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Configurational Stability of Chlorophosphines

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The configurational stability of chlorophosphines is investigated. Several mechanisms involving chlorophosphine monomer, dimers, and adducts with HCl are evaluated by density functional theory calculations. The presence of HCl in the medium is found to catalyze the P-center chiral inversion at room temperature. The reaction involves a two-step mechanism with low transition states (10 kcal·mol^{-1}) and a stabilized achiral intermediate (–2.6 kcal·mol^{-1}). Further calculations and experiments on the halogen exchange with HBr corroborate this mechanism, with bromophosphines being formed instantaneously. Finally, to avoid the racemization, the borane is found to be a very promising protecting group for the configurational stability of the P-chirogenic chlorophosphines.

Introduction

During the past 3 decades, there has been considerable development in asymmetric transition metal catalyzed reactions,[1] especially in the area of chiral ligands,[2] where chiral P(III)—organophosphorus derivatives (diphosphines,[3] diphosphinites,[4] aminophosphine—phosphinites,[5] chelating monophosphines[6]) have been widely used. The synthesis of these ligands is usually performed using achiral chlorophosphines **1** (Scheme 1, $R^1 = R^2$), either as electrophilic[7] (Scheme 1a) or nucleophilic reagents,[8] in the latter case, through the formation of phosphides (Scheme 1b).

It is interesting to note that the most commonly used P(III)—organophosphorus ligands generally bear the chirality on the carbon backbone. If enantiomerically enriched chlo-

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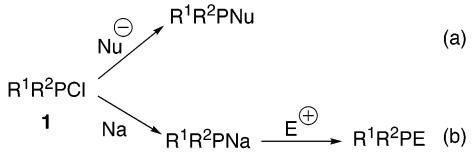
Scheme 1



1	a	b	c	d	e	f
R^1	Me	Ph	*t*-Bu	Ph	Ph	Ph
R^2	Me	Ph	*t*-Bu	*t*-Bu	Et	*o*-An

rophosphines **1** (Scheme 1, $R^1 \neq R^2$) were available, they could be useful building blocks for the synthesis of a new class of bulky, hybrid, or functionalized P−chirogenic ligands, which would bring the chiral center close to the metal.

Previous studies on the pyramidal inversion of chlorophosphines indicate that they are configurationally stable, with even higher energy barriers than tertiary phosphines, 40.0 and 35.6 kcal·mol^{-1}, respectively.[9] It is well-established that this increased barrier in chlorophosphines originates from both the σ attracting and the π donating abilities of the chlorine substituent. Both favor the pyramidalization of the phosphorus and hence increase the monomeric inversion barrier.[9b,10]

However, only the partially enantiomerically enriched *tert*-butylchlorophenylphosphine (**1d**) has been described to date.[11,12] This compound, which was obtained by a phosphonium salt decomposition at low temperature (Scheme 2a), or by kinetic resolution, slowly racemized at room temperature. The pioneering work of Horner and Jordan[13] described the formation of a racemic chlorophosphine **1e** from enantiomerically enriched ethylphenylaminophosphine (Scheme 2b). These authors postulated that the aminophosphine acidolysis with HCl was stereoselective and the resulting chlorophosphine **1e** was believed to racemize by intermolecular ligand exchange through the dimeric species **2e**.

To date, the origin of the racemization has not been clearly established and remains unclear. It might be due either to the acidolysis step conditions or to the inherent configurational instability of the chlorophosphines as postulated by Horner and Jordan.[13] To clarify this point, we envisaged various racemization processes.

In the present paper, we report the results of our investigation on the configurational stability of chlorophosphines and on the racemization mechanism with acids (HCl, HBr).[14] We describe herein experimental and computational studies on the halogen exchange between a chlorophosphine and HBr.

Computational Details

The calculations were carried out using a gas-phase model with the Gaussian 98 package.[15] Cartesian D orbitals were used throughout this study.

All geometry optimizations were done using the density functional theory (DFT) approximation B3LYP.[16] In a first stage, the geometries were optimized using the CEP-31G(D) basis set. The core electrons of the P, Cl, and Br atoms were thus described with a "core" potential, while the other electrons were described with a double ζ basis set plus polarization function on the heavy atoms P, Cl, Br, and C.

These geometries were then used as starting geometries for subsequent geometry optimizations using the "all-electron" basis set, the B3LYP/6-31+G(2d) level, which avoids the core potential and provides, on the heavy atoms, both diffuse functions and a double ζ quality of the gaussian basis. These reoptimizations led in fact to very small stabilizations of each structure, between 0.5 and 1.2 kcal/mol. These converging results show the good quality of the optimization level. The stationary points were then characterized as minimum or transition state (TS) by analytical frequency calculations. Corresponding unscaled zero point correction (ZPC) and entropy are indicated in the tables. The energies obtained using this optimization level (B3LYP/6-31+G(2d)) are denoted ΔE^{opt} in the following.

The energies were then calculated within the same B3LYP model, using the more extended basis set 6-311++G(2d,p). In this paper, we mainly comment on the results from these "dual-level" calculations (noted, as usual, B3LYP/ 6-311++G(2d,p)//B3LYP/ 6-31+G(2D)). Those triple ζ calculations provide the data for what we called ΔE^{TZ}. When ΔE^{TZ} is corrected for the ZPC, it is denoted in the following as ΔH^{TZ}_{ZPC}. Gas-phase Gibbs free energies at room temperature ΔG^{298}, are also indicated in the tables.

Results and Discussion

Computational Results. The computational investigation was carried out using the chlorodimethylphosphine (**1a**, $R^1 = R^2 =$ Me) as a model. While this species is not chiral, it was useful in studying the different racemization mecha-

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(14) (a) For a recent high-level computational work on the S_N2 reactions of halide ions on *neutral* halophosphines in the gas phase, see: Sølling, T. I.; Pross, A.; Radom, L. *Int. J. Mass Spectrom.* **2001**, *210/211*, 1−11. (b) For corresponding gas-phase measurements: Van Doren, J. M.; DePuy, C. H.; Bierbaum, V. M. *J. Phys. Chem.* **1989**, *93*, 1130−1134.

