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2*H*-Azirine 3-Phosphonates: A New Class of Chiral Iminodienophiles. Asymmetric Synthesis of Quaternary Piperidine Phosphonates

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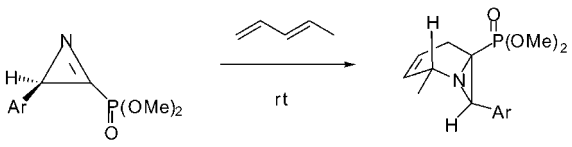
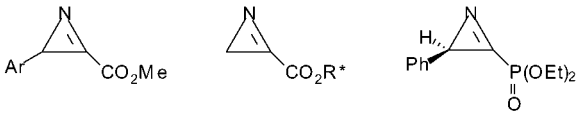
ABSTRACT



Diels–Alder reactions of enantiomerically enriched 2*H*-azirine 3-phosphonates and dienes stereoselectively furnish optically pure, bicyclic aziridine adducts that on hydrogenation afford the first examples of enantiopure quaternary piperidine phosphonates.

The theoretical, mechanistic, and synthetic chemistry of 2*H*-azirines, the smallest unsaturated nitrogen heterocycles, has been extensively explored.[1] Activated by the high ring strain, the C−N π-bond and nitrogen lone pair participate in a wide variety of reactions with electrophiles and nucleophiles, including cycloaddition reactions. Although simple 2*H*-azirines are more reactive than acyclic imines, which are generally poor dienophiles, they only participate in Diels−Alder reactions with highly reactive dienes.[2] Studies by Gilchrist and co-workers, however, have shown that activated 2*H*-azirines such as **1** are effective iminodienophiles and can participate in a variety of cycloaddition reactions (Scheme 1).[3] These additions were observed to be highly regio- and stereoselective and were consistent with endo addition of the azirine to the diene. Because of the remoteness of the auxiliary from the azirine three-membered ring, in chiral 2*H*-azirine 3-carboxylate **2** (R* = (*N*,*N*-diethylsulfamoyl)-isoboronyl) this azirine displays poor diastereoselectivities in cycloaddition reactions.[4] Methods for the asymmetric synthesis of **1** have not been reported.

Scheme 1



(±)-**1** **2** (*R*)-(+)-**3**

Recently we disclosed the first asymmetric synthesis of 2*H*-azirine 3-phosphonate (*R*)-(+)-**3** by Swern oxidation of the corresponding NH-aziridine phosphonate (Scheme 1).[5,6] 2*H*-Azirine 3-phosphonate **3** is the major product, which was unexpected because similar oxidations of NH-aziridine carboxylates afford the 2*H*-azirine 2-carboxylate exclusively.[7]

(1) For reviews on the chemistry of azirines, see: (a) Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry*; Lowowski, W., Ed; Pergamon Press: Oxford, 1984; Vol. 7, Chapter 5, p 47. (b) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C.; Padwa, A. *Comprehensive Heterocyclic Chemistry II*; Pergamon Press: Oxford, 1996; Chapter 1, p 1; (c) Nair, V. In *Heterocyclic Compounds*; Hassner, A., Ed.; John Wiley & Sons: New York, 1983; Chapter 2, p 215. (d) Fowler, F. W. In *Advances in Heterocyclic Chemistry*; Academic Press: New York, 1971; p 45.

(2) For a review, see: Anderson, D. J.; Hassner, A. *Synthesis* **1975**, 483.

(3) For a review, see: Gilchrist, T. L. *Aldrichimica Acta* **2001**, *34*, 51.

(4) Alves, M. J.; Bickley, J. F.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1399.

(5) Davis, F. A.; McCoull, W. *Tetrahedron Lett.* **1999**, *40*, 249.

(6) For the asymmetric synthesis of 2*H*-azirine 2-phosphonates (up to 52% ee) using the Neber reaction, see: Palacios, F.; de Retana, A. M. O.; Gil, J. I. *Tetrahedron Lett.* **2000**, *41*, 5363.

