines readily undergo the aza Diels–Alder reaction with dienes to give enantiomerically pure bi- and tricyclic aziridine carboxylates in good yields. Highlights of this methodology include the following: (1) a new method for the asymmetric synthesis of 2-substituted aziridine 2-carboxylates; and (2) the first synthesis of a stable *N*-unprotected α -halo amino ester. Photodesulfinylation of sulfinamides represents an

(15) For leading references to attempts to prepare α -fluoro- α -amino acids see: Huber, D. P.; Stanek, K.; Togni, A. *Tetrahedron: Asymmetry* **2006**, *17*, 658.

important new procedure, not requiring acids or bases, for removal of the valuable amine *N*-sulfinyl protecting group.

Acknowledgment. We thank Fang Yu (Temple University) for aid with the photochemical apparatus. This work was supported by grants from the NIH-NIGMS (GM578970 and GM51982).

Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL070365P