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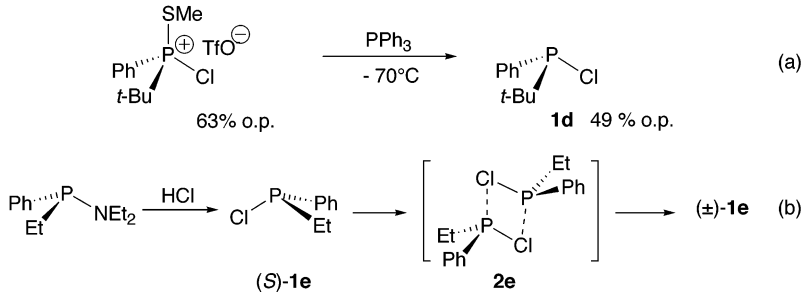
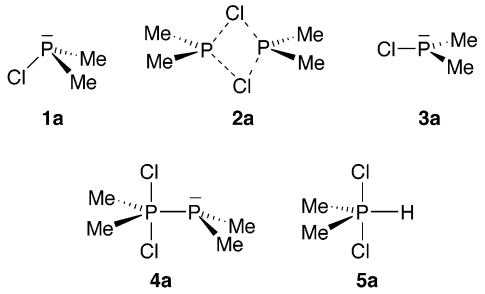
Scheme 2



nisms under consideration. Since the racemization of P−chirogenic chlorophosphines must pass through at least one TS or one intermediate bearing an achiral phosphorus center, we considered pathways involving such species. Consequently, we envisaged the species **TS2a**−**5a** as possible origins of this process. The monomeric planar **TS3a**, known as an impossible pathway for a room-temperature chiral inversion (vide supra), is included here for the sake of completeness.



If we consider a mechanistic explanation involving two molecules of **1a**, two kinds of species (intermediate or transition state) can be hypothesized: the dimeric species **2a**, similar to **2e** previously proposed by Horner,[13] with two chlorine atoms bridging the two phosphorus atoms, and the pentacoordinate phosphorane **4a**. In this hypervalent species, a phosphorus−phosphorus bond is formed in the equatorial position, and the two chlorine atoms are in apical positions. Other stereoisomers with one or two chlorine atoms in the equatorial position were not investigated, due to the strong apicophilicity of this substituent.[17] Finally, structure **5a** results from the HCl addition to **1a**. The formation of such a pentacoordinate phosphorus derivative could be considered under the acidolysis conditions of the aminophosphine precursor.

The optimized structures for the intermediates and transition states derived from **1a** and their corresponding energies are reported in Figure 1 and Table 1, respectively. The transition state **TS3a**, resulting from an umbrella inversion, is found to be 51.6 kcal·mol^{-1} higher in energy than **1a** (Table 1, entry 2). Not surprisingly, the energy barrier is much too high to consider a stereochemical path passing through this TS at room temperature.[9,10]

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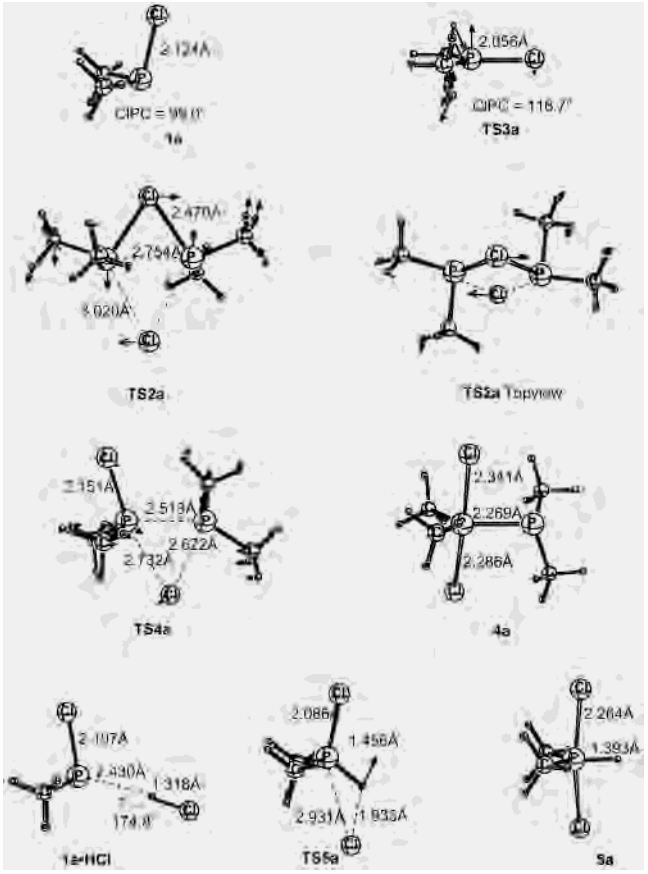


Figure 1. B3LYP/6-31+G(2d) optimized geometries for transition states or intermediates derived from **1a**. Arrows are displayed for the transition state structures (**TS2a**, **TS3a**, **TS4a,** and **TS5a**) to indicate the corresponding reaction coordinates.

