Stereochemistry of hydrophosphonylation of 9-aminoquinine Schiff bases

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Dedicated to Professor Paweł Kafarski on the occasion of his anniversary

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Abstract

Reaction of imines derived from 9-amino-deoxyquinine and *p*-chlorobenzaldehyde with diethyl phosphite was studied. Under the experimental conditions the addition to imine of 9*S* configuration proceeded with complete diastereoselectivity for 1″*S* and in 60% practical yield. In contrast, the imine of 9*R* configuration was much less reactive and gave only 22% of the 1:1 mixture of two 1″-epimers. The configuration of the newly created stereogenic centers were established using homo- and hetero-NOE NMR techniques and comparing the experimental and calculated (GIAO/DFT) spectra. Stereochemical models explaining the observed high diastereoselectivity of hydrophosphonylation in one case and its lack in the other were discussed.

Keywords: Alpha-aminophosphonates, Cinchona alkaloids, quinine aminophosphonate, Pudovik reaction

Introduction

Aminophosphonates, phosphorus analogs of natural amino acids enjoy much interest as biologically active compounds. They resemble the tetrahedral intermediates formed in the hydrolysis of carboxylic acid derivatives that results in an inhibition of certain enzymes.[1] Aminophosphonates were studied as the transition-metal coordinating compounds, also for the biomedical applications.[2] The concept of attaching α-aminophosphonate to an alkaloid was exercised on *Vinca* alkaloids where it improved pharmacological properties.[3] Taking into account other potential applications of α-aminophosphonates, we believe that the field of their conjugates is rather unexplored. Although *Cinchona* alkaloids were applied as catalysts in the asymmetric synthesis of α-hydroxyphosphonates[4] and α-aminophosphonates,[5] there is no report

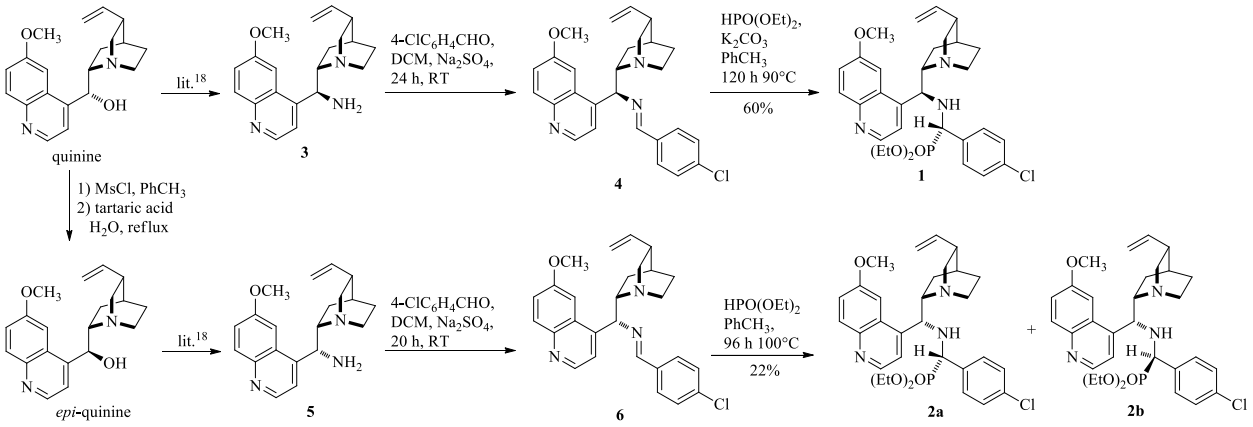
on α-aminophosphonates as derivatives of these alkaloids. So far, relatively few attempts have been made to obtain phosphorus derivatives of *Cinchona* alkaloids, including phosphates,[6] phosphites,[7] and phosphinites[8] at the 9-OH group. Additionally, phosphorus was introduced as a part of larger groups like triaryl phosphines attached via an ester[9] or amide[10] bonds, or a phosphine core dendrimer,[11] or finally a phosphonate on an extended chain at the 3-vinyl group.[12] Most of the attempted applications of these derivatives were aimed at the formation of metal complexes, with some good results in the field of catalysis.[10] Furthermore, both the *Cinchona* alkaloids[13] and the phosphonates[14] were used as chiral stationary phases, but their synthetic combination was never tested. Additionally, the presence of ^{31}P nuclei with relatively high receptivity and unobstructed window in NMR experiments could provide quick insight into the conformation of the alkaloids, similarly to the ^{19}F experiment.[15]

With all these facts in mind and our previous experience in the chalcogen chemistry of *Cinchonae* we decided to examine the preparation of α-aminophosphonates derived from both epimers of 9-aminoquinine.

Results and Discussion

One of the most straightforward methods of α-aminophosphonate synthesis is the addition of phosphite to imines (the Pudovik reaction).[16] Since 9-amino-9-deoxy-alkaloids are accessible as pure diastereomers through the Mitsunobu reaction,[17,18] we decided to use them as external scaffolds for aminophosphonates **1** and **2**.

First, obtained from the natural alkaloid, 9*S*-amino-deoxyquininie (**3**) was converted to the corresponding imine[18] with 4-chlorobenzaldehyde in dichloromethane in the presence of mild dehydrating agent. As shown by the respective ^1H NMR spectrum, no further purification was necessary. The solvent was changed to toluene and the imine **4** was allowed to react with diethyl phosphite (Scheme 1).



Scheme 1. Synthesis of quinine aminophosphonates **1** and **2**.

While no product was observed when the reaction was run at room temperature for 12 h, the conversion increased to around 24% when potassium carbonate was added and stirring was continued for 36 h at 70-80 °C. The crude reaction mixture after filtration and evaporation showed **1** along with unreacted **4** and phosphite. In the next experiment, the reaction time was extended to 5 days at 90 °C, and the product **1** was isolated in 60% yield. The reaction proceeded very selectively, as evidenced by NMR spectra of the crude product that contained essentially **1** and unreacted starting materials.

Then, we turned to 9*R*-amino-deoxyquinine (**5**) obtained from 9-*epi*-quinine. Under similar conditions, **5** gave the corresponding imine **6** but it did not react further. When the reaction was carried in the absence of K_2CO_3 at 100-109 °C for 4 days, two separable isomeric products **2a** and **2b** were isolated in ca. 1:1 ratio in a total yield of 22%. When dimethyl phosphite was used instead of diethyl phosphite in both reactions of imines **4** and **6**, we obtained complex mixtures containing only traces of the desired products.