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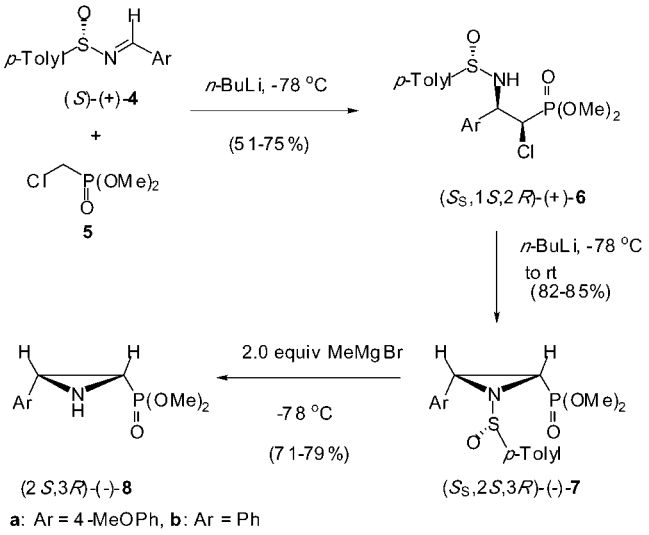
We attributed this finding to the fact that the acidifying effect of a C-2 carboxylate ester is much less than the phosphonate ester: the former cannot easily stabilize a pyramidal α-anion on an aziridine ring.[5] We have found that 2*H*-azirine 3-phosphonates, a new class of chiral iminodienophiles, undergo the Diels−Alder reaction with a variety of dienes and that the adducts are useful precursors of novel enantiopure α-amino phosphonates. α-Amino phosphonates are important surrogates of α-amino acids and as such exhibit a range of biological activities.[8]

Synthesis of 2*H*-Azirine 3-Phosphonates. Treatment of dimethyl chloromethylphosphonate (**5**)[9] (2 equiv) and the anisaldehyde- or the benzaldehyde-derived sulfinimines (*S*)-(+)-**4a** or (*S*)-(+)-**4b**[10] (1 equiv) with *n*-butyllithium (2.1 equiv) at −78 °C afforded α-chloro-*β*-amino adducts (S_S,1*S*,2*R*)-(+)-**6** (Scheme 2). Flash chromatography gave

Scheme 2

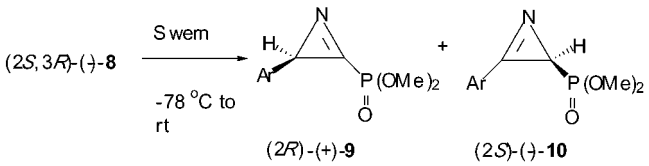


(+)-**6a** and (+)-**6b** in 51 and 58% isolated yields, respectively.[11] Minor amounts, 10 to 15%, of the other α-chloro-*β*-amino isomers were detected by ^{1}H NMR, but were not isolated. The α-chloro-*β*-amino adducts **6** were readily transformed into the corresponding aziridines (S_S,2*S*,3*R*)-(−)-**7a**,**b**, in excellent yield (82−85%), by reaction with 1.1 equiv of *n*-BuLi at −78 to rt. The absolute stereochemistry of these aziridines was based on analogy to (*R*)-(+)-**3**,[5] and the cis relationship of the C-2 and C-3 substituents was assigned by the coupling constant of 7.5 Hz.[5,12]

The sulfinyl auxiliary in *N*-sulfinyl aziridines is normally easily removed under acidic conditions with TFA/MeOH.[5,12] Indeed NH-aziridine (−)-**8b** was obtained in 71% yield using this protocol. However, application of these conditions to **7a** led to decomposition, undoubtedly related to the activating effect of the *p*-methoxy group, which results in ring-opening reactions. The sulfinyl group in **7a**,**b** was readily removed, without ring-opening, on reaction with 2 equiv of MeMgBr to afforded methyl *p*-toluenesulfoxide and NH-aziridines **8a** and **8b** in 71−79% yield (Scheme 2).

