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Efficient Phosphorus Catalysts for the Halogen-Exchange (Halex) Reaction

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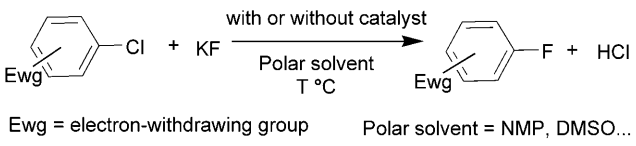
Abstract: New families of monomeric to dendritic, and monocationic to multicationic (PNP) compounds have been prepared and tested as catalysts in halogen exchange (Halex) reactions. Some of them allow an increase in the efficiency of these reactions which are performed in some cases under the mildest conditions reported up to now.

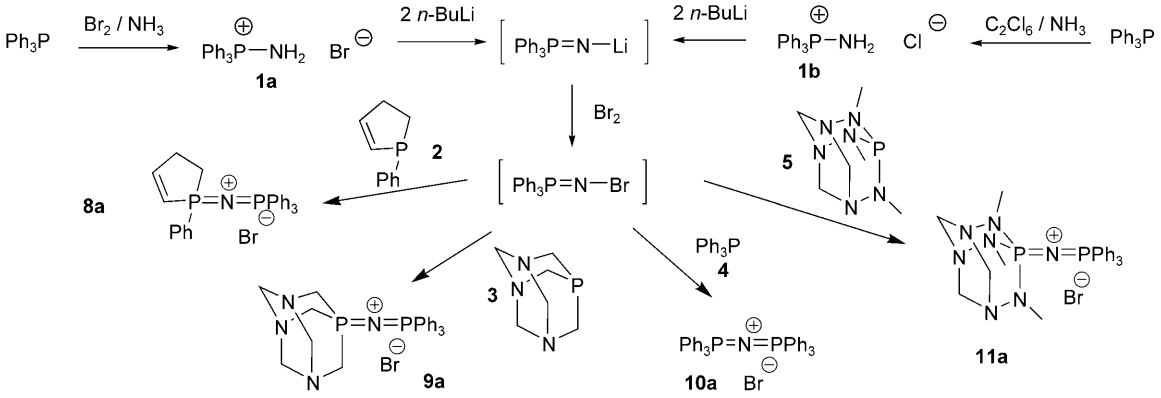
Keywords: arylation; catalysts; fluorination; halogen exchange (Halex) reaction; phosphorus

Fluorinated aromatic compounds are a very important class of organic molecules due to their intensive use as pharmaceutical or agrochemical products and for their biological applications.[1] A tremendous amount of work has been done both from the academic world and the chemical industry concerning their preparation. However, there are still numerous drawbacks to overcome in order to propose milder conditions to introduce fluorine on aromatic compounds.[2] The halogen-exchange reaction (Halex reaction, Scheme 1) is one of the most important procedures for the preparation of fluoroarenes. Such a process consists of reacting an activated halogenated aromatic ring (chloronitrobenzene, for example) with a source of fluoride *via* a nucleophilic aromatic substitution. Generally, the Halex reaction is performed in aprotic, strongly polar solvents with potassium fluoride as fluorinating agent because it represents a good compromise between cost and activity.[3–6] However, because of the poor solubility of metal fluorides in organic solvents, high temperatures reactions (250–300 °C) are usually required,[7] which can pose problems for industrial applications. It has been demonstrated that the use of phase-transfer catalysts gives good results on activated aryl chlorides because it enables one to extract and solubilize fluoride anion from the solid to the solution.[8,9]



Scheme 1. The Halex reaction.

Catalysts generally used, tetraalkylammonium[10] or phosphonium[11,12] salts, are quite robust in mild conditions but tend to decompose at high temperature. Over the last years, guanidinium[13] or carbophosphazenium salts were also used allowing one to decrease the temperature to 170–190 °C, that is to say a drop of 30–60 °C in the case of the conversion of 4-chloro- to 4-fluoronitrobenzene in 96% yield.[14] Bis(phosphoranylidene)ammonium salts $(PNP)^+$ are big lipophilic cations, soluble in a number of solvents, easy to prepare and to handle, and very stable at high temperature.[15,16] Therefore they may represent an alternative as efficient catalysts for the Halex reaction. Having in mind these observations we prepared numerous new compounds of this type, playing with several factors such as the constraint structure, i.e., the rigidity of the molecule, the possibility to form dicationic salts instead of monocationic ones, or even the possibility to work with polycationic species, that is to say dendrim-



Scheme 2. Synthesis of $(PNP)^+$ salts **8a–11a** (counter-anion is Br^-) and of the corresponding chlorides **8b–11b** (counter-anion is Cl^-).

ers bearing six or twelve terminal $(PNP)^+$ cations. Syntheses of these salts by an original method are reported as well as their catalytic properties in a model reaction: the conversion of 4-chloronitrobenzene to 4-fluoronitrobenzene.

The synthesis of the monