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Synthesis of chiral *ortho*-thio-substituted phenyl phosphonodiamidates via a P–S to P–C rearrangement

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Abstract—The *ortho*-lithiation of a phenyl phosphorodiamidothioate derived from an enantiopure C_2-symmetric diamine is studied. It is shown that the migration of the diaminophosphoryl group from sulfur to carbon, leading to an *ortho*-sulfanylated phenyl phosphonodiamidate, only occurs in the presence of an alkylating agent or a Lewis acid as $BF_3{\cdot}Et_2O$. The influence of the chiral diaminophosphoryl group on the stereoselectivity of the oxidation of the *ortho*-sulfanyl or alkylsulfanyl group is also examined.

During the last three decades, the syntheses of a large variety of chiral ligands have contributed to the considerable development of asymmetric catalysis based on organometallic chemistry.[1] Among the bidentate ligands, 1,2-difunctionalized aryl derivatives, in particular chiral *ortho*-hydroxyaryl-substituted organophosphorus derivatives, have been successfully used.[2] One of the more convenient ways to prepare such compounds is the *ortho*-lithiation of an aryl phosphate[3] or an aryl phosphorodiamidate,[4] which is usually followed by a 1,3-sigmatropic migration of the phosphorylated moiety from oxygen to carbon. More recently, a similar rearrangement has been described through a halogen–lithium exchange from a 2-bromoarylphosphinite.[5] With a chiral phosphorus center, a complete retention of configuration was observed and the rearrangement was, respectively, applied by the groups of Buono and Jugé to the asymmetric synthesis of a P-stereogenic 2-hydroxyarylphosphonamide and a 2-hydroxyarylphosphine–borane complex.[5,6] Some applications of these difunctional compounds (and of their methoxy analogues) as ligands for asymmetric synthesis have already been described, the stereogenic moiety being a diaminophosphoryl group derived from an asymmetric diamine or aminoalcohol.[7]

Like their 2-hydroxy analogues,[2a] 2-sulfanylarylphosphonodiamidates derived from chiral diamines could be useful ligands for asymmetric synthesis provided that they can be easily synthesized. Moreover, the sulfanyl group can be readily alkylated into a sulfide and then oxidized into a sulfoxide, another stereogenic center, which has also good metal chelating properties. In particular, recent studies by Hiroi et al. have shown that an enantiopure 2-alkylsulfinylphenyl-diphenyl-phosphine can be used as chiral catalyst in a Tsuji–Trost allylation reaction (ee up to 85%).[11]

Any investigation on the potential of 2-sulfanylarylphosphonodiamidates or their derivatives as chiral ligands in asymmetric synthesis needs an efficient method to prepare them. Few years ago, our group has demonstrated that the rearrangement aryl phosphorothioate–*ortho*-sulfanylarylphosphonate is possible provided that the *O*,*O*′-alkyl substituents on phosphorus are relatively bulky such as isopropyls, in order to avoid the nucleophilic addition of the LDA to the phosphoryl function.[8] To our knowledge, as far as aryl phosphorodiamidothioates are concerned, only two examples of such a 1,3-sigmatropic migration are mentioned in the literature. The first one is connected to the synthesis of the *N*,*N*-dimethyl 2-methylsulfanylphenyl phosphonodiamidate by *ortho*-lithiation of the corresponding phenyl phosphorodiamidothioate at low temperature (−100 °C) with subsequent addition of methyl iodide (any attempt to prepare the corresponding thiol is not mentioned).[9] The second example is the *ortho*-lithiation of a phenyl phosphorodiamidothioate derived from an

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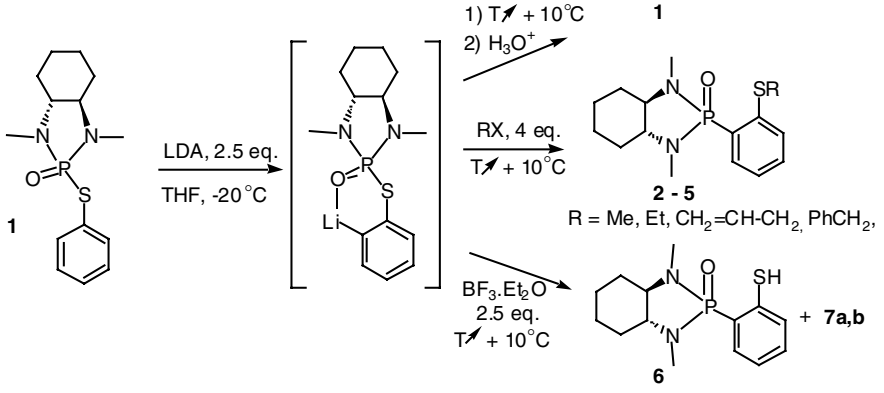
enantiopure 2-anilinomethylpyrrolidine followed by a protonation step, which actually leads to the preparation of the corresponding arylthiol but in a low yield (20%).[10] We report here our first results related to the *ortho*-lithiation of a phenyl phosphorodiamidothioate prepared from an enantiopure *trans*-*N*,*N*′-dimethyl cyclohexane-1,2-diamine. This work demonstrates that, with such a diamidothioate, the S → C migration is not spontaneous, as observed for their oxygen analogues, and how it is possible to induce this rearrangement by addition of an alkylating agent or a Lewis acid. Moreover, procedures allowing the stereoselective preparation of the corresponding 2-alkylsulfinylphenyl phosphonodiamidate are also investigated.

The starting phenyl phosphorodiamidothioate **1** was readily obtained in good yield (75%) by reaction of the sodium salt of benzenethiol with a diaminophosphorochloridate, which was prepared from the commercially available (1*R*,2*R*)-diaminocyclohexane, according to known procedures.[12,13] The *ortho*-lithiation of **1** (Scheme 1) by addition of 2.5 equiv of LDA in THF was monitored by ^{31}P NMR. At temperatures between −20 and +10 °C, the signal of the starting material at 41 ppm was replaced by a new signal at 44 ppm. However, after protonation of the mixture, at room temperature, with water (NH_4Cl) or D_2O, starting compound **1** or its *ortho*-deuterated analogue was nearly quantitatively recovered. This clearly indicates that, although the *ortho*-lithiation occurred (the signal at 44 ppm corresponds to the *ortho*-lithiated derivative), no P–S to P–C rearrangement took place.

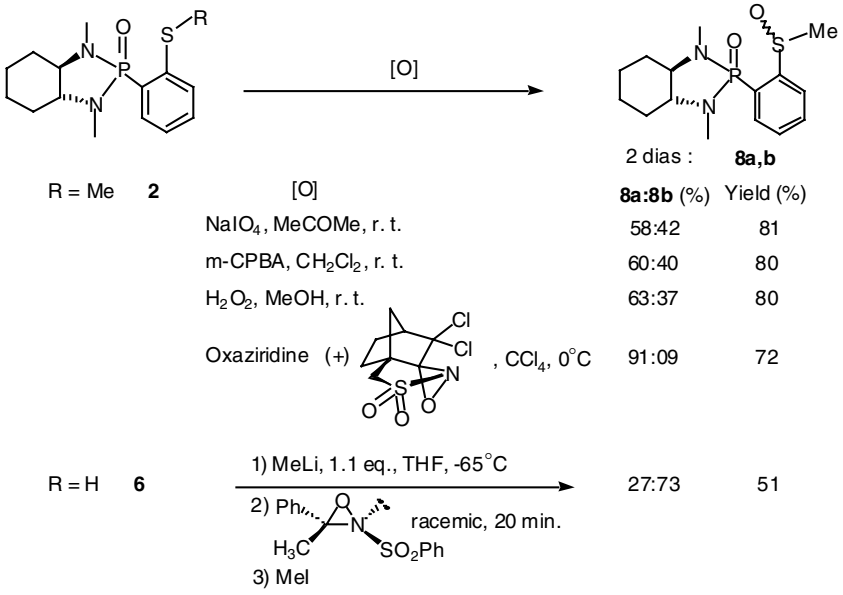
Therefore, we examined the effect of the addition of an alkylating agent (methyl iodide) to the *ortho*-lithiated intermediate. Monitored by ^{31}P NMR, this experiment showed that, as soon as methyl iodide was added to *ortho*-lithiated **1**, the 44 ppm peak disappeared completely and a new signal at 35 ppm was observed. The latter corresponds to the S-methylated rearranged product, the 2-methylsulfanylphenyl phosphonodiamidate **2**, which was actually isolated in a 78% yield after purification.[14] No *ortho*-C alkylation of **1** could be detected in the crude product. The same procedure was repeated with ethyliodide, allylbromide, and benzylbromide. Thus 2-(ethyl-, allyl-, and benzyl-sulfanyl)phenyl phosphonodiamidates **3**, **4**, and **5** were, respectively, isolated in 58%, 68%, and 71% yields. The lower yield was obtained with ethyliodide, the less efficient alkylating agent.