Swern oxidation [DMSO/$(COCl)_2$ and then Et_3N] of (−)-**8a** and (−)-**8b** at −78 °C to rt gave the corresponding 2*H*-azirine 3-phophonates (2*R*)-(+)-**9** and 2*H*-azirine 2-phosphonate (2*S*)-(+)-**10** (Scheme 3). The major azirines (+)-**9**

Scheme 3



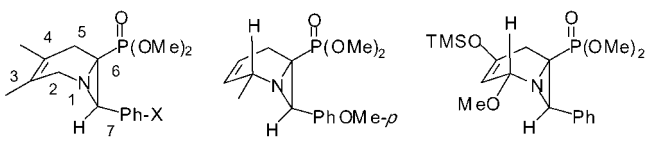
Ar =	(2*R*)-(+)-**9**:(2*S*)-(-)-**10**	% yield of **9**
a: Ar = 4-MeOPh	6:1	68 (12)*
b: Ar = Ph	10:1	72

*yield of **10a**

were isolated in 68−72% yield and are characterized by the C-2 proton at *δ* 3.1 ppm in the ^{1}H NMR and the absorption at *δ* 3.9 ppm in the ^{31}P NMR. In the minor isomer the ^{1}H and ^{31}P NMR absorptions appear at *δ* 2.1 and 25.5 ppm, respectively. 2*H*-Azirine 3-phophonates (2*R*)-(+)-**9** can be stored in solution (benzene or toluene) for several days without decomposition. As neat liquids they decompose in less than a day and are sensitive to moisture. By contrast (2*S*)-(−)-**10a** was stable for several months.

Cycloaddition Reactions. Diels−Alder reactions were conducted by stirring 100 equiv of 2,3-dimethylbutadiene or *trans*-piperylene with (2*R*)-(+)-**9** for 2−4 days at rt (Scheme 4). Bicyclic aziridines **11a**,**b** and **12** were isolated

Scheme 4



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

(8) For reviews: (a) Kafarski, P.; Lejczak, B. *Phosphorus Sulfur Silicon* **1991**, *63*, 193. (b) Seto, H.; Kuzuyama, T. *Nat. Prod. Rep.* **1999**, *16*, 589. (c) *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*; Kukhar, V. P.; Hudson, H. R., Eds.; Wiley: Chichester, UK, 2000.

(9) For a method to prepare **5**, see: Savignac, P.; Petrova, J.; Dreux, M.; Coutrot, P. *Synthesis* **1975**, 535.

(10) (a) Davis, F. A.; Zhang, Y.; Andemichael Y.; Fang, T.; Fanelli, D. L.; Zhang, H., *J. Org. Chem.* **1999**, *64*, 1403. (b) Fanelli, D. L.; Szewczyk, J. M.; Zhang, Y.; Reddy, G. W.; Burns, D. M.; Davis, F. A. *Org. Synth.* **1999**, *77*, 50.

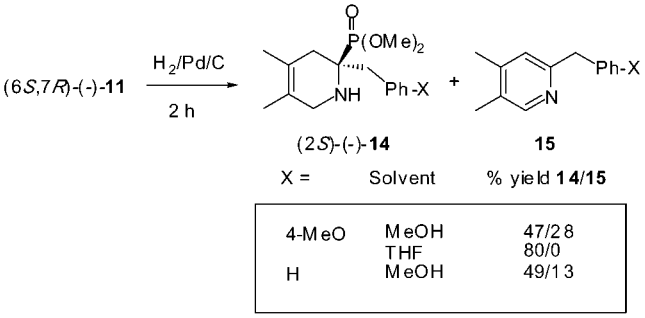
(11) We have found it easier to work with dimethyl phosphonate analogues of aziridine phosphonates rather than the diethyl derivatives **3**. Not only is the diastereoselectivity for the addition of the dimethyl chloromethylphosphonate anion to the sulfinimine better (dr 72:28 (other isomers) vs 59:41 for **3**) but the products are more easily separated by chromatography and give simpler NMR spectra.

as single stereoisomers by flash chromatography in 89−98% yields. The reaction of (2*R*)-(+)-**9b** and 5 equiv of 1-methoxy-3-trimethylsilyloxybuta-1,3-diene (Danishefsky's diene) at rt required only 8 h and afforded **13** as a single isomer in >90% yield. Isolation consisted of passing the reaction mixture through a short plug of silica gel; longer contact times resulted in decomposition. This material was sensitive to moisture and could only be stored for a few days at −10 °C. It is interesting to note that the reaction time for **1** and this diene was only 15 min,[4] suggesting that 2*H*-azirine 3-carboxylates are more reactive as iminodienophiles than **9**. The likely cause for this effect is the greater steric bulk of the tetrahedral phosphonate group vs the smaller, planar carboxylate group.

