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Highly diastereoselective hydrophosphonylation of cyclic imines using BINOL as source of chirality†

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Abstract

The first highly diastereoselective (*dr* up to >95:5) hydrophosphonylation of heterocyclic imines by a chiral phosphorus nucleophile is introduced. Addition of binaphthol ester of phosphorus acid towards BF_3-activated 3-thiazolines gives the corresponding (*aR**,4*R**)-4-thiazolidinylphosphonates almost exclusively as elucidated by X-ray analysis.

Keywords: thiazolines; phosphorus acids and derivatives; diastereoselection.

The stereoselective preparation of optically active organophosphorus compounds has been of great interest over the last few years.[1] The highly diastereoselective addition reaction of an enantiomerically pure phosphorus nucleophile to C=O and C=N double bonds, respectively, and subsequent cleavage from the chiral auxiliary connected to the phosphorus moiety may serve as a general concept for the preparation of enantiomerically pure α-hydroxy and α-amino phosphonates. However, only a few chiral phosphorus nucleophiles (on the basis of ephedrine[2], glucose[3] and *trans*-1,2-cyclohexyldiamine[4]) have been reported to be diastereoselective phosphonylating reagents towards aromatic aldehydes. The selectivity achievable in the phosphonylation of achiral imines is much lower in general. As a consequence, a chiral phosphorus nucleophile for the highly stereoselective C–P bond formation especially with imines would be desirable. In addition, accessibility of both enantiomers of the chiral auxiliary would be advantageous. BINOL (binaphthol) has already shown excellent chiral recognition properties in other systems[5] and both enantiomers are readily accessible. However, silylphosphite esters of BINOL have shown rather low abilities to act as phosphonylating agents towards benzaldehyde.[6]

Herein, we present for the first time a highly diastereoselective hydrophosphonylation of heterocyclic imines of type **1** using BINOL-phosphite **2**[6] leading to the pharmaceutically interesting 4-thiazolidinylphosphonates **3**[7] as depicted in Scheme 1. Hydrophosphonylation of 3-thiazolines

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† Dedicated to Peter Köll on the occasion of his 60th birthday.

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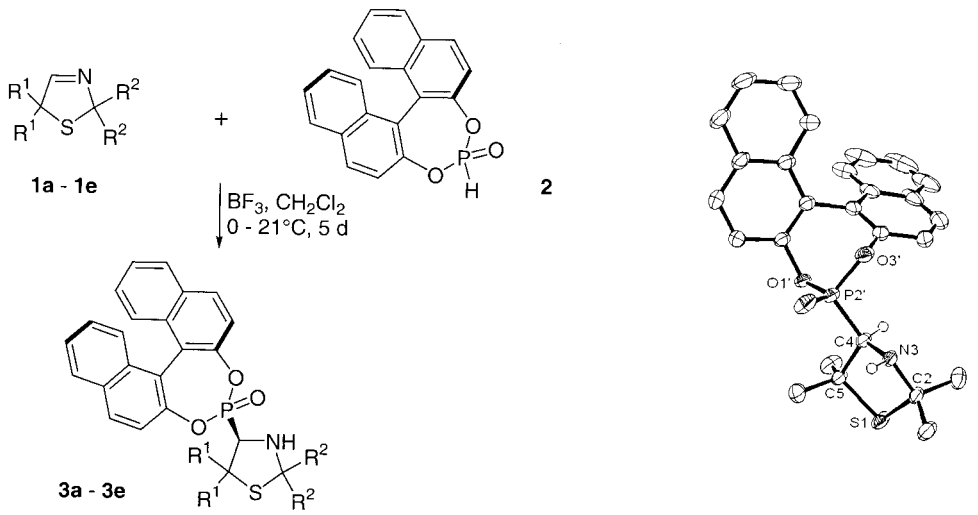

Scheme 1. Diastereoselective hydrophosphonylation and crystal structure of **3a**[10] (only one enantiomer of the racemic compound **2** and **3** is shown, and only major isomer is shown of **3a** and **3c**).

has been limited to a low distereoselectivity of 60:40.[8] Application of the readily available BINOL ester of phosphorus acid in the BF_3-activated hydrophosphonylation of cyclic imines **1** provides high stereoselection (Table 1). The chiral phosphorus nucleophile **2** has been prepared using racemic BINOL in this work but the enantiomerically pure forms of **2**[9] are available by the same method.