The bimolecular species **TS2a** was characterized as a transition state rather than an intermediate (Figure 1). In this structure, one chlorine atom is bonded to both phosphorus atoms, while the other is further apart. The reaction coordinate, as indicated by the arrows, clearly shows the chlorine exchange between the phosphorus atoms. Thus, **TS2a** can indeed be involved in the racemization process. It corresponds to an intermolecular nucleophilic substitution at the phosphorus center. The top view of **TS2a** shows the important distortion of the phosphorus substituents with two methyl groups in the plane of the square formed by the phosphorus and the chlorine atoms, and two others in the axial position. This distortion is attributed to the phosphorus−phosphorus lone pair repulsion (Scheme 3a). Because this repulsion cannot be completely avoided, the energy of **TS2a** is high, 58.3 kcal·mol^{-1} above the energy of the starting

Scheme 3

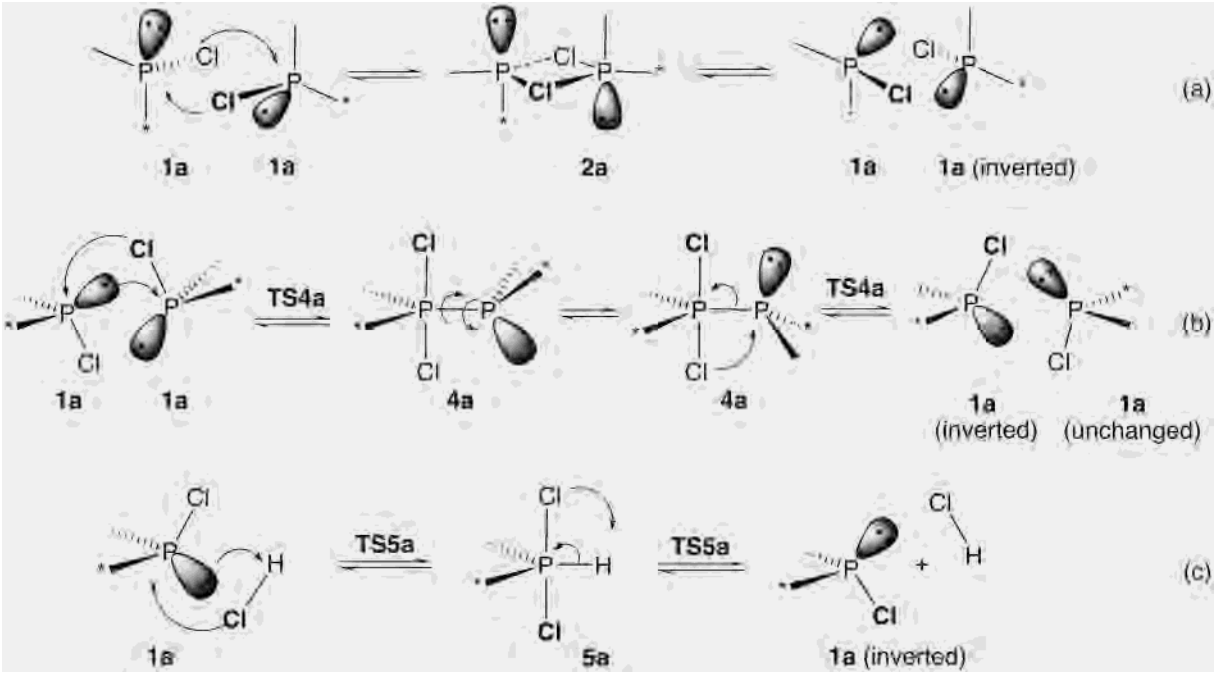


Table 1. Energy Variations (kcal.mol^{-1}), unless Otherwise Stated, for the Transition States and the Intermediates Displayed in Figure 1

entry		ΔE^{opt} [a]	ΔZPC[a]	$\Delta S^{a,b}$	ΔE^{TZ} [c]	ΔH^{TZ}_{ZPC} [c]	ΔG^{298} [c]
1	**1a**	0.0	0.0	0.0	0.0	0.0	0.0
2	**TS3a**	52.0	−0.4	1.2	52.0	51.6	51.2
3	**TS2a**[d]	60.2	−0.9	−33.9	59.3	58.3	68.5
4	**TS4a**[d]	29.1	0.7	−39.5	28.7	29.4	41.2
5	**4a**[d]	5.5	2.0	−40.2	5.1	7.0	19.0
6	**1a**·HCl[e]	−3.7	1.1	−23.1	−3.8	−2.7	4.2
7	**TS5a**[e]	8.6	1.1	−31.7	9.3	10.4	19.9
8	**5a**[e]	−6.2	3.5	−32.4	−4.7	−1.2	8.5

[a] Geometry optimizations and related data (energy (E^{opt}), zero point correction (ZPC), and entropy (S)) were obtained from B3LYP/6-31+G(2d) calculations. [b] Entropy changes, ΔS, are in entropy units (cal·mol^{-1}·K^{-1}). [c] The "TZ" energies are obtained from B3LYP/6-311++G(2d,p)//B3LYP/6-31+G(2d) calculations. [d] Relative to two isolated chlorophosphines **1a**. [e] Relative to one chlorophosphine **1a** and one HCl molecule.

chlorodimethylphosphine **1a** (Table 1, entry 3). Since such high activation energy is clearly unattainable at room temperature, we rejected this pathway for the racemization.

A better mechanism, which would reduce the phosphorus−phosphorus lone pair repulsion, should consider the phosphorus atoms as both nucleophilic and electrophilic centers (biphilicity).[18] In this case (Scheme 3b), the lone pair of the phosphorus atom of one chlorodimethylphosphine **1a** reacts to displace the chlorine of the other. This leads to the pentacoordinate intermediate **4a** through the transition state **TS4a**. It can be pointed out in Figure 1 that the optimized structure **4a** is asymmetric because the two P−Cl bond lengths are not identical, 2.341 and 2.286 Å, respectively. However, **4a** easily leads to a symmetric conformer by rotation around the P−P bond, which requires a negligible activation energy (≈1 kcal·mol^{-1}).[19] Such a facile rotation allows the inversion of the configuration at one of the phosphorus center, through a final transition state similar to **TS4a**. Meanwhile, the second chlorophosphine **1a** is restored into its original configuration (Scheme 3b).

From an energetic point of view, **TS4a** involves a much lower energy than **TS2a**, ΔH^{TZ}_{ZPC} = +29.4 and +58.3 kcal·mol^{-1}, respectively (Table 1, entries 3, 4). This is attributed to the smaller phosphorus−phosphorus lone pair interaction in this biphilic mechanism. Moreover, **4a** is somewhat low in energy, with ΔH^{TZ}_{ZPC} = +7.0 kcal·mol^{-1} (entry 5). While this mechanism would appear more likely than the monomeric "umbrella" inversion or Horner's mechanisms, the activation energy required to reach **TS4a** is still too high for a room-temperature process. The racemization of the chlorophosphines must still involve another mechanism.