The 9*S*-quinine amino-phosphonate **1** (appropriate HRMS) initially appeared in the NMR spectra as two distinct species with a ratio of approximately 6:4 both in the ^{1}H and ^{31}P experiments. It was initially thought that two different isomers at the newly introduced stereocenter were formed. However, on titration of **1** with trifluoroacetic acid both species coalesce and the spectral pattern of a single compound was observed when at least 1 equivalent of the acid was added. When the mixture after titration was washed with base, the recovered product exhibited the same 6:4 pattern as the initial sample (See section 4 in Supplementary Material). Thus, it was identified as a single isomer in which a constrained rotation around a single bond causes two populations of rotamers to be observed on an NMR timescale. It is most likely that the rotation around the C-4′ and C-9 bond causes the quinoline ring to adopt either *syn* or *anti* conformation separated by a high barrier. Previously reported $\Delta G^{\ddagger}$ for such rotations for derivatives with congested C-9 centers were as high as 18 kcal/mol[15] and 24 kcal/mol.[19] It is expected that the rotation barrier is not influenced significantly by protonation, however the conformational equilibrium is shifted towards one dominant species.

The two separated products **2a** and **2b** formed in the addition of phosphite to 9*R*-aminoquinine imine (**6**) revealed the same *m/z* and identical isotope distribution pattern as that found for **1**. Thus, the mass spectrometry suggested that **2a** and **2b** were isomers differing in the configuration of the newly created stereocenter. The NMR spectra for both the samples of **2a** and **2b** display larger inequalities in rotamer quantities (approximately 1:4). Here, like for **1**, the addition of acid greatly simplified the spectra, which also corroborate with the presence of an intact framework of quinine.

Configuration of **1** was established with the help of nuclear Overhauser effect NMR experiments on the sample treated with 1.5 equiv of trifluoroacetic acid. Strong NOESY correlation of H-9 with H-6, H-7 but only a faint cross peak with H-8, as well as $^{3}J_{(H8\text{-}H9)}$= 11.2 Hz suggested that H-9 and H-8 are in antiperiplanar conformation (*open* conformation). Correlation of the quinoline H-3′ and H-5′ atoms with H-8 and H-9 respectively allows establishing the *anti* orientation of the ring. Additionally, NOE of appreciable intensity was

observed between the H-9 and the central CH-1″ of the aminophosphonate. A very weak correlation of the ethoxy group of the phosphonate with H-6 could have been found and was in line with the *S* configuration of the aminophosphonate unit. A ^{31}P, ^{1}H heteronuclear Overhauser effect experiment (HOESY) revealed correlations well above the noise level of the phosphorus atom with H-9 and one of the H-6 atoms (δ 4.60 ppm) that could be well explained only for the *S* configuration of the aminophosphonate moiety (Figure 1).

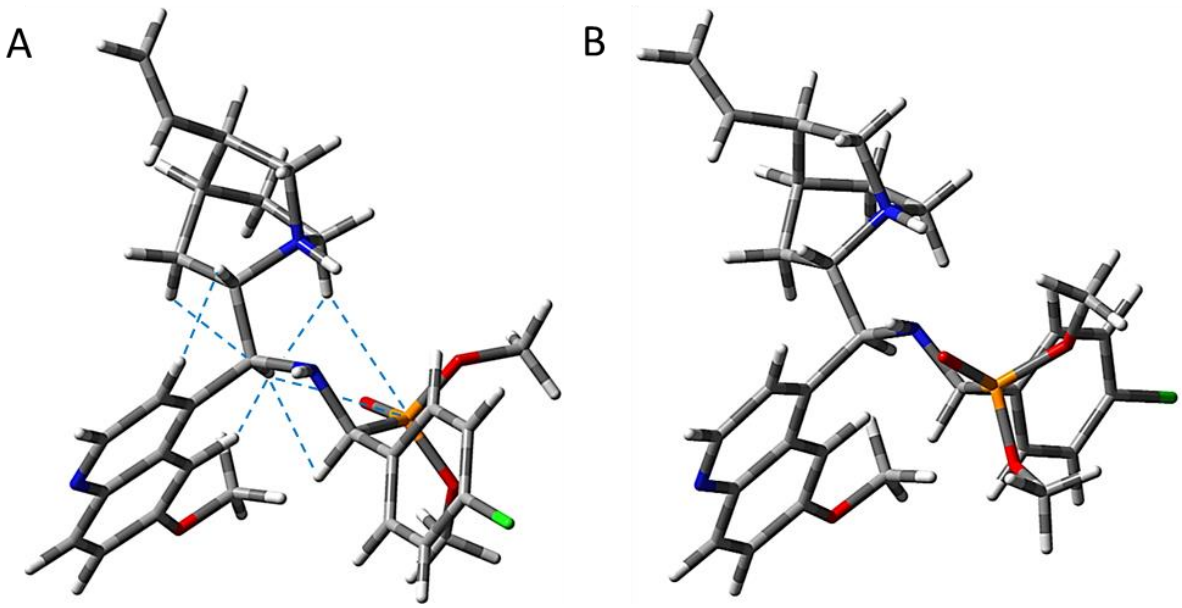


Figure 1. Calculated DFT/B3LYP/6-31G(d,p) models of (A) 1″-*S* and (B) 1″-*R* aminophosphonates derived from 9*S*-aminoquinine in protonated form. Calculated structures were simplified by replacing ethoxy with methoxy groups. Distances corresponding to crucial NOE interactions observed in **1** are marked with dashed lines.

In order to augment the assignment of configuration, a molecular model was calculated for the protonated forms of both possible isomers of the aminophosphonate on a DFT/B3LYP/6-31G(d,p) level of theory using the Gaussian code.[20] The model was simplified by replacing the diethyl phosphonate with dimethyl phosphonate group, also orientation of 6′-methoxy group was assumed to be identical to that found in all the X-ray crystal structures of quinine derivatives. For the initial input the *anti-open* conformation of *Cinchona* alkaloid indicated by NOESY experiment was used. Optimization of the geometry led to structures (Figure 1) that were used for calculation of NMR shieldings with the GIAO method. The calculated shieldings were converted to chemical shifts using values calculated for tetramethylsilane, and correlated with experimental data. Calculations for the *S*-isomer are in better agreement with the experiment than calculations for the *R*-isomer both for ^{13}C NMR (R^2= 0.994 *vs*. 0.993; RMS_{err} 0.71 *vs*. 0.78; Max_{err} 9.83 *vs*. 10.00) and significantly for ^{1}H NMR (R^2= 0.98 *vs*. 0.93; RMS_{err} 0.06 *vs*. 0.12; Max_{err} 0.80 *vs*. 1.59), and are within the range expected for correctly assigned molecules of

similar size (Figure 2). Moreover, the unprecedented downfield shift of one of the hydrogens of the 6-CH_2 group (δ 4.60 ppm) is well accounted in the calculation for the *S* isomer, although the extent is slightly overestimated, whereas the calculation for *R* isomer does not predict any unusual chemical shift. Also in the calculated geometry the interatomic distances for hydrogen atoms interacting with phosphorus in the HOESY experiment are within 3.4 Å.