The stereochemistry of adducts **11**−**13** was established by COSY, NOESY, and NOE experiments and was consistent with exclusive addition of the diene to the less hindered face of the azirine. In **11a**,**b**, **12**, and **13** the H-7 proton appears as a doublet in the narrow range of δ 3.12−3.27 ppm, indicative of shielding by the C−C double bond and coupling with the phosphorus atom (J_{PH} = 6 Hz). Irradiation of H-7 in **11b** resulted in enhancement of the signals for the C-3 and C-4 methyl groups. The assigned regiochemistry of the unsymmetrical adducts is supported by the C-5 carbon chemical shifts in **12** and **13** appearing at δ 22.1 and 27.4 ppm, respectively, and coupled with the phosphorus atom (J_{PC} = 11 Hz). A COSY spectrum of **12** reveals cross-ring coupling between H-2 and H-5. Gilchrist observed similar stereoselective addition of dienes to azirines **1** and **2**.[4,13]

Hydrogenation of Aziridine Adducts. Catalytic hydrogenation of aryl C-3 aziridines 2-carboxylates and 2-phosphonates results in aziridine ring-opening at the C-3−N bond to furnish α-amino acids[12,14] and α-amino phosphonates, respectively.[5,15] Comparable ring-opening of aziridine adducts **11**−**13** would afford novel, enantiopure α-amino phosphonates. Thus catalytic hydrogenation of **11a**,**b** for 2 h (Pd/C/H_2balloon pressure) resulted in two products. The major products, isolated in 47−49% yield, were identified as quaternary piperidine phosphonates (2*S*)-(−)-**14a**,**b**, which resulted from the expected cleavage of the C-7−N bond in **11** (Scheme 5). In each case the 3,4 carbon−carbon double bond remained intact. The minor products, obtained in 28% and 13% yield, respectively, were identified as pyridines **15a**,**b**. That the pyridines are derived from **14** was confirmed by hydrogenolysis of **14a**,**b** to **15** in 64−66% yield. In THF solvent (−)-**11a** gave **14** exclusively. Cleavage of a carbon−phosphorus bond is rare, and to the best of our knowledge reductive elimination of phosphite under these conditions has not been described.[16,17] Aromatization of the intermediate

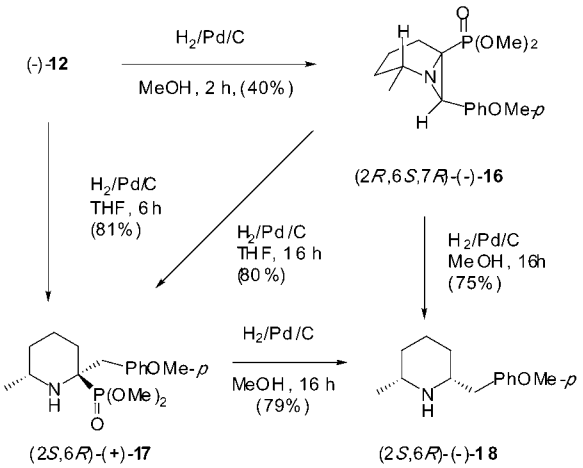
Scheme 5



piperidine enimine, resulting from 1,2-elimination of HP(O)$(OMe)_2$ from **14**, must be particularly facile under the reductive conditions. The piperidines and pyridines had HRMS and spectral properties consistent with their structures.