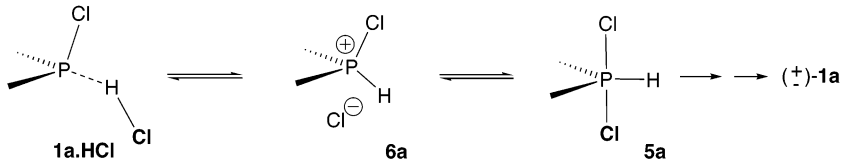
If traces of HCl were present in the medium, for example due to the aminophosphine acidolysis in toluene,[20] the formation of the pentacoordinate intermediate **5a** could be envisaged occurring via the transition state **TS5a** (Scheme 3c, Figure 1). The racemization would occur if the hydrogen atom of the achiral pentacoordinate intermediate **5a** left with one or the other chlorine substituent, leading to a halogen exchange between the chlorophosphine and HCl. From the energetic point of view, this pathway requires +10.4 kcal·mol^{-1}, which is much lower than the energies of the other paths previously envisaged (entry 7). In addition, the intermediate **5a** is also more stable than the pentacoordinate species **4a**, ΔH^{TZ}_{ZPC} = −1.2 and +7.0 kcal·mol^{-1}, respectively (entries 5, 8). According to our theoretical results, the

(18) For the concept of biphilicity, which is related to dual electrophilic and nucleophilic properties of the phosphorus center, see: (a) Ivanov, B. E.; Zheltukhin, V. F. *Russ. Chem. Rev.* **1970**, *39*, 358−372. (b) Smith, D. J. H. In *Comprehensive Organic Synthesis*, Vol. 2; Sutherland, I. O., Ed.; Pergamon Press: Oxford, U.K., 1979; pp 1121−1187.

(19) More details on this minor aspect of the mechanism are provided in the Supporting Information.

(20) A purely ionic mechanism would require a complete charge separation $H^+ + Cl^-$ that does not occur in toluene.

Scheme 4



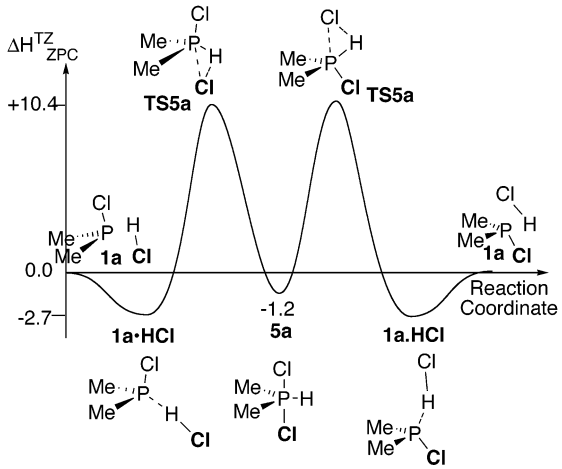
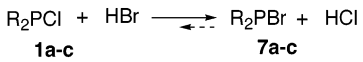


Figure 2. Thermodynamic and stereochemical pathway for the phosphorus inversion of **1a** with HCl. Energies are in kilocalories per mole.

Scheme 5



thermodynamic pathway of the inversion of configuration for **1a** can be sketched by the symmetric curve in Figure 2. The HCl, which acts as a catalyst, is released at the end of the reaction.

It is noteworthy that this reaction mechanism passes through a hydrogen-bonded complex **1a**·HCl with such a small bonding energy that it is entropically disfavored, as shown by the enthalpy and the free energy values for the reaction: $\Delta H^{TZ}_{ZPC} = -2.7$ kcal·mol^{-1} and $\Delta G^{298} = +4.2$ kcal·mol^{-1} (entry 6). As for proton transfer from the HCl moiety to the phosphorus, we expected **1a**·HCl to convert into the phosphonium salt **6a** before racemization via the achiral pentacoordinate species **5a** (Scheme 4). While the ionic species **6a** could not be found in the gas-phase calculations (the optimization leads directly back to **1a**·HCl), such a mechanism cannot be totally excluded in solution, if the solvent favors ion pairs (polar solvent).

Finally, our theoretical studies show that acidolysis conditions (HCl) catalyze the racemization of the chlorophosphines as they are formed. The inversion of the chlorophosphine is analogous to a halogen exchange and should thus occur with other halides.

Chlorophosphine Halide Exchange. In this context, and in order to illustrate this racemization, we performed complementary computational and experimental studies on the reaction of achiral chlorophosphines **1a**−**c** with HBr (Scheme 5).

Experimental Studies. Experimentally, the halide exchanges with diphenyl- or di-*tert*-butylchlorophosphines (**1b** or **1c**) were performed in toluene, using HBr (0.65 M in toluene). The conversions, determined by ^{31}P NMR, are summarized in Table 2. With the addition of 0.5 equiv of HBr, **1b** was partially converted into the corresponding bromo derivative **7b** (entry 1).[21] The proportion of the products did not change after 30 min. When 1 equiv of HBr was added to **1b**, a complete conversion into **7b** was observed in 2 min at room temperature (entry 2). For the same reaction performed at −70 °C, the conversion into **7b** reached 85% in 2 min, thus demonstrating the ease of the halide exchange (entry 3). On the other hand, when 5 equiv of HCl were added to a toluene solution of **7b**, the reverse formation of **1b** was less than 20% after 14 h at room temperature.

Table 2. Halide Exchange with the Chlorophosphines **1b**,**c**

	R_2PCl **1**		exptl conditions[a]			R_2PBr **7**	
entry	R		reagent	T (°C)	time (min)		conv[b] (%)
1	Ph	**1b**	HBr (0.5 equiv)	room temp	45	**7b**	50
2	Ph	**1b**	HBr (1 equiv)	room temp	2	**7b**	100
3	Ph	**1b**	HBr (1 equiv)	−70	2	**7b**	85
4	Ph	**1b**	LiBr (1 equiv)[c]	room temp	90	**7b**	40
5	Ph	**1b**	LiBr (4 equiv)[d]	room temp	90	**7b**	100
6	t-Bu	**1c**	LiBr (4 equiv)[d]	room temp	30	**7c**	100

[a] All reactions were performed in dry toluene. [b] Determined by ^{31}P NMR. [c] LiBr (1 M) in THF. [d] Dry LiBr.