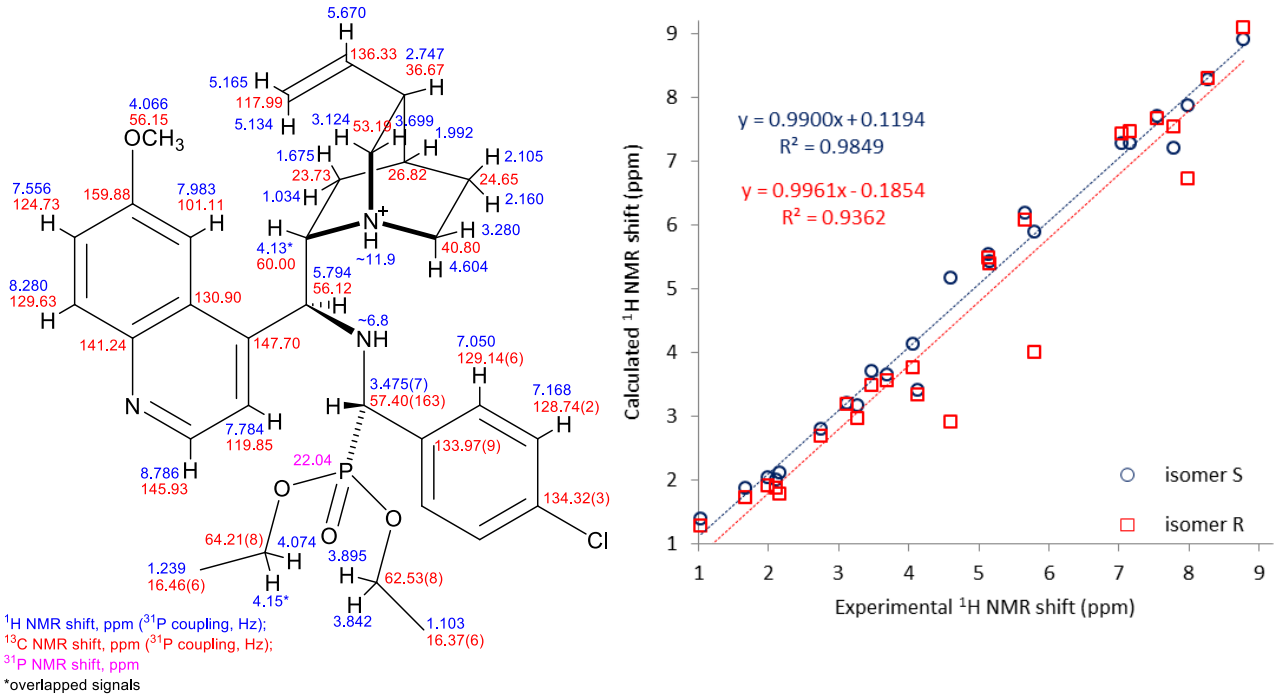
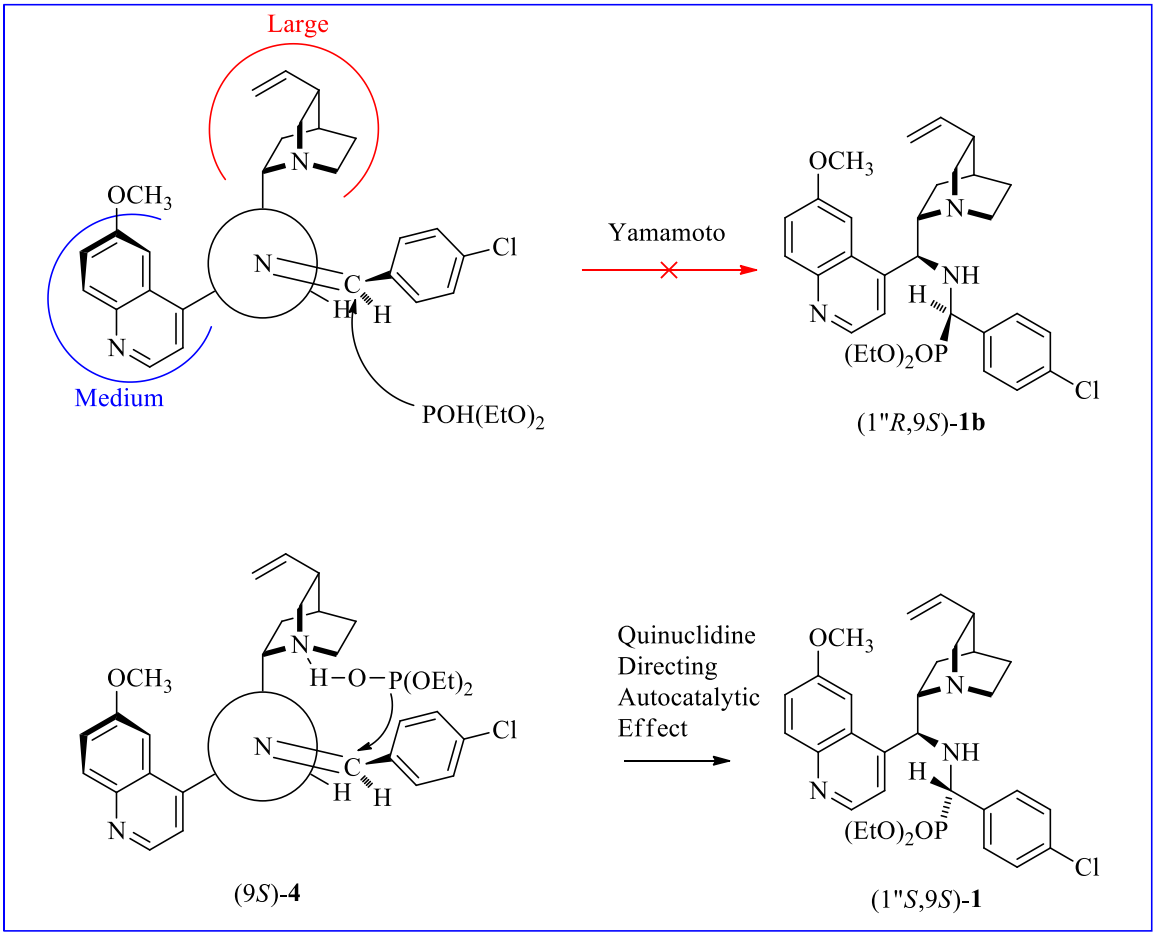


