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Asymmetric Synthesis of Cis-5-Substituted Pyrrolidine 2-Phosphonates Using Metal Carbenoid NH Insertion and δ-Amino β-Ketophosphonates

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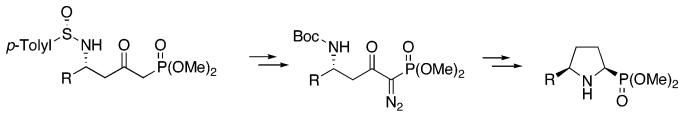
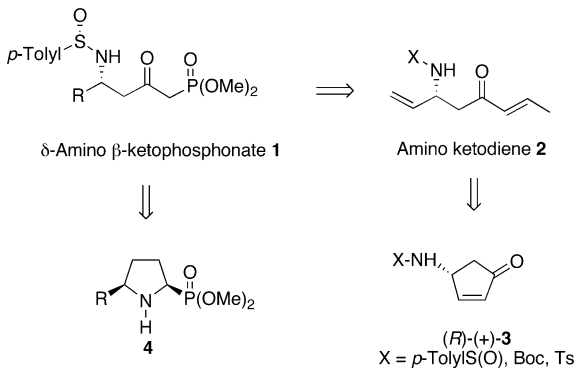
ABSTRACT



Cis-5-substituted pyrrolidine phosphonates, proline surrogates, are prepared by a highly stereoselective intramolecular metal carbenoid N–H insertion from a sulfinimine-derived δ-amino α-diazo β-ketophosphonate.

Recently, we introduced the new sulfinimine-derived chiral building block *N*-sulfinyl δ-amino β-ketophosphonate **1** and reported its utility, using Horner−Wadsworth−Emmons (HWE) chemistry, for the asymmetric synthesis of β-amino ketodienes **2** (Scheme 1).[1,2] With ring-closing metathesis, the amino ketodienes were transformed to (*R*)-(+)-4-amino-cyclopentenone derivatives **3**, which are key building blocks for the asymmetric synthesis of antiviral and anticancer carbocyclic nucleosides.[2] We describe here the application of **1** to the highly efficient asymmetric synthesis of cis-5-substituted pyrrolidine 2-phosphonates **4** and the first example of an intramolecular NH carbenoid insertion from an α-diazophosphonate.

Scheme 1



α-Amino phosphonic acids have found widespread use as surrogates and structural analogues of α-amino acids.[3] For these reasons, and the fact that chirality is a central issue for biologically active molecules, the enantioselective synthesis of α-amino phosphonic acids and their derivatives is an important objective. In this regard, the highly diastereoselective addition of metal phosphites to sulfinimines (*N*-sulfinyl imines) is a particularly attractive method for the asymmetric synthesis of diversely substituted α-amino phosphonates including cyclic examples.[4−6] Catalyzed by metals, intramolecular NH insertion reactions within α-diazoketones

(1) For reviews on the syntheses and applications of sulfinimine-derived chiral building blocks, see: Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003.

(2) Davis, F. A.; Wu, Y. *Org. Lett.* **2004**, *6*, 1269.

(3) For reviews, see: (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.

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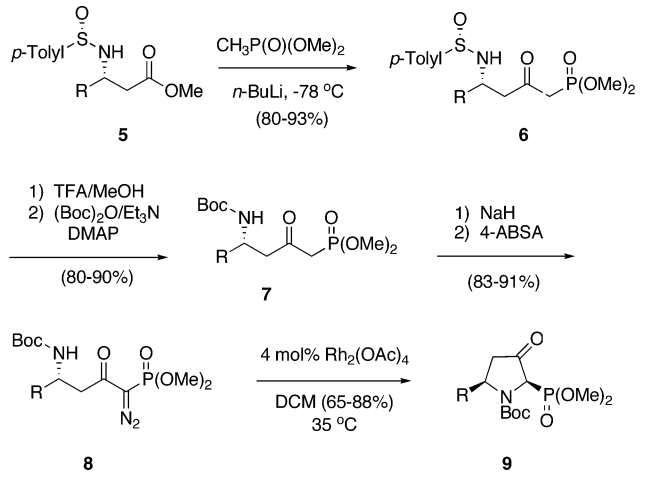
and δ-amino α-diazo β-ketoester have been used to prepare a variety of nitrogen heterocycles, including the asymmetric synthesis of cis-5-substituted prolines.[7−9] However, there is no comparable report of this protocol being used to prepare 5-substituted pyrrolidine 2-phosphonates.[10,11]

***N*-Sulfinyl δ-Amino α-Diazo β-Ketophosphonates.** The requisite enantiopure *N*-sulfinyl δ-amino β-ketophosphonates **6** were prepared, as previously described, by treatment of the corresponding *N*-sulfinyl β-amino esters **5** with 5.0 equiv of the lithium dimethyl methylphosphonate (Scheme 2).[2]

Scheme 2



a: R = Ph; **b**: R = CH_2=CH; **c**: R = Me; **d**: R = *n*-Bu; **e**: R = *t*-Bu

Chromatography followed by Kugelrohr distillation to remove the excess dimethyl methylphosphonate afforded **6** in good to excellent yields (80−93%). Next, the sulfinyl group was removed with TFA/MeOH and replaced with a Boc group, affording **7** in good to excellent yields (Table 1).

Conversion of **7** to the α-diazo compounds **8** proved to be more difficult. While δ-amino β-ketoesters were readily converted to their α-diazo derivatives with 4-carboxybenzenesulfonyl azide and Et_3N, similar treatment of **7** resulted in a very slow reaction.[7−9] With 5 equiv of the sulfonyl azide, the process required more than 16 h for completion and the product was extremely tedious to isolate. With Et_3N and 4-acetamido-benzenesulfonyl azide (4-ABSA),[12] the process required only 2 equiv and 16 h for completion, but again the product was difficult to purify. The optimum combination of reagents proved to be 0.99 equiv of 4-ABSA (commercially available) with NaH as the base, which afforded the diazo compounds **8** in 1 h in good to excellent yields (83−91%, Table 1). The byproduct, 4-acetamidobenzsulfonamide, precipitated from the $CHCl_3$ solution and was removed by filtration. The α-diazo compounds were purified by chromatography (Scheme 2).

Table 1. Isolated Yields of Phosphonates[a]

entry	R	**6**	**7**	**8**	**9** (cis/trans)[b]	**12**	**13**	**4**
1	a: Ph	84	90	83	68 (81:19)	81	93	81
2	b: CH=CH_2	83	87	83	65 (92:8)			
3	c: Me	88	80	85	88 (96:4)	88	90	68
4	d: *n*-Bu	93	83	91	79 (95:5)	76	85	86
5	e: *t*-Bu	80	87	85	84 (99:1)	76	85	70

[a] Isolated yield of isomer mixture. [b] Determined by ^{31}P and ^1H NMR on the crude reaction mixture.

With the α-diazophosphonates in hand, treatment with 4 mol % $Rh_2(OAc)_4$ in DCM for 16 h at 35 °C afforded the corresponding 3-oxo pyrrolidine phosphonates **9** in 65−88% isolated yield (Table 1). The cis:trans ratio, determined by ^{31}P and ^1H NMR on the crude reaction mixtures, varied from a low of 81:19 for (2*R*,5*R*)-**9a** (R = Ph) to a high of >99:1 for (2*R*,5*R*)-**9e** (R = *t*-Bu) (Table 1, entries 1 and 5). Intramolecular cyclopropanation is often observed in the metal carbenoid reactions when suitably positioned vinyl substituent is present.[12c] The fact that such products were not detected in the decomposition of diazophosphonate (*R*)-**8b** (R = CH_2=CH) suggests that intramolecular NH insertion is much faster than cyclopropanation.