Hydrogenation of (−)-**12** for 2 h in MeOH resulted in reduction of the C−C double bond, affording the bicyclic aziridine (2*S*,7*R*)-(−)-**16** in 40% isolated yield along with a complex mixture of products that could not be identified (Scheme 6). If the hydrogenation of (−)-**12** is carried out in

Scheme 6



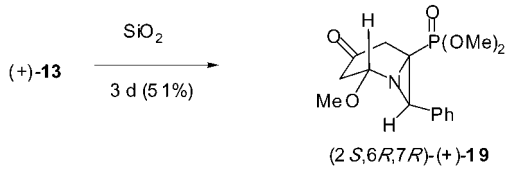
THF for 6 h, piperidine phosphonate (2*S*,6*R*)-(+)-**17** was isolated in 81% yield. That this material results from cleavage of the C-7−N bond in (−)-**16** was demonstrated by the hydrogenation of **16** to **17**. Interestingly, when the bicyclic aziridine (−)-**16** was hydrogenated for 16 h in MeOH, *cis*-2-(*p*-methoxybenzyl)-6-methylpiperidine (**18**) was obtained exclusively in 75% yield.[18] Products were identified by their HRMS and had spectral properties consistent with their structures.

The reason the C−C double bond was hydrogenated in **12** but was not in **11** is unclear but may be related to greater steric hindrance in the latter adduct. We suggest that

(12) Davis, F. A.; Liu, H.; Zhou, P.; Fang, T.; Reddy, G. V.; Zhang, Y. *J. Org. Chem.* **1999**, *64*, 7559.
(13) (a) Bhullar, P.; Gilchrist, T. L.; Maddocks, P. *Synthesis* **1997**, 271. (b) Alves, M. J.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 299.
(14) (a) Davis, F. A.; Liang, C.-H.; Liu, H. *J. Org. Chem.* **1997**, *62*, 3796. (b) Davis, F. A.; Zhang, Y.; Rao, A.; Zhang, Z. *Tetrahedron* **2001**, *57*, 6345.
(15) Davis, F. A.; McCoull, W.; Titus, D. D. *Org. Lett.* **1999**, *1*, 1053.
(16) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley: New York, 2000.
(17) For an example of C−P bond cleavage, see: Berkowitz, D. B.; Bose, M.; Asher, N. G. *Org. Lett.* **2001**, *3*, 2009.

(18) Piperidine imines (H_2/Pd−C) are stereoselectively reduced to 2,6-*cis*-piperidines. See: Davis, F. A.; Zhang, H.; Lee, S. H. *Org. Lett.* **2001**, *3*, 759.

Scheme 7



(2*S*,6*R*,7*R*)-(+)-**19**

piperidine **18** results from elimination of methyl phosphite from **17**, as was observed in the formation of pyridines **15**, to furnish an intermediate imine that is stereoselectively reduced.[18] Indeed, hydrogenation of **17** gave **18** (Scheme 6). We further speculate that the palladium catalyst associates with the nitrogen and phosphorus atoms, which promotes 1,2-elimination of dimethyl phosphite, to furnish an intermediate imine that was not detected.

Hydrogenolysis of **13** under the standard protocol resulted in decomposition with a variety of different catalyst [Pd/C, $Pd(OH)_2$, $Pd/BaSO_4$] and solvent (MeOH, THF, DCM) combinations. However, exposure to silica gel in $CHCl_3$ for 3 days afforded the ketone (2*S*,6*S*,7*R*)-(+)-**19** as a single isomer in 51% yield (Scheme 7). The aziridine ketone was isolated by chromatography and proved to be stable for several weeks at −10 °C, in contrast to **13**. This ketone was characterized by HRMS and had spectral properties consistent with its structure. Unfortunately, catalytic hydrogenation (Pd/C, THF) of **19** resulted in decomposition.

In summary, enantiomerically enriched 2*H*-azirine 3-phosphonates, a new class of chiral iminodienophiles, afford bicyclic aziridine Diels−Alder adducts in good to excellent yields. Hydrogenation of these bicyclic aziridine adducts results in a ring-opening that affords the first examples of optically pure quaternary piperidine phosphonates. Continued hydrogenation of these materials gives pyridines and piperidines.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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