Figure 2. ^{1}H, ^{13}C and ^{31}P NMR spectrum assignment (left), and correlation of experimental ^{1}H NMR data with calculated chemical shifts for two possible stereoisomers, 1″*S* and 1″*R* of the product (right). Signals corresponding to NH and ethoxy groups were excluded from the correlation.

A set of NOE correlation experiments was used to match the *S* and *R* configuration at the newly introduced stereogenic center in compounds **2a** and **2b**. Both isomers exhibit an *anti* conformation, as indicated by strong H-9 / H-5′ with virtually no H-9 / H-3′ signal. Also in both isomers H-8 / H-9 correlation is observed, however in the case of **2b** the interaction of H-9 with H-1″ is of larger magnitude. Additionally, interaction of H-1″ with H-6x is visible only in case of **2b**. A HOESY experiment for **2b** showed only interaction of quinine structure with H-6x. These interactions allow with reasonable confidence to assign 1″*R* configuration to **2b** and the opposite 1″*S* configuration to **2a** (for the details, see Supplementary Material).

Two possible stereochemical outcomes can be predicted for the hydrophosphonylation reaction. One involves specific interactions with the basic quinuclidine nitrogen atom and the other solely relays on the steric interactions (Figure 3). The assumption that the only interactions are caused by different sterical demands would, according to the Yamamoto model,[21] require the

phosphite to approach from the side opposite to the quinuclidine (the most sterically demanding substituent) and result in a predominant formation of the isomer *R* for reaction of **4** and *S* for reaction of **6**. In a similar example of the addition of phosphites to imines obtained from enantiomeric α-methyl-benzylamine the diastereoselectivity was relatively low, typically not exceeding 60% de for room temperature reactions, unless a tailored phosphite and aldehyde components were used.[22] Similarly, diastereoselectivities observed so far for reactions of *Cinchona* alkaloids that rely mainly on the steric interactions span widely, and to the best of our knowledge in such cases good selectivity was never achieved at elevated temperatures.[23]



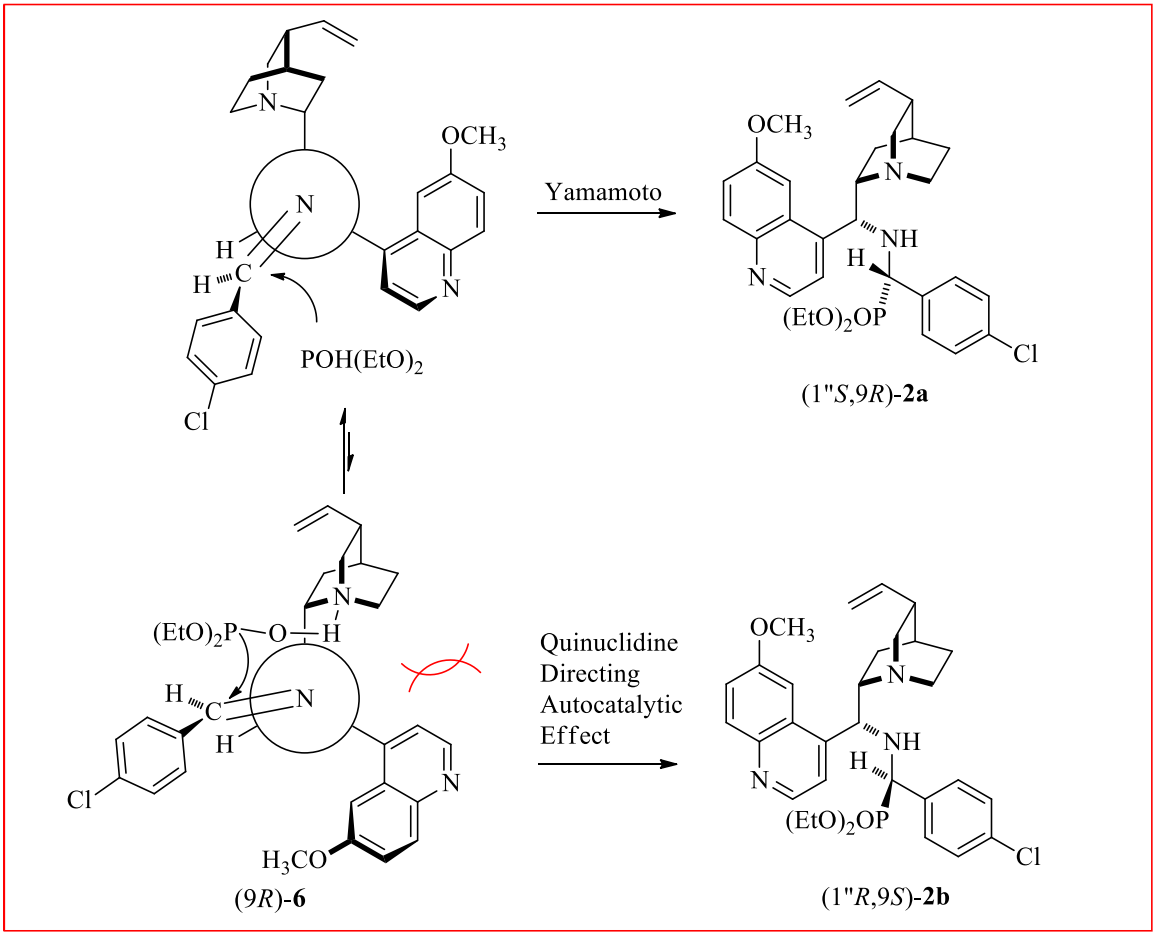


Figure 3. Suggested rationales of the reaction stereochemistry for 9S and 9R alkaloid imines.