Although no intermediate species, e.g., a pentacoordinated or a tetracoordinated phosphorus, was clearly identified by ^{31}P NMR, we observed a facile halide exchange on the chlorodiphenylphosphine even at −70 °C. This is in good agreement with the HCl catalyzed racemization mechanism, discussed in the theoretical section.

In addition, the halide exchange was studied with LiBr. When 1 equiv of LiBr was used, **1b** afforded the corresponding **7b** with a conversion of only 40% after 90 min at room temperature (entry 4). The lower efficiency of LiBr with respect to HBr could be explained by the heterogeneity of the reaction mixture. Using 4 equiv of dry LiBr, the conversion of **1b** was complete within the same reaction time (entry 5). When the halide exchange was carried out using **1c** and LiBr (4 equiv), a complete conversion into **7c** was obtained in 30 min (entry 6).

Computational Studies. The computational study of this halide exchange reaction was carried out with **1a** as a model of the chlorophosphine used experimentally (**1b**,**c**), reacting with HBr. We applied the same levels of calculation previously used.

The results for the halide exchange are displayed in Table 3 and Figure 3 for the energies and geometries, respectively. After a weak preliminary hydrogen-bonded complex **1a**·HBr, the first transition state **TS8a** is found to be lower in energy

(21) The foremost preparation of **7b** by reaction of an excess of HBr with **1b** has been described by: Dörken, C. *Chem. Ber.* **1888**, *21*, 1506−1515.

Table 3. Energy Variations (kcal·mol^{-1}), unless Otherwise Stated, of Intermediates and Transition States for Halide Exchange between **1a** and HBr[a]

entry		ΔE^{opt} [b]	ΔZPC[b]	ΔS[b,c]	ΔE^{TZ} [d]	ΔH^{TZ}_{ZPC} [d]	ΔG^{298} [d]
1	**1a** + HBr	0.0	0.0	0.0	0.0	0.0	0.0
2	**1a**·HBr	−3.8	1.1	−23.7	−3.2	−2.1	5.0
3	**TS8a**	3.3	1.3	−32.1	4.7	6.0	15.6
4	**8a**	−8.6	3.6	−32.0	−5.3	−1.7	7.9
5	**TS8a**	5.6	1.4	−32.2	8.3	9.6	19.2
6	**7a**·HCl	−7.0	1.4	−23.8	−5.0	−3.6	3.5
7	**7a** + HCl	−3.2	0.2	−0.1	−1.4	−1.2	−1.1

[a] Corresponding structures are displayed in Figure 3. These energies are relative to one chlorophosphine **1a** and one HBr molecule. [b] Geometry optimizations and related data (energy (E^{opt}), zero point correction (ZPC), and entropy (S)) were obtained from B3LYP/6-31+G(2d) calculations. [c] Entropy changes, ΔS, are in entropy units (cal·mol^{-1}·K^{-1}). [d] The "TZ" energies are obtained from B3LYP/6-311++G(2d,p)//B3LYP/6-31+G(2d) calculations.

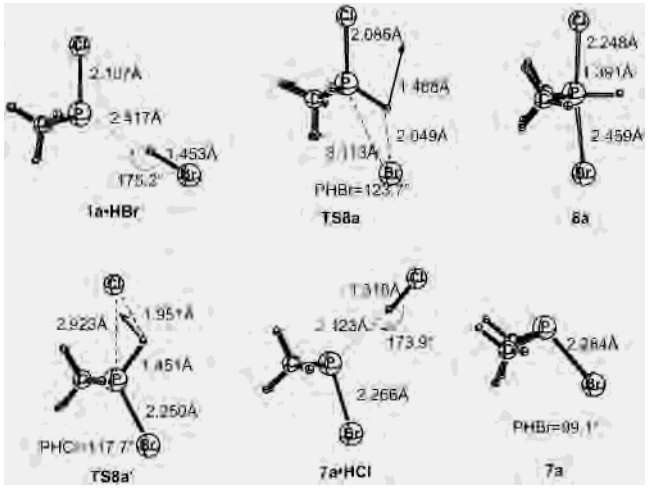


Figure 3. B3LYP/6-31+G(2d) optimized geometries for the halide exchange between **1a** and HBr. The arrows displayed on the transition-state structures (**TS8a**, **TS8a′**) indicate the reaction coordinates.

(ΔH^{TZ}_{ZPC} = +6.0 kcal·mol^{-1}; Table 3, entry 3) than the corresponding HCl analogue **TS5a** (+10.4 kcal·mol^{-1}; Table 1, entry 7). The rest of the reaction profile with HBr is closer to that of the HCl analogue. The pentacoordinated intermediate **8a** and the second transition state **TS8a′** are only very slightly lower in energy than those obtained with HCl (Table 3, entries 4, 5; Table 1, entries 7, 8). Finally, the reaction goes through a weak hydrogen-bonded complex **7a**·HCl to give the products of the halide exchange $(Me)_2PBr$ (**7a**) and HCl. The thermodynamic pathway of the halide exchange is shown in Figure 4, and it is noteworthy that the products are slightly lower in energy than the reactants: ΔH^{TZ}_{ZPC} = −1.2 kcal·mol^{-1}. The computational results are thus in favor of an easy conversion of **1a** into its bromide derivative **7a** and are in good agreement with the experiments. The thermodynamic pathways of the halogen exchange of **1a** with HCl or with HBr are very similar (Figures 2 and 4). As HBr reacts with **1a** to lead to the corresponding **7a**, HCl is also expected to perform the halide exchange and consequently the racemization.