In order to get a phenyl phosphonodiamidate *ortho*-substituted by a thiol function, we then added a Lewis acid to the solution of *ortho*-lithiated **1**, with the aim to increase the electrophilicity of the phosphorus. Four Lewis acids were tested. $ZnCl_2$ has no effect, $TiCl_4$ and $ClSiMe_3$, respectively, produced degradation or incomplete conversion. Only the use of 2.5 equiv of $BF_3{\cdot}Et_2O$ gave a complete transformation of **1** (this need of an excess of Lewis acid being probably linked to the 2.5 equiv of LDA used for a complete *ortho*-lithiation). Two products were isolated, both resulting from the expected *ortho*-lithiation–1,3-migration sequence. The main one was the expected 2-sulfanylphenyl phosphonodiamidate **6** (72%).[15] The isolated by-product (17%) is the corresponding disulfide **7** which, at room temperature, appears as a nearly 1:1 mixture of two rotamers **7a** and **7b** (δ $^{31}P_{DMSO} = 33.45$ and 33.40) with a coalescence temperature of 50 °C (δ $^{31}P_{DMSO} = 33.12$). Analogous slow rotation has already been observed for *ortho*-substituted benzenedisulfides.[17]

The effect of an alkylating agent or of a Lewis acid on the course of the reaction merits some comments. Compared to the *ortho*-lithiated phenylthiophosphate analogue, which rearranges spontaneously,[8] initially formed *ortho*-lithiated phenyl phosphorodiamidothioate is probably more stabilized due to the electrondonating effect of the two nitrogen atoms, which increases the oxygen–lithium chelation and reduces the electrophilicity of the phosphorus. Therefore protonation gives back the starting phosphorodiamidothioate **1**. The addition of an alkylating agent with a possible partial linkage of its halogen to lithium may destabilize this initial lithiated species, which is then more easily converted into the bipyramidal transition state suggested for the P–S to P–C migration.[6] From this transition state, the cleavage of the P–S bond to give the final rearranged product might be also assisted by a simultaneous addition of the alkyl group on the sulfur atom. The effect of the Lewis acid, $BF_3{\cdot}Et_2O$, can be interpreted by the chelation of the oxygen of the P=O group, which both destabilizes the



Scheme 1.



Scheme 2.

initial *ortho*-lithiated species and increases the electrophilicity of the phosphorus atom, thus facilitating the formation of the C–P bond.