Table 1
Diastereoselective hydrophosphonylation of 3-thiazolines **1**

entry	product	educt	R^1 / R^1	R^2 / R^2	dr^a	yield (%)
1	**3a**[11]	**1a**[12]	Me / Me	Me / Me	83:17	47
2	**3b**[13]	**1b**[12]	Me / Me	$-(CH_2)_5-$	>95:5	47
3	**3c**[14]	**1c**[15]	$-(CH_2)_5-$	Me / Me	80:20	37
4	**3d**[16]	**1d**[15]	$-(CH_2)_5-$	$-(CH_2)_5-$	>95:5	68
5	**3e**[17]	**1e**[18]	H / H	$-(CH_2)_5-$	>95:5	30

[a] The *dr*-value was determined from the crude product by ^{1}H NMR spectroscopy.

The hydrophosphonylation reaction has been carried out in dry dichloromethane with the 3-thiazoline **1** being activated with 1 equivalent of the Lewis acid BF_3. The desired thiazolidinylphosphonates **3** have easily been purified and in the case of **3a** and **3c** the diastereomers have been separated by column chromatography.

The thiazolidinylphosphonates **3** are formed in moderate yields but with excellent selectivity. The almost exclusively formed major diastereomer was found to have (*aR**,4*R**)-configuration by X-ray analysis of the major diastereomer of thiazolidinylphosphonate **3a**. It should be noted that stereoselection of the BINOL-phosphite **2** seems to be independent of the steric demand of the

nearby substituents R^1. By contrast, the nature of the more distant substituent (R^2) of the N/S-acetalic carbon atom influences the diastereoselectivity to a larger extent. BINOL–phosphite already provides good selectivity in the hydrophosphonylation of 3-thiazolines **1a** and **1c** (R^2 = Me; entries 1 and 3 in Table 1) but a higher steric demand of R^2 (R^2/R^2 = –$(CH_2)_5$–; entries 2, 4 and 5 in Table 1) leads to the formation of only one diastereomer of the corresponding thiazolidinylphosphonates **3**.

In conclusion, we have presented the first highly diastereoselective hydrophosphonylation of heterocyclic imines, namely 3-thiazolines by a chiral phosphorus nucleophile. BINOL has served as source of chirality. The relative configuration of BINOL and the newly formed stereogenic center in the α-amino phosphonic acid derivatives **3** have been elucidated by X-ray analysis.

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10. Single crystals of the major isomer of **3a** were crystallized from ether, mounted in inert oil and transferred to the cold gas stream of the diffractometer. Crystal data: $C_{27}H_{26}NO_3PS$, M = 475.52, triclinic, a = 8.2388(5), b = 11.8642(7), c = 13.3079(9) Å, U = 1186.55(13) Å^3, T = 193(2) K, space group $P1$, Z = 2, absorption coefficient = 0.234 mm^{-1}, 14439 reflections measured, 4303 unique (R_{int} = 0.0362) which were used in all calculations. The final $\omega R(F^2)$ was 0.0425 (all data). Crystallographic data (excluding structure factors) for **3a** have been deposited with the Cambridge Crystallographic Data Centre, Cambridge, UK, as supplementary publication number CCDC 146344. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
11. Data for (*aR**,4*R**)-**3a** (major isomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] = 1.44, 1.59, 1.75, 1.77 (4 s, 12H), 3.01 (s, 1H), 3.36 (d, $^2J_{PH}$ = 16.5 Hz, 1H), 7.32–7.64, 8.00–8.09 (2 m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm] = 28.3, 29.4, 31.9, 32.8, 61.6 (d, $^2J_{CP}$ = 4.4 Hz), 64.0 (d, $^1J_{CP}$ = 140.4 Hz), 75.1 (d, $^3J_{CP}$ = 24.8 Hz), 119.8, 120.9, 121.5, 121.7, 125.8, 125.9, 126.8, 126.9, 127.2, 128.5, 131.3, 131.7, 131.9, 132.3, 145.4, 147.2 (2 d, $^2J_{CP}$ = 10.6 Hz, $^2J_{CP}$ = 10.4 Hz). Data for (*aR**,4*S**)-**3a** (minor isomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] = 1.32, 1.47, 1.68, 1.87 (4 s, 12H), 2.37 (s, 1H), 3.80 (d, $^2J_{PH}$ = 20.4 Hz, 1H), 7.27–7.57, 7.88–8.05 (2 m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm] = 28.5, 28.7, 31.7, 32.3, 62.1, 67.2 (d, $^1J_{CP}$ = 135.7 Hz), 75.4 (d, $^3J_{CP}$ = 23.5 Hz), 121.2, 121.6, 125.4, 125.8, 126.4, 126.7, 127.1, 127.1, 128.5, 129.3, 131.2, 133.5, 145.1, 149.2 (2 d, $^2J_{CP}$ = 8.7 Hz, $^2J_{CP}$ = 10.9 Hz).