Stereochemistry of the Acidolysis with HCl in the Case of the Diastereomerically Pure Aminophosphine 9 (or 9′·BH$_3$). In connection with our continued work on chiral phosphorus borane chemistry,[22] we have investigated the

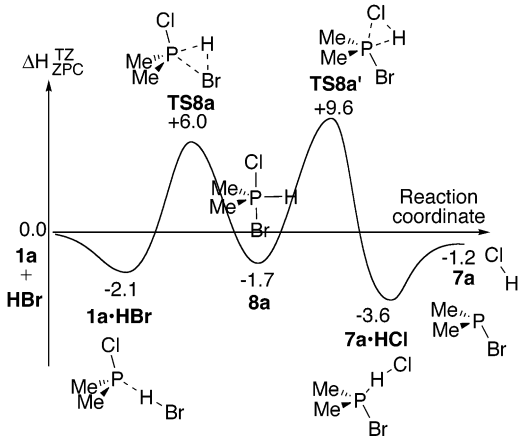


Figure 4. Illustration of the thermodynamic pathway of halogen exchange for **1a** with HBr in the gas phase. Energies are in kilocalories per mole.

stereoselective synthesis of **1f** or **1f**·BH$_3$, by HCl acidolysis of the diastereomerically pure aminophosphines **9**, or the borane adduct **9′**·BH$_3$, respectively (Scheme 6). The stereoselectivity of the acidolysis was determined by quenching **1f** (or **1f**·BH$_3$) with methyllithium. In the first case, the complexation of the *o*-anisylmethylphenylphosphine **10** was made using BH$_3$·DMS and W(CO)$_5$·THF (DMS = 4,6-dimethoxybenzene-1,3-disulfonyl chloride; THF = tetrahydrofuran). These complexations are well-established to proceed with retention of the configuration.[23,24] Both complexes **10**·BH$_3$ and **10**·W(CO)$_5$ were obtained as quasi-racemic, and this result did not depend on the reaction time (10 min to 1 h) or the HCl concentration (0.04−0.12 M in toluene).

Since P(III)−chirogenic compounds usually react stereoselectively with the organolithium reagents,[25] in agreement with our computed and experimental studies, the racemization must originate from the reaction of the chlorophosphine with residual HCl. However, the reaction of the chlorophosphine with organolithium reagent affords also LiCl as a byproduct, and it cannot be excluded that the racemization originates in part from the halide exchange of **1f** with this salt.

In the second case, the acidolysis of **9′**·BH$_3$ leads to the chlorophosphine borane **1f**·BH$_3$, and, after reaction with the

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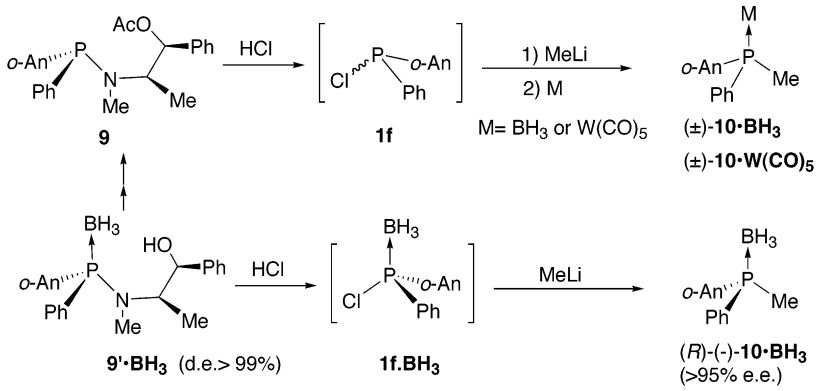
Scheme 6



methyllithium reagent, to the phosphine complex (*S*)-**10**·BH_3 in 80% yield and with 95% e.e. (Scheme 6b). Thus, the complexation of the aminophosphine by the borane, used as a protecting group, avoid fast the racemization of the chlorophosphine during the acidolysis step.

Conclusion

In this dual experimental and computational study on the configurational stability of the chlorophosphines, we have shown that HCl acts as a catalyst for the inversion at the P-center. The mechanism of the racemization is explained by the phosphorus nucleophilic attack on H, with a concerted backside attack by the chlorine on the phosphorus center. The reaction intermediate, as indicated by the gas-phase computation, is an achiral pentacoordinated phosphorus with two chlorine atoms in the axial position. Other mono- or dimeric mechanisms that we envisaged required too high activation energies for a room-temperature process.

The experiments and the calculations on the HBr reaction with chlorophosphines showed an easy halide exchange, which corroborates the easy racemization of the P−chirogenic analogue. Thus, bromophosphines were easily obtained under mild conditions by simple halide exchange, constituting a practical method for their synthesis.

Finally, we showed that *pure* chlorophosphines would be configurationally stable at the phosphorus atom but that traces of acids (HX) or halides, which are almost unavoidable in the experimental conditions, carry out no stereoselectivity for the aminophosphine reaction with HX. Since the inversion process is a simple acid−base reaction involving the lone pair of the phosphorus, the remedy for avoiding the racemization is found in the deactivation of the lone pair's basicity, using the borane protecting group. This opens a very promising way for the synthetic applications of the chiral chlorophosphine borane, as P−chirogenic building blocks.