The stereochemistry in **9a** and **9d** was determined by NOE experiments. The enhanced signals observed between the Ph and P(O)$(OMe)_2$ protons and between the C-2 (H) and C-5 (H) protons argue strongly for their cis relationship. Similar results were observed for metal carbenoid NH insertion in δ-amino α-diazo β-ketoesters.[7−9]

The mechanisms for metal carbenoid insertion into a CH bond is generally thought to be concerted.[13,14] The situation for metal carbenoid insertion into polar NH bonds is less clear, but stepwise mechanisms involving ylides have been

(4) **α-Amino Phosphonates.** (a) Lefebvre, I. M.; Evans, S. A., Jr. *J. Org. Chem.* **1997**, *62*, 7532. (b) Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J. *Tetrahedron: Asymmetry* **1997**, *8*, 3991. (c) Davis, F. A.; Lee, S.; Yan, H.; Titus, D. D. *Org. Lett.* **2001**, *3*, 1757. (d) Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J. *Tetrahedron: Asymmetry* **2002**, *13*, 2571. (e) Davis, F. A.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 7249.

(5) **Aziridine 2-Phosphonates.** (a) Davis, F. A.; McCoull, W. *Tetrahedron Lett.* **1999**, *40*, 249. (b) Davis, F. A.; McCoull, W.; Titus, D. D. *Org. Lett.* **1999**, *1*, 1053. (c) Davis, F. A.; Wu, Y.; Yan, H.; Prasad, K. R.; McCoull, W. *Org. Lett.* **2002**, *4*, 655. (d) Davis, F. A.; Wu, Y.; Yan, H.; McCoull, W.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 2410. (e) Davis, F. A.; Ramachandar, T.; Wu, Y. *J. Org. Chem.* **2003**, *68*, 6894.

(6) **Cyclic α-Amino Phosphonates.** Davis, F. A.; Lee, S. H.; Xu, H. *J. Org. Chem.* **2004**, *69*, 3774.

(7) For leading references, see: Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599.

(8) Davis, F. A.; Yang, B.; Deng, J. *J. Org. Chem.* **2003**, *68*, 5147.

(9) Davis, F. A.; Deng, J. *Tetrahedron* **2004**, *60*, 5111.

(10) Intramolecular CH insertion has been used to prepare β-lactam 3-phosphonates and γ-lactam 4-phosphonates in low yields as mixtures of isomers. Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2003**, 3798.

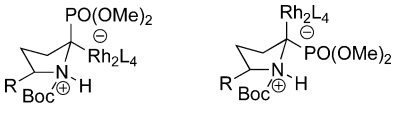
(11) Intermolecular N−H insertion using metal carbenoids has been reported. For leading references, see: (a) Moody, C. J.; Morfitt, C. N.; Slawin, A. M. Z. *Tetrahedron: Asymmetry* **2001**, *12*, 1657. (b) Nakamura, Y.; Ukita T. *Org. Lett* **2002**, *4*, 2317.

(12) (a) Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R. *Tetrahedron* **1968**, *24*, 3655. (b) Davies, H. M. L.; Cantrell, W. R.; Romines, K. R.; Baum, J. S. *Org. Synth.* **1992**, *70*, 93. (c) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860.

(13) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

(14) (a) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547. (b) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **1998**, *63*, 3717.

Scheme 3

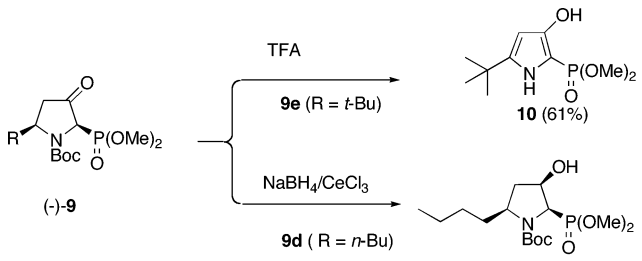


TS-1 **TS-2**

proposed (Scheme 3).[15] The somewhat lower selectivity noted for the NH insertion reactions of **8** compared to δ-amino α-diazo β-ketoesters may be related to the geometry and much larger size of the phosphonate versus carboxylate. Here the phosphonate may compete with the metal carbenoid group for the axial position in **TS-1** and **TS-2**, leading to the major cis and minor trans products. Alternatively, epimerization at C-2 could occur if proton transfer in the metal species is slower in the phosphonate. Another possibility is epimerization on chromatographic work, but this was not detected in the purification of **9a**.[16]

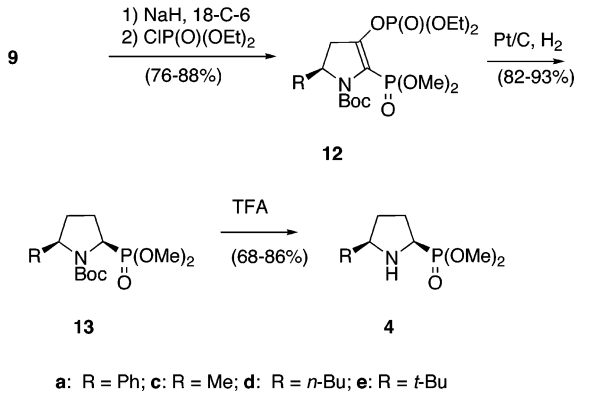
The chemistry of the new 3-oxo pyrrolidine phosphonates **9** was briefly explored. When (2*R*,5*R*)-(−)-**9e** (R = *t*-Bu) was treated with TFA at room temperature and stirred in DCM with silica gel for 24 h, dimethyl 5-*tert*-butyl-3-hydroxy-1*H*-pyrrole 2-phosphonate (**10**) was obtained in 61% isolated yield (Scheme 4). The structure of the 2-phosphonopyrrole was supported by its lack of optical activity and the downfield shifts of carbons in the ^{13}C NMR spectra to δ 149−158 ppm. These compounds may be useful scaffolds for combinatorial library generation, and our procedure also represents a novel entry to functionalized derivatives of this class of aromatic heterocycles.[17] Luche reduction ($NaBH_4$/$CeCl_3$) of (2*R*,5*S*)-(−)-**9d** (R = *n*-Bu) gave alcohol (2*R*,3*R*,5*S*)-(−)-**11** in 89% yield as a single isomer. Hydride addition is expected to add from the least hindered direction, which would afford the all-cis 2,3,5-trisubstituted pyrrolidine phosphonate.[9]

Scheme 4



Removal of the 3-oxo group in **9** is required to give the cis-5-substituted pyrrolidines **4**. This was efficiently accomplished by conversion of **9** into the corresponding enol phosphonates **12** by treatment with NaH, 18-crown-6, and diethyl chlorophosphonate (Scheme 5, Table 1). Hydrogenation (Pt/C, H_2) gave **13**, which on removal of the Boc group with TFA afforded the cis-5-substituted pyrrolidines **4**. The overall yields were good to excellent (Table 1). The assignment of a cis relationship for the C-2 and C-5 substituents follows from the method of synthesis (hydrogenation) and NOE experiments on **4** where H-2 and H-5 showed a strong enhancement.

Scheme 5



a: R = Ph; **c**: R = Me; **d**: R = *n*-Bu; **e**: R = *t*-Bu

In summary, new methodology has been introduced for the asymmetric synthesis of cis-5-substitiuted pyrrolidine 2-phosphonates **4**, important proline surrogates. The intramolecular metal carbenoid NH insertion reaction from a α-diazophosphonate, the first such example, proved to be highly stereoselective and afforded the cis product. These α-diazophosphonates are prepared from *N*-sulfinyl δ-amino β-ketophosphonates, a new sulfinimine-derived chiral building block.

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

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(15) For a review of the relevant literature, see: Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc*. **2002**, *124*, 7181.

(16) When (−)-**9d** (R = *n*-Bu) was treated with DBU in acetonitrile for 16 h, a 55:45 mixture of cis:trans isomers resulted, as determined by ^{31}P and ^{1}H NMR.

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