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13. Data for (*aR**,4*R**)-**3b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] = 1.29–2.00 (m, 10H), 1.41, 1.73 (2 s, 6H), 3.36 (d, $^{2}J_{PH}$ = 16.5 Hz, 1H), 7.31–7.64, 7.95–8.08 (2 m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm] = 23.6, 25.2, 25.5, 41.1, 41.3, 28.1, 29.5, 59.0, 63.1 (d, $^{1}J_{CP}$ = 139.7 Hz), 80.7 (d, $^{3}J_{CP}$ = 24.0 Hz), 119.8, 120.9, 121.5, 121.7, 125.8, 125.9, 126.6, 126.9, 126.9, 127.2, 128.5, 131.3, 131.7, 131.8, 132.3, 145.5, 147.5 (2 d, $^{2}J_{CP}$ = 10.3 Hz, $^{2}J_{CP}$ = 10.3 Hz).
14. Data for (*aR**,4*R**)-**3c** (major isomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] = 1.19–2.18 (m, 10H), 1.58, 1.75, 3.06 (s, 1H), 3.32 (d, $^{2}J_{PH}$ = 17.0 Hz, 1H), 7.32–7.66, 7.93–8.08 (2 m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm] = 23.7, 25.5, 27.3, 37.2, 38.4, 31.9, 32.7, 64.3 (d, $^{1}J_{CP}$ = 140.4 Hz), 69.6, 74.1 (d, $^{3}J_{CP}$ = 25.7 Hz), 119.9, 121.1, 121.5, 121.8, 125.9, 126.8, 126.9, 127.2, 128.5, 131.3, 131.7, 131.9, 132.3, 145.5, 147.4 (2 d, $^{2}J_{CP}$ = 10.9 Hz, $^{2}J_{CP}$ = 10.9 Hz). Data for (*aR**,4*S**)-**3c** (minor isomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] = 1.19–2.26 (m, 10H), 1.26, 1.46 (2 s, 6H), 2.51 (s, 1H), 3.75 (d, $^{2}J_{PH}$ = 20.9 Hz, 1H), 7.24–7.66, 7.91–8.07 (2 m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm] = 23.6, 25.2, 27.4, 36.2, 38.5, 31.7, 32.2, 67.5 (d, $^{1}J_{CP}$ = 135.7 Hz), 70.1 (d, $^{2}J_{CP}$ = 5.1 Hz), 73.3 (d, $^{3}J_{CP}$ = 24.5 Hz), 120.9, 121.2, 121.3, 121.8, 121.8, 125.3, 125.7, 126.3, 126.6, 127.0, 127.1, 128.2, 128.4, 129.9, 131.0, 131.2, 131.2, 131.4, 145.2, 149.3 (2 d, $^{2}J_{CP}$ = 9.6 Hz, $^{2}J_{CP}$ = 10.9 Hz).
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17. Data for (*aR**,4*R**)-**3e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] = 1.27–2.02 (m, 6H), 2.33 (s, 1H), 3.13 (ddd, $^{2}J_{HH}$ = 10.4 Hz, $^{3}J_{HH}$ = 6.1 Hz, $^{3}J_{PH}$ = 1.5 Hz, 1H), 3.27 (ddd, $^{3}J_{PH}$ = 11.0 Hz, $^{3}J_{HH}$ = 11.0 Hz, $^{2}J_{HH}$ = 10.4 Hz, 1H), 3.49 (ddd, $^{2}J_{PH}$ = 13.8 Hz, $^{3}J_{HH}$ = 11.0 Hz, $^{3}J_{HH}$ = 6.1 Hz, 1H), 7.32–7.66, 7.96–8.07 (2 m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm] = 23.7, 25.2, 25.7, 40.0, 40.6, 35.7, 54.6 (d, $^{1}J_{CP}$ = 147.8 Hz), 83.2 (d, $^{3}J_{CP}$ = 22.0 Hz), 120.0, 120.9, 125.9, 126.0, 126.9, 127.0, 127.2, 128.5, 131.4, 131.9, 132.4, 145.2, 147.0 (2 d, $^{2}J_{CP}$ = 10.9 Hz, $^{2}J_{CP}$ = 10.9 Hz).
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