Experimental Section

All reactions were carried out under an argon or nitrogen atmosphere in dried glassware. THF and toluene were dried and freshly distilled under a nitrogen atmosphere over sodium/benzophenone. Hexane and ethanol for HPLC were of chromatographic grade and were used without further purification. *n*-Butyllithium, 2-bromoanisole, (+)-ephedrine, BH_3·$S(CH_3)_2$, 1,4-diazabicyclo-[2.2.2]octane (DABCO), chlorodiphenylphosphine, and di-*tert*-butylchlorophosphine were purchased from Aldrich, Acros, and Avocado. Commercially available 2-bromoanisole was distilled before use. HBr in toluene was prepared by bubbling the gas previously generated by reaction of concentrated sulfuric acid with NaBr and titrated before use. The (*Rp*)-*N*-methyl-[(1*R*,2*S*)-(2-hydroxy-1-phenyl)ethyl]amino-*o*-anisylphenylphosphine borane (**9′**·BH_3) was prepared according to the litterature.[22e] HPLC analyses were performed on a Gilson 305/306 or Shimadzu chromatograph equipped with an UV detector. Flash chromatography was performed on silica gel (60AC.C, 35−70 mm) or neutral aluminum oxide (Carlo Erba; ref. 417241). All NMR spectra were recorded on Bruker DPX 250, Avance 300−500 spectrometers, with the deuterium signal of the solvent as the lock, tetramethylsilane (TMS) as the internal reference for ^{1}H (250 MHz) and ^{13}C NMR (62.9 MHz), and 85% phosphoric acid as the external reference for ^{31}P NMR (101.3 MHz). The ^{31}P NMR chemical shifts (δ) are calculated as negative values upfield of phosphoric acid. IR spectra were recorded on a Perkin-Elmer 1600 FT or a Bruker Equinox 55 or Vector 22 spectrometer. Melting points were measured on a Büchi melting point apparatus and are uncorrected. Optical rotation values were determined at 20 °C on a Perkin-Elmer 241 polarimeter. Mass spectral analyses were performed on a JEOL MS 700 and KRATOS Concept S, at the Mass Spectroscopy Laboratories of ENS Paris and Burgundy University (Dijon). Elemental analyses were measured with a precision superior to 0.4% at the Microanalysis Laboratories of P. & M. Curie (Paris) and Burgundy (Dijon) Universities.

(*Rp*)-(−)-*N*-Methyl-*N*-[(1*S*,2*R*)-(1-acetoxy-2-methyl-1-phenyl-prop-2-yl)]amino-o-anisylphenylphosphine (9). This compound was obtained by decomplexation from its borane complex, previously prepared from (+)-ephedrine according to the published procedure.[22i] In a two-necked flask equipped with a reflux condenser, a magnetic stirrer, and an argon inlet, 500 mg (1.15 mmol) of borane complex and 515 mg (4.6 mmol) of diazabicyclooctane were dissolved in 10 mL of dry and degassed toluene. The mixture was heated at 50 °C for 10 h. The crude product was rapidly filtered off on a neutral alumina column (15 cm height, 2 cm diameter) using 9:1 toluene/AcOEt as eluent, to give 444 mg of **9** (yield, 91%; colorless viscous oil). ^{1}H NMR ($CDCl_3$): δ 0.5−2.0 (3H, br, B*H*$_3$), 1.30 (3H, d, $^3J_{HH}$ = 7, CHC*H*$_3$), 1.93 (3H, s, C*H*$_3$CO), 2.22 (3H, d, $^3J_{HH}$ = 3, NC*H*$_3$), 3.60 (s, OC*H*$_3$), 3.90 (1H, m, $^3J_{HH}$ = $^3J_{PH}$ = 7, $^3J_{HH}$ = 8, NC*H*), 5.75 (1H, d, $^3J_{HH}$ = 8, PhC*H*), 6.54 (1H, m, *H* arom), 7.84−7.34 (13H, m, *H* arom). ^{13}C NMR ($CDCl_3$): δ 15.9 (d, $^3J_{PNCC}$ = 6, CH*C*H$_3$), 21.2 (*C*H$_3$CO), 31.9 (d, $^2J_{PNC}$ = 9, N*C*H$_3$), 55.1 (O*C*H$_3$), 63.5 (d, $^2J_{PNC}$ = 40, N*C*H), 78.4 (d, $^3J_{PNCC}$ = 9, *C*HO), 109.9 (*C* arom), 120.6 (*C* arom), 125.2−129.9 (*C* arom), 131.3 (d, J_{PC} = 19, *C* arom), 131.8 (d, J_{PC} = 3,

C arom), 138.1 (d, $J_{PC} = 7$, *C* arom), 139.1 (*C* arom), 160.4 (d, $J_{PC} = 17$, *C* arom), 170.1 (*C* arom). ^{31}P NMR ($CDCl_3$): δ +56.

HCl Acidolysis of 9 into the *o*-Anisylchlorophenylphosphine (1f). In a 100 mL two-necked flask equipped with a magnetic stirrer, an argon inlet, and a rubber septum, 600 mg of **9** (0.95 mmol) was dissolved in 32.5 mL of toluene. A solution of HCl in toluene (0.37 M, 5.3 mL, 2 mmol) was added at room temperature with stirring. After 1 h, the ephedrine hydrochloride was filtered off on a Millipore 4 μm filter, and the solution of **1f** was used immediately without further purification.

Correlation of 1f into *o*-Anisylmethylphenylphosphine Complexes 10·BH$_3$ and 10·W(CO)$_5$. The previous filtrate was then cooled to −78 °C, and 2.2 mL of MeLi (1.33 M) was added. The reaction was kept at this temperature for 30 min, after which the cooling bath was removed and the temperature allowed to warm to room temperature. Half of the reaction mixture was quenched by 0.5 mL of BH_3·DMS (10 M; DMS = dimethyl sulfide). After hydrolysis, the solvent was removed under reduced pressure and the aqueous layer was extracted with 3 × 25 mL of CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on a short column of silica gel with a 7:3 toluene/petroleum ether mixture as eluent to give 50 mg of **10**·BH_3 [22f] (43% yield). The enantiomeric excess of the phosphine borane complex **10**·BH_3 (e.e. 3%) was determined by HPLC on a Chiralcel OK Daicel column with 70:30 hexane/EtOH as eluent (flow rate, 1 mL· min^{-1}; (*R*) enantiomer $t_R = 11.1$ min; (*S*) enantiomer $t_R = 21.4$ min).