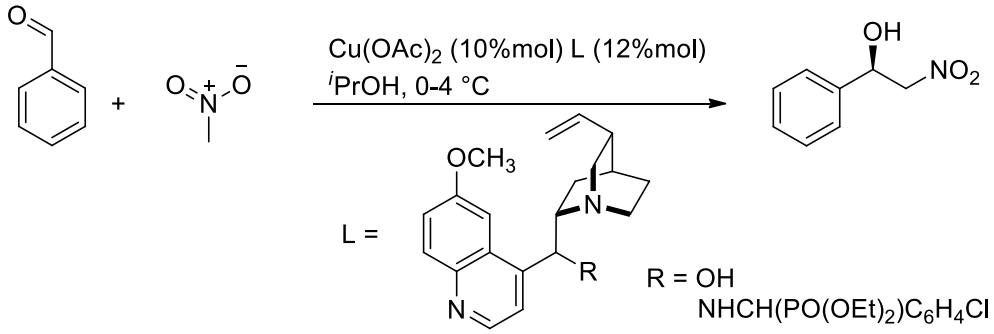
Cinchona alkaloids have already been used as catalysts in the asymmetric Pudovik reaction and the outcomes were explained by the enantioselective additions of phosphites to imines occurring from the side of the quinuclidine moiety.[5] Thus in our case a hydrogen bond between the quinuclidine nitrogen and the phosphite could also direct the attack of the nucleophile. Moreover, this interaction should enhance the nucleophilicity of the attacking phosphite by shifting the phosphite/phosphonate equilibrium thus accelerating the reaction. The replacement of proton with an alkaline metal ion previously provided similar result.[5] The stereochemistry of the quinuclidine directed reaction results in a product of opposite configuration to the predicted by the Yamamoto model (Figure 3). Finally, the configuration assigned to the product **1** makes this reaction pathway the most likely for imine **4**. It has to be noted that in many transformations of *Cinchona* alkaloids, where good to excellent stereoselectivites were obtained, they were mostly attributed to the quinuclidine nitrogen participation.[24] Some of these reactions were carried out at higher temperatures, without much impact on the stereoselectivity.

While **1** was obtained with excellent diastereoselectivity, no selectivity could be achieved for the 9*R* imine **6**. The most likely explanation is that in the alkaloids of native configuration at the

C-9 center, a conformation where quinuclidine nitrogen points toward the imine is much less favorable. Thus, the addition of the phosphite is no longer facilitated, and as a result, the Yamamoto pathway becomes effective. The diastereoselectivity of such transformation, especially at elevated temperatures is not expected to be very high due to the reasons indicated previously. Additionally, certain contribution of the quinuclidine-mediated reaction giving the product of opposite configuration would further diminish the diastereoselectivity.

In a preliminary application study the newly obtained alkaloid derivatives were tested as a chiral ligand in the asymmetric Henry reaction. Higher enantiomeric excess was achieved with isomer **1** of 9*S* configuration. However, both the reactivity and selectivity of the phosphonates were surpassed by the unmodified alkaloids.[25]

Table 1. Asymmetric Henry reaction



Entry	Alkaloid	Reaction time	Yield, %	%ee (configuration)
1	**1**	7 d	15	66 (*R*)
2	**2b**	7 d	21	25 (*S*)
3	Quinine[25]	3 d	87	86 (*S*)

Each reaction run on a 0.5 mmol scale.

We have also tested the ability of the aminophosphonate **1** to differentiate enantiomers of *N*-Boc-phenylglycine. The results were rather disappointing with no effect seen in the ^{31}P spectrum and low Δδ values (up to 0.04 ppm) observed in the ^{1}H spectrum.

Conclusions

New diethyl (*S*)-(4-chlorophenyl)((8*S*,9*S*)-6′-methoxycinchonan-9-ylamino)methanephosphonate (**1**) was obtained in good yield by a two-step procedure without purification of the intermediate product. The high diastereoselectivity of this transformation was attributed to the directing effect of the quinuclidine nitrogen. The separable products of 9*R* configuration (**2a**, **2b**) were obtained

both in inferior yields and with no diastereoselectivity. The configuration of the products was established by a combination of NMR experiments and DFT calculations.

Experimental Section

Preparation of aminophosphonate (1). 9-(*epi*)-Amino-deoxyquinine (253 mg, 0.783 mmol) and 4-chlorobenzaldehyde (117 mg, 0.832 mmol, 1.06 equiv) were dissolved in CH_2Cl_2 (2.5 mL) to form a cloudy solution, and anhydrous Na_2SO_4 (1.0 g) was added. The mixture was stirred for 24-48 h at room temperature. Then the solid was filtered off, washed with CH_2Cl_2 and evaporated in a resealable tube. The obtained crude imine was dissolved in dry toluene (1.6 mL), and diethyl phosphite (0.14 mL, 1.09 mmol, 1.38 equiv) and solid potassium carbonate (0.3 g) were added. The tube was sealed and the mixture stirred at 90 °C for 5 days. The mixture was then allowed to attain room temperature and filtered through Celite, and washed with toluene. Column chromatography on silica gel with $CHCl_3$/EtOH/acetone 20:1:5 gave 275 mg (60%) of product **1** as light brown glass.

Diethyl (*S*)-(4-chlorophenyl)((8*S*,9*S*)-6′-methoxycinchonan-9-ylamino)methanephosphonate (1). R_f 0.42 ($CHCl_3$/MeOH/Acetone 10:1:2). $[\alpha]_D^{21}$ –19 (c = 0.83, 96% EtOH), $[\alpha]_D^{21}$ –57 (c = 0.83, 96% EtOH / 0.3% CH_3CO_2H). ^{1}H NMR (600MHz, $CDCl_3$, 1.5 equiv TFA): δ 11.9 (br. s, ~1H), 8.79 (d, *J* = 4.7 Hz, 1H), 8.28 (d, *J* = 9.1 Hz, 1H), 7.98 (br. s, 1H), 7.78 (d, *J* = 4.7 Hz, 1H), 7.55 (d, *J* = 9.1 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.05 (br. d, *J* = 8.0 Hz, 2H), 6.7 (br. s, ~1H), 5.79 (d, *J* = 11.2 Hz, 1H), 5.67 (ddd, *J* = 17.4, 10.4, 6.7 Hz, 1H), 5.16 (d, *J* = 10.4 Hz, 1H), 5.13 (d, *J* = 17.4 Hz, 1H), 4.60 (t, *J* = 11.7 Hz, 1H), 4.12-4.20 (m, 2H), 4.08 (m, 1H), 4.07 (s, 3H), 3.90 (m, 1H), 3.84 (m, 1H), 3.70 (m, 1H), 3.48 (d, $^2J_{H\text{-}P}$= 6.8 Hz, 1H), 3.28 (m, 1H), 3.12 (dd, *J* = 12.2, 8.0 Hz, 1H), 2.75 (q, *J* = 7.7 Hz, 1H), 2.05-2.20 (m, 2H), 1.99 (br. s), 1.68 (t, *J* = 12.2 Hz, 1H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.11 (t, *J* = 6.9 Hz, 3H), 1.03 (dt, *J* = 14.0, 4.2 Hz, 1H). ^{13}C{^{1}H} NMR (151MHz, $CDCl_3$, 1.5 equiv TFA): δ 159.9, 147.7, 145.9, 141.2, 136.3, 134.3 (d, $^5J_{C\text{-}P}$ = 3.4 Hz), 134.0 (d, $^2J_{C\text{-}P}$ = 8.8 Hz), 130.9, 129.6, 129.1 (d, $^3J_{C\text{-}P}$ = 5.5 Hz), 128.7 (d, $^4J_{C\text{-}P}$ = 2.2 Hz), 119.9, 118.0, 60.0, 64.2 (d, $^2J_{C\text{-}P}$ = 7.7 Hz), 62.5 (d, $^2J_{C\text{-}P}$ = 7.7 Hz), 57.4 (d, $^2J_{C\text{-}P}$ = 163 Hz), 56.21, 56.15, 53.2, 40.8, 36.7, 26.8, 24.6, 23.7, 16.5 ($^4J_{C\text{-}P}$= 5.8 Hz), 16.4 ($^4J_{C\text{-}P}$ = 5.5 Hz). ^{31}P{^{1}H} (243 MHz, $CDCl_3$, 1.5 equiv TFA): δ 21.0. ^{31}P{^{1}H} (121MHz, $CDCl_3$): δ 25.0 (0.4P), 24.8 (0.6P). IR (KBr): 3300 (m), 2934 (s), 1620 (s), 1589 (m), 1507 (s), 1490 (s), 1474 (s), 1433 (s), 1357 (m), 1240 (s), 1092 (s), 1048 (s), 1025 (s), 963 (s), 854 (s), 736 (s), 708 (m), 565 (s). HR-MS (ESI): calculated for $[C_{31}H_{39}{}^{35}ClN_3O_4P+H]^+$: 584.2439 found 584.2441, calculated for $[C_{31}H_{39}{}^{37}ClN_3O_4P+H]^+$: 586.2410 found 586.2574; calculated for $[C_{31}H_{39}{}^{35}ClN_3O_4P+2H]^{2+}$: 292.6256 found 292.6264

Preparation of aminophosphonates (2a) and (2b)

9-(*nat*)-Amino-deoxyquinine (253 mg, 0.783 mmol) and 4-chlorobenzaldehyde (118 mg, 0.839 mmol, 1.07 equiv) were dissolved in CH_2Cl_2 (2.5 mL) to form a cloudy solution, and anhydrous

Na_2SO_4 (1.4 g) was added. The mixture was stirred for 20 h at room temperature. Then the solid was filtered off, washed with CH_2Cl_2 and evaporated in a resealable tube. The residue was dissolved in dry toluene (1.5 mL), and diethylphosphite (0.29 mL, 2.26 mmol, 2.8 equiv) was added. The tube was sealed and the mixture stirred at 100-109 °C for 4 days. The solution during the reaction run turned dark red. The mixture was then allowed to attain room temperature, diluted with toluene, filtered through Celite, and washed with toluene. Column chromatography on silicagel with $CHCl_3$/EtOH/Acetone 20:1:3 gave 52 mg of product **2a** (11%) and 51 mg of **2b** (11%) both as light brown oils and 17 mg of unreacted **6**.

Diethyl (*R*)-(4-chlorophenyl)((8*S*,9*R*)-6′-methoxycinchonan-9-ylamino)methanephosphonate (2b). Light brown oil. R_f 0.33 ($CHCl_3$/MeOH 10:1). $[\alpha]_D^{21}$ +72.5 (c = 2.5, EtOH, 96%). ^{1}H NMR (600MHz, $CDCl_3$, 1.5 equiv TFA): δ 13.1 (br. ~1H), 8.65 (d, *J* = 4.5 Hz, 1H, H-2′), 7.97 (d, *J* = 9.1 Hz, 1H, H-8′), 7.36 (d, *J* = 9.1 Hz, 1H, H-7′), 7.24 (d, *J* = 4.5 Hz, 1H, H-3′), 7.20 (s, 1H, H-5c), 7.03 (d, *J* = 7.8 Hz, 2H, *o*Ar-H), 6.76 (d, *J* = 7.8 Hz, 2H, *m*Ar-H), 5.60 (ddd, *J* = 17.1, 9.9, 7.2 Hz, H-10), 5.51 (br. s, 1H, H-9), 5.03-5.08 (m, 2H, H-11), ~4.7 (br. ~1H), 4.59 (m, 1H, H-6x), 4.36 (d, $^2J_{H\text{-}P}$ = 21.9 Hz, 1H, C*H*P), 4.14-4.20 (m, 2H, POCH_2), 3.95 (s, 3H, 6′-OCH_3), 3.76-3.83 (m, 1H, POCH_2), 3.45-3.52 (m, 2H, H-2t, POCH_2), 3.27 (m, 1H, H-6n), 3.08-3.16 (m, 2H, H-8, H-2c), 2.88 (br., ~1H), 2.73 (br. s, H-3), 2.16-2.27 (m, 3H, H-5x, H-4, H-7x), 1.94 (m, 1H, H-5n), 1.83 (t, *J* = 11 Hz, H-7n), 1.35 (t, J = 6.7 Hz, 3H, POCH$_2$*CH$_3$*), 0.95 (t, J = 6.9 Hz, 3H, POCH$_2$*CH$_3$*). ^{13}C{^{1}H} NMR (151MHz, $CDCl_3$, 1.5 equiv TFA): δ 159.4 (CH-6′), 147.1 (C-4′), 144.9 (CH-2′), 142.2 (C-9′), 137.4 (CH-10), 134.2 (d, $^5J_{P\text{-}C}$ = 2.4 Hz, *p*Ar-C), 133.8 (*ipso*Ar-C), 130.3 (d, $^3J_{P\text{-}C}$ = 6.6 Hz, *o*Ar-CH), 129.9 (CH-8′), 128.2 (*m*Ar-CH), 126.5 (C-10′), 124.5 (CH-7′), 118.0 (CH-3′), 117.7 (CH_2-11), 100.2 (CH-5′), 63.9 (d, $^3J_{P\text{-}C}$ = 6.7 Hz, PO*C*H_2), 62.4 (d, $^3J_{P\text{-}C}$ = 6.7 Hz, PO*C*H_2), 59.7 (d, $^1J_{P\text{-}C}$ = 157.6 Hz, P*CH*), 59.7 (CH-8), 56.5 (OCH_3), 55.5 (d, $^3J_{P\text{-}C}$ = 18.7 Hz, CH-9), 54.7 (CH_2-2), 43.1 (CH_2-6), 37.2 (CH-3), 27.0 (CH-4), 24.8 (CH_2-5), 20.8 (CH_2-7), 16.5 (d, $^4J_{P\text{-}C}$ = 6.6 Hz, POCH$_2$*CH$_3$*), 16.2 (d, $^4J_{P\text{-}C}$ = 5.6 Hz, POCH$_2$*CH$_3$*). ^{31}P{^{1}H} (243 MHz, $CDCl_3$, 1.5 equiv TFA): δ 22.0. ^{31}P{^{1}H} (121 MHz, $CDCl_3$): δ 24.7 (0.2P), 23.4 (0.8P). HR-MS (ESI): calculated for $[C_{31}H_{39}{}^{35}ClN_3O_4P+H]^+$: 584.2439 found 584.2441, calculated for $[C_{31}H_{39}{}^{37}ClN_3O_4P+H]^+$: 586.2410 found 586.2463, calculated for $[C_{31}H_{39}{}^{35}ClN_3O_4P+2H]^{2+}$: 292.6256 found 292.6357.