Then, in order to check if the asymmetric *ortho*-diaminophosphoryl group can be an efficient chiral inductor in the oxidation of the sulfur atom, we examined the reaction of sulfide **2** with $NaIO_4$, *m*-chloroperbenzoic acid, and hydrogen peroxide (Scheme 2). With such achiral reagents, a mixture of diastereomers **8a** and **8b** was obtained with poor diastereomeric excesses (up to 26%), as determined by ^{31}P NMR ($CDCl_3$, $\delta = 35.15$ and 32.20, respectively).[16] This clearly indicates a weak asymmetric induction by the chiral phosphonamido group. A similar conclusion can be drawn from the reaction of sulfide **2** with the commercially available enantiopure (+)-(2*S*,8a*R*)-8,8-dichloro-camphorsulfonyloxaziridine, which led also to **8a** as the major diastereomer. Although a much better diastereomeric excess (very probably resulting from a match effect) was obtained (82%), this de is relatively close to that we previously observed for the oxidation of the achiral 2-methylsulfanylphenyl phosphonate (de = 73%) using the same enantiopure oxaziridine.[18,19]

A method of direct oxidation of aromatic thiol into sulfoxide, by a deprotonation–oxidation–alkylation sequence involving an intermediate lithium sulfenate, has been described by Perrio and co-workers.[20] Thiol **6** was oxidized according to this procedure, racemic *N*-phenylsulfonyl *tert*-butyl methyl oxaziridine being used for the oxidation step (Scheme 2). A mixture of the two diastereomeric sulfoxides **8a**, **8b** was obtained in a ratio 27:73, isolated in a nonoptimized yield of only 51% due to the formation of disulfide of the starting thiol (disulfide **7** is isolated in 23% yield). The diastereomeric excess for the sulfoxide **8** (46%) is still modest but the stereoselectivity is opposite to that obtained for the direct oxidation of sulfide **2** by achiral oxidants. Such an interesting inversion of stereoselectivity has already been observed for the two types of oxidation procedures applied to (*R*)-2-(1-dimethylaminoethyl)benzenethiol and to its *S*-methyl derivative.[21]

In conclusion, this work describes efficient syntheses of a new chiral *ortho*-sulfanylphenyl phosphonamide, and some of its corresponding sulfides, derived from an enantiopure *trans*-1,2-cyclohexane diamine by using the *ortho*-lithiation–1,3-migration sequence. The procedures described here and involving either a Lewis acid or an alkylating agent open a way to the synthesis of a variety of new potential mixed P,S-chiral bidentate ligands prepared from other C_2-symmetric diamines. A rather good diastereoisomeric excess of 82% was here observed for the oxidation of the sulfide **2** into the corresponding sulfoxide but this needed the use of an enantiopure chiral oxaziridine. In order to get such *ortho*-difunctionalized benzene derivatives (bearing both a phosphoramide and a sulfoxide as stereogenic centers) with higher stereoselectivity, and without the requirement of an enantiopure oxidizing agent, it will be worth studying more extensively the synthesis and oxidation of analogues of sulfide **2** and thiol **6** prepared from other chiral diamines, in particular those bearing more bulky substituents.

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13. Synthesis of **1**: Benzenethiol (3 mmol) was added at 0 °C to a suspension of sodium hydride (3.1 mmol) in dry THF (5 mL) under nitrogen. The mixture was stirred for 30 min. Then diaminophosphorochloridate[12] (3 mmol) was added. The solution was stirred for 12 h at room temperature, quenched by the addition of a saturated NH_4Cl solution (10 mL) and extracted with diethyl ether (2×10 mL). After drying and evaporation of the solvent, the residue was purified by flash chromatography on a silica gel column (ethyl acetate/petroleum ether, 25/75) to give colorless crystals, mp 51 °C; $[\alpha]_D^{20}$ −16.8 (*c* 2.55, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.73 (m, 1H), 0.94 (m, 1H), 1.06 (m, 1H), 1.23 (m, 1H), 1.59 (m, 1H), 1.71 (m, 3H), 1.90 (m, 1H), 2.63 (d, $J = 13.0$, 3H), 2.73 (m, 1H), 2.74 (d, $J = 11.6$, 3H), 7.28–7.36 (m, 3H), 7.53–7.56 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 24.35 (s), 24.44 (s), 28.07 (d, $J = 9.1$), 28.34 (d, $J = 8.7$), 28.40 (d, $J = 3.6$), 28.68 (d, $J = 4.1$), 63.80 (d, $J = 7.5$), 64.80 (d, $J = 7.5$), 129.07 (d, $J = 3$, 2C), 129.10 (d, $J = 7.1$), 129.21 (s), 136.59 (d, $J = 2.7$, 2C). ^{31}P NMR ($CDCl_3$): δ 44.65. $C_{14}H_{21}N_2OPS$: calcd: C, 56.74; H, 7.14; N, 9.45; S, 10.82; found: C, 56.95; H, 7.10; N, 9.60; S, 10.58.
14. Synthesis of **2** (typical procedure for the preparation of **2** to **5**): Phenyl phosphorodiamidothioate **1** (1 mmol) was slowly added to a stirred solution of LDA (2.5 mmol) in dry THF (5 mL) under nitrogen at −20 °C. The mixture was allowed to warm to 10 °C and alkyl halide (5 mmol) was added. After 30 min at this temperature, the reaction is quenched by the addition of a saturated NH_4Cl solution (5 mL) and extracted with diethyl ether (3×5 mL). The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (ethyl acetate). Compound **2** was isolated in 78% yield as colorless crystals, mp 112 °C; $[\alpha]_D^{20}$ −9.1 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.22–1.45 (m, 2H), 1.78–1.92 (m, 2H), 1.97–2.13 (m, 3H), 2.44 (d, $J = 11.1$, 3H), 2.46 (s, 3H), 2.51 (d, $J = 12.0$, 3H), 2.52–2.63 (m, 1H), 2.88–3.09 (m, 2H), 7.17 (ddt, $J = 1.1$, $J = 2.5$, $J = 7.4$, 1H), 7.24–7.29 (m, 1H), 7.43 (tt, $J = 1.5$, $J = 7.4$, 1H), 7.97 (ddd, $J = 1.5$, $J = 7.4$, $J = 13.9$, 1H). ^{13}C NMR ($CDCl_3$): δ 16.37 (s), 24.72 (s), 24.85 (s), 28.55 (s), 28.70 (d, $J = 5.8$), 28.91 (d, $J = 7.0$), 29.38 (d, $J = 2.0$), 64.84 (d, $J = 5.9$), 64.89 (d, $J = 7.8$), 124.15 (d, $J = 12.6$), 125.23 (d, $J = 11.5$), 127.44 (d, $J = 151.3$), 132.22 (d, $J = 2.6$), 136.92 (d, $J = 8.9$), 144.65 (d, $J = 8.4$). ^{31}P NMR ($CDCl_3$): δ 34.54. $C_{15}H_{23}N_2OPS$: calcd: C, 58.04; H, 7.47; N, 9.02; found: C, 58.48; H, 7.70; N, 9.06.