The second half of the reaction mixture (~20 mL) was quenched by 8.5 mL of a freshly prepared solution of W(CO)$_5$·THF (0.05 M). After 2 h, the reaction mixture was hydrolyzed and the solvent removed under reduced pressure. After extraction of the aqueous layer with 3 × 25 mL of CH_2Cl_2, the combined extracts were dried over $MgSO_4$ and then concentrated. The residue was purified by chromatography on a column of silica gel with a 15:1 cyclohexane/AcOEt mixture as eluent to give 96 mg of **10**·W(CO)$_5$ (36% yield): o.p. <2%; $[\alpha]_D^{20} = -0.95$ (c 0.5, $CHCl_3$); lit.[24] $[\alpha]_D^{20} = -77$ (c 2.3, $CHCl_3$).

HCl Acidolysis of 9′·BH$_3$ into (*S*)-(−)-*o*-Anisylchlorophosphine Borane (1f·BH$_3$). In a 50 mL two-necked flask, equipped with a magnetic stirrer, an argon inlet, and a rubber septum, 2 mmol of **9′**·BH_3 was introduced. A solution of HCl in toluene (0.38 M, 11.05 mL, 4.2 mmol, 2.1 equiv) was then added at room temperature under stirring, without previous solubilization of **9′**·BH_3. After 1 h, the precipitate of ephedrine hydrochloride was filtered off with a Millipore 4 μm filter. The excess of HCl was then removed by several vacuum/argon cycles, and the toluenic solution of **1f**·BH_3 directly used for its reaction with the methyllithium reagent (vide infra). The analysis was realized after purification by filtration on a short column of silicagel, with toluene as eluent[22h] (

yield, 99%; colorless viscous oil). $R_f = 0.8$ (toluene). $[\alpha]_D^{20} = -11.1$ (c 8.6, $CHCl_3$). e.e. = 95 ± 5%. IR (NaCl, ν cm^{-1}): 3058−3010 (C−H), 2941−2839 (C−H), 2394 (B−H), 1589, 1575, 1478, 1433, 1280, 1252, 1181, 1165, 1136, 1055, 1020, 900. ^{1}H NMR ($CDCl_3$): δ 0.40−2.20 (3H, m, BH_3), 3.63 (3H, s, OCH_3), 6.91 (1H, dd, $J = 4.6$, $J = 8.3$, H arom), 7.11 (1H, td, $J = 2.6$, $J = 7.6$, H arom), 7.39−7.61 (4H, m, H arom), 7.72−7.82 (2H, m, H arom), 7.95 (1H, ddd, $J = 1.6$, $J = 7.7$, $J = 14.9$, H arom). ^{13}C NMR ($CDCl_3$): δ 55.7 (OCH_3), 112.0 (d, $J_{P-C} = 4.4$, C arom), 117.6 (d, $^1J_{P-C} = 47.7$, C arom), 121.1 (d, $J_{P-C} = 12.3$, C arom), 128.5 (d, $J_{P-C} = 11.5$, C arom), 128.7 (d, $^1J_{P-C} = 50.8$, C arom), 131.1 (d, $J_{P-C} = 12.9$, C arom), 132.0 (d, $J_{P-C} = 2.6$, C arom), 134.6 (d, $J_{P-C} = 14.3$, C arom), 135.5 (d, $J_{P-C} = 1.8$, C arom), 161.1 (d, $J_{P-C} = 2.4$, C arom). ^{31}P NMR ($CDCl_3$): δ +91.9 (brd, $^1J_{P-B} = 51.4$).

Correlation of 1f·BH$_3$ into (*R*)-(−)-Phosphine Borane (10•BH$_3$). The methyllithium reagent (2.5 equiv.) is slowly added at −78 °C to the toluene solution of **1f**·BH_3 freshly prepared as described above. The mixture is allowed to warm to room temperature and then hydrolyzed with 20 mL of water. The aqueous layer is extracted twice with dichloromethane. The combined organic phase is dried over magnesium sulfate and condensed under reduced pressure. The residue is purified over silica gel using 7:3 toluene/petroleum ether as eluent, giving (*R*)-(−)-**10**·BH_3 in 80% yield, with satisfactory analytical data.[22f] The enantiomeric excesses have been determined by HPLC analysis on a Chiralcel OK Daicel column, as described above.

Halide Exchange with the Chlorophosphines 1b,c. Typical Procedure for HBr Reaction: Preparation of the Bromodiphenylphosphine (7b). In a 50 mL two-necked flask equipped with a magnetic stirrer, an argon inlet, and a rubber septum, 0.9 mL of freshly distilled **1b** [5 mmol; ^{31}P NMR ($CDCl_3$): δ +82] was added to 14 mL of HBr in toluene (0.65 M, 9 mmol). After stirring at room temperature for 15 min, ^{31}P NMR analysis revealed complete conversion into **7b**. After removal of the solvent under vacuum, the orange oily residue was distilled under vacuum (0.08 mbar) to give 700 mg as the main fraction (isolated yield, 53%).

^{1}H NMR ($CDCl_3$): δ 7.33−7.36 (6H, sl, *H* arom), 7.57−7.65 (4H, sl, *H* arom). ^{13}C NMR ($CDCl_3$): δ 128.5 (d, $^2J_{PCC} = 7$, C_{ortho}), 130.2 (s, C_{para}), 132.5 (d, $^3J_{PCCC} = 24$, C_{meta}), 137.0 (d, $^1J_{PC} = 36$, C_{ipso}). ^{31}P NMR ($CDCl_3$): δ +72; lit.[26] +72.4.

Typical Procedure for LiBr Reaction: Preparation of the Bromodi-*tert*-butylphosphine (7c).

In a 50 mL two-necked flask equipped with a magnetic stirrer, an argon inlet, and a rubber septum, 0.5 mL of freshly distilled **1c** [2.9 mmol; ^{31}P NMR ($CDCl_3$): δ +146], and 1.05 g of LiBr (11.6 mmol, 4 equiv) was added to 3 mL of dry toluene (0.65 M, 9 mmol). After stirring at room temperature for 30 min, ^{31}P NMR analysis revealed complete conversion into **7c**.

^{31}P NMR ($CDCl_3$): δ +150; lit.[27] +152.

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Supporting Information Available: Computational results, *XYZ* coordinates, and absolute energies for all the computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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