Diethyl (*S*)-(4-chlorophenyl)((8*S*,9*R*)-6′-methoxycinchonan-9-ylamino)methanephosphonate (2a). Light brown oil. R_f 0.22 ($CHCl_3$/MeOH 10:1). $[\alpha]_D^{21}$ –38.6 (c = 0.99, EtOH, 96%). ^{1}H NMR (300MHz, $CDCl_3$, 1.5 equiv TFA): δ ~13.5 (br.~1H), 8.81 (d, *J* = 4.6 Hz, 1H, H-2′), 8.01 (d, *J* = 9.2 Hz, 1H, H-8′), 7.38 (d, *J* = 4.6 Hz, 1H, H-3′), 7.36 (dd, *J* = 9.2, 2.6 Hz, 1H, H-7′), 7.26 (d, *J* = 8.5 Hz, 2H, *m*Ar-H), 7.08 (dd *J* = 8.5 Hz, $^4J_{P\text{-}H}$ = 2.2 Hz, 2H, *o*Ar-H), 6.98 (d, J = 2.5 Hz, H-5′), 5.57 (ddd, *J* = 17.0, 10.5, 7.0 Hz, 1H, H-10), 5.12-5.20 (m, 1H, H-9), 5.03 (d, J =10.4 Hz, 1H, H-11t), 5.03 (d, J = 17.0 Hz, 1H, H-11c), 4.50 (br., 1H, H-6x), 3.71-3.82 (m, 4H, PO*C*H_2CH$_3$), 3.77 (s, 3H, OCH_3), 3.76 (d, $^2J_{H\text{-}P}$ = 17.4 Hz, 1H, P*CH*) 3.47 (dd, J = 13.5, 11.0 Hz, 1H, H-2t), 3.37 (m, 1H, H-6n), 3.25 (m, 1H, H-8), 3.11 (br., ~1H), 3.03 (m, 1H, H-2c), 2.68 (m, 1H, H-3), 2.18 (m, 1H, H-4), 1.86-2.17 (m, 3H, H-5x, H-7x, H-5n) 1.81 (m, 1H, H-7n), 1.18 (t, *J* = 7.1 Hz, 3H, POCH$_2$*CH$_3$*) 1.13 (t, *J* = 7.1 Hz, 3H, POCH$_2$*CH$_3$*). ^{13}C{^{1}H} NMR (151MHz,

$CDCl_3$, 1.5 equiv TFA): δ 159.4, 147.0, 144.9, 141.2, 137.4, 134.8 (d, J_{P-C}= 4.2 Hz), 131.85, 131.78, 130.4 (d, $^3J_{P-C}$ = 6.4 Hz), 129.1 (d, J_{P-C}= 1.9 Hz), 127.5, 123.8, 117.6 (2C overlap), 99.5, 63.6 (d, J_{P-C} = 7.7 Hz), 62.9 (d, J_{P-C} = 7.7 Hz), 58.8, 57.8 (d, J_{P-C} = 153.1 Hz), 56.4, 54.5, 53.9 (d, J_{P-C} = 15.5 Hz), 43.3, 37.0, 27.1, 24.8, 20.7, 16.5 (d, J_{P-C} = 5.4 Hz), 16.3 (d, J_{P-C} = 5.5 Hz). $^{31}P\{^1H\}$ (121 MHz, $CDCl_3$): δ 23.1 (0.2P), 22.9 (0.8P). HR-MS (ESI): calculated for $[C_{31}H_{39}{}^{35}ClN_3O_4P+H]^+$: 584.2439 found 584.2419, calculated for $[C_{31}H_{39}{}^{37}ClN_3O_4P+H]^+$: 586.2410 found 586.2791, calculated for $[C_{31}H_{39}{}^{35}ClN_3O_4P+2H]^{2+}$: 292.6256 found 292.6256.

(8*S*,9*R*)-*N*-[(4-chlorophenyl)methylene]-6′-methoxycinchonan-9-amine (6). ^1H NMR (300 MHz, $CDCl_3$): δ 8.71 (d, *J* = 4.6 Hz, 1H), 8.38 (s, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 2.8 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.37 (dd, *J* = 9.2, 2.8 Hz, 1H), 5.82 (ddd, *J* = 17.2, 10.3, 7.7 Hz, 1H), 5.14 (d, *J* = 6.4 Hz, 1H), 4.99 (dt, *J* = 17.2, 1.4 Hz, 1H), 4.95 (dt, *J* = 10.3, 1.4 Hz, 1H), 3.97 (s, 3H), 3.54 (m, 1H), 3.10 (m, 1H), 3.08 (dd, *J* = 13.7, 10.1 Hz, 1H), 2.54-2.72 (m, 2H), 2.26 (m, 1H), 1.96 (br., 1H), 1.83 (m, 1H), 1.61-1.77 (m, 3H), 1.53 (m, 1H).