15. Synthesis of **6**: To a stirred solution of LDA (2.5 mmol) in dry THF (5 mL) under nitrogen, was slowly added *S*-phenyl phosphorodiamidate **1** (1 mmol) at −20 °C. The mixture was allowed to warm to 10 °C and $BF_3{\cdot}Et_2O$ (2.5 mmol) was added dropwise at 0 °C. The solution was allowed to warm to rt, stirred for an hour and then added to a saturated NH_4Cl solution (5 mL). The product was extracted with diethyl ether (3×5 mL). After usual work up, the residue was purified by flash chromatography on a silica gel column (ethyl acetate) to afford **6**, as a green oil, in 73% yield. ^1H NMR ($CDCl_3$): δ 1.32–1.39 (m, 2H), 1.53–1.72 (m, 2H), 2.39 (d, $J = 11.5$, 3H), 2.40–2.68 (m, 4H), 2.58 (d, $J = 11.7$, 3H), 2.65–2.72 (m, 1H), 2.90–2.96 (m, 1H), 7.12–7.20 (m, 1H), 7.27–7.38 (m, 2H), 7.66 (ddd, $J = 1.3$, $J = 7.8$, $J = 14.1$, 1H). ^{13}C NMR ($CDCl_3$): δ 24.59 (s), 24.70 (s), 28.52 (d, $J = 1.5$), 28.82 (d, $J = 5.5$), 28.90 (d, $J = 5.0$), 29.27 (d, $J = 1.5$), 64.39 (d, $J = 6.2$), 65.55 (d, $J = 7.0$), 124.65 (d, $J = 12.6$), 126.08 (d, $J = 151.2$), 130.98 (d, $J = 12.3$), 132.01 (d, $J = 2.7$), 134.81 (d, $J = 9.0$), 141.04 (d, $J = 8.6$). ^{31}P NMR ($CDCl_3$): δ 37.62. $C_{14}H_{21}N_2OPS$: calcd: C, 56.74; H, 7.14; N, 9.45; S, 10.82; found: C, 56.81; H, 7.16; N, 9.32; S, 10.96.
16. Characterization of the mixture of diastereomers **8a** and **8b** purified by flash chromatography (silica gel; ethyl acetate) as a slightly brown solid. Compound **8a**: ^1H NMR ($CDCl_3$): δ 1.19–1.45 (m, 4H), 1.87–1.92 (m, 2H), 2.09 (m, 3H), 2.35 (d, $J = 11.9$, 3H), 2.58 (d, $J = 10.2$, 3H), 2.89 (m, 1H), 2.96 (s, 3H), 7.55 (m, 2H), 7.77 (m, 1H), 8.36 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 24.60 (s), 24.77 (s), 28.27 (d, $J = 8.0$), 28.77 (d, $J = 4.9$), 29.03 (s), 29.20 (d, $J = 2.9$), 46.31 (s), 64.18 (d, $J = 6.7$), 64.79 (d, $J = 7.7$), 124.35 (d, $J = 10.9$), 128.11 (d, $J = 139.5$), 130.64 (d, $J = 11.8$), 132.75 (d, $J = 8.7$), 133.12 (d, $J = 2.8$), 153.27 (d, $J = 10.6$). ^{31}P NMR ($CDCl_3$): δ 35.15. Compound **8b**: ^1H NMR ($CDCl_3$): δ 1.19–1.45 (m, 4H), 1.91–1.97 (m, 2H), 2.13 (m, 3H), 2.46 (d, $J = 10.6$, 3H), 2.49 (d, $J = 12.6$, 3H), 2.87 (s, 3H), 3.10 (m, 1H), 7.54 (m, 1H), 7.59 (m, 1H), 7.78 (m, 1H), 8.35 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 24.55 (s), 24.69 (s), 28.57 (d, $J = 5.7$), 28.78 (d, $J = 6.1$), 29.12 (s), 29.48 (d, $J = 2.0$), 45.64 (s), 64.98 (d, $J = 5.5$), 65.89 (d, $J = 7.6$), 124.48 (d, $J = 10.9$), 128.26 (d, $J = 153.3$), 130.69 (d, $J = 12.3$), 133.41 (d, $J = 2.8$), 134.20 (d, $J = 9.4$), 152.80 (d, $J = 10.1$). ^{31}P NMR ($CDCl_3$): δ 32.20. $C_{15}H_{23}N_2O_2PS$: calcd: C, 55.20; H, 7.10; N, 8.58; S, 9.82; found: C, 55.85; H, 7.27; N, 8.83; S, 9.36.
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19. The absolute configuration of the sulfoxide group for each diastereomer **8a** and **8b** has not yet been determined. We were not able to separate pure samples of these isomers, by chromatography or crystallization, for a study by X-ray diffraction. Moreover, our attempt to convert them into the corresponding dimethyl phosphonates of known configuration[18] led us to a racemic mixture. Very probably, the strong acidic conditions needed to hydrolyse the phosphonamido group racemized the sulfoxyde function.
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