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References

1. (a) Kafarski, P.; Lejczak, B. In *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*; Kukhar, V.P.; Hudson, H.R., Eds.; John Wiley & Sons: Chichester, 2000; pp. 407-442. (b) Grembecka, J.; Mucha, A.; Cierpicki, T.; Kafarski, P. *J. Med. Chem.* **1989**, *32*, 2461.
2. (a) Kiss, T.; Balla, J.; Nagy, G.; Kozłowski, H.; Kowalik, J. *Inorg. Chim. Acta* **1987**, *138*, 25. (b) Kiss, T.; Lázár, I.; Kafarski, P. *Metal-Based Drugs* **1994**, *1*, 247. (c) Bligh, A.S.W.; McEwen, A.B.; Harding, C.T.; Sadler, P.J.; Kelly J.D.; Marriott J.A. *Polyhedron* **1994**, *13*, 1937.
3. (a) Pierre, A.; Lavielle, G.; Hautefaye, P.; Seurre, G.; Leonce, S.; Saint-Dizier, D.; Boutin, J. A.; Cudennec, C. A. *Anticancer Res*. **1990**, *10*, 139. (b) Lelievre, E.; Guillaudeux, J.; Cardona, H.; Bourguignat, A.; Lokiec, F.; Solere, P.; Lucas, C.; Sauveur, C. *Cancer. Res.* **1993**, *53*, 3536.
4. Wang, F.; Liu, X.; Cui, X.; Xiong, Y.; Zhou, X.; Feng , X. *Chem. Eur.* **2009**, *15*, 589.
5. (a) Pettersen, D.; Marcolini, M.; Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzani, V.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 6269. (b) Nakamura, S.; Hayashi, M.; Hiramatsu, Y.; Shibata, N.; Funahashi, Y.; Toru, T. *J. Am. Chem. Soc.* **2009**, *131*, 18240.

6. (a) Gazaliev, A. M.; Balitskii, S. N.; Fazylov, S. D.; Kasenov, R. Z. *Zh. Obshch. Khim*. **1991**, *61*, 2365. (b) Gavrilov, K. N.; Mikhel', I. S. *Rus. J. Inorg. Chem.* **1994**, 39, 101. (c) Gavrilov, K. N.; Mikhel, I. S.; Lechkin, D. V.; Timofeeva, G. I. *Phosphorus, Sulfur Silicon Relat. Elem*. **1996**, *108*, 285.
7. (a) Chodkiewicz, W. *J. Organomet. Chem.* **1984**, *273*, C 55. (b)Wang, Q.-F.; He, W.; Liu, X.-Y.; Chen, H.; Qin, X.-Y.; Zhang, S.-Y. *Tetrahedron: Asymmetry* **2008**, *19*, 2447.
8. (a) Chodkiewicz W.; Jore, D.; Pierrat, A.; Wodzki W. *J. Organomet. Chem.* **1979**, 174, C 21. (b) Vannoorenberghe, Y.; Buono, G. *Tetrahedron Lett.* **1988**, *29*, 3235. (c) Mizuta, S.; Sadamori, M.; Fujimoto, T.; Yamamoto, I. *Angew. Chem. Int. Ed.* **2003**, *42*, 3383
9. Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.
10. Sladojevich, F.; Dixon, D. J.; Trabocchi, A.; Guarna, A. *J. Am. Chem. Soc.* **2011**, *133*, 1710.
11. Brunner, H.; Janura, M.; Stefaniak, S. *Synthesis* **1998**, 1742.
12. Ma, X.; Wang, Y.; Wang, W.; Cao, J. *Catal. Commun.* **2010**, *11*, 401.
13. (a) Lämmerhofer M.; Lindner, W. *J. Chromatogr. A* **1996**, *741*, 33. (b) Mandl, A.; Nicoletti, L.; Lämmerhofer, M.; Lindner, W. *J. Chromatogr. A* **1999**, *858*, 1.
14. Pirkle, W. H.; Burke, J. A. *Chirality*, **1989**, *1*, 57.
15. Prakash, G. K. S.; Wang, F.; Ni, C.; Shen, J.; Haiges, R.; Yudin, A. K.; Mathew, T.; Olah, G. A. *J. Am. Chem. Soc.* **2011**, *133*, 9992.
16. (a) Pudovik, A. N. *Doklady Akad. Nauk SSSR*, **1952**, *83*, 865; *Chem. Abstr.* **1953**, *47*, 4300. (b) Pudovik, A. N.; Konovalova, I. V. *Synthesis* **1979**, 81. (c) Merino, P.; Marques-Lopez, E.; Herreraa, R. P. *Adv. Synth. Catal.* **2008**, *350*.
17. Brunner, H.; Schiessling, H. *Angew. Chem., Int. Ed.* **1994**, *33*, 125.
18. Brunner, H.; Bügler, J. *Bull. Soc. Chim. Belg.* **1997**, *106*, 77.
19. Boratyński, P. J.; Turowska-Tyrk, I.; Skarżewski, J. *J. Org. Chem.* **2008**, 73, 7357.
20. Frisch, M. J.; *et al.*, Gaussian 09, Revision B.01, Gaussian, Inc., Wallingford CT, 2010.
21. (a) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *106*, 5031. (b) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Tomatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778.
22. (a) Yager, K. M.; Taylor, C. M.; Smith, A. B. III *J. Am. Chem. Soc.* **1994**, *116*, 9377. (b) Lewkowski, J.; Karpowicz, R. *Heteroatom Chem.* **2010**, *21*, 326
23. Hoffmann, H. M. R.; Frackenpohl, J. In *Cinchona Alkaloids in Synthesis & Catalysis*; Song, C. E. Ed.; Wiley-VCH: Weinheim, 2009; pp. 359-418.
24. (a) Gutzwiller, J.; Uskoković, M. R. *Helv. Chim. Acta* **1973**, *56*, 1494. (b) Braje, W. M.; Holzgrefe, J.; Wartchow, R.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2085. (c) Hintermann, L.; Schmitz, M.; Englert, U. *Angew. Chem., Int. Ed.* **2007**, *46*, 5164. (d) Boratyński P. J.; Turowska-Tyrk, I.; Skarżewski, J. *Org. Lett.* **2008**, *10*, 385.
25. Zielińska-Błajet, M.; Skarżewski J. *Tetrahedron: Asymmetry* **2011**, *22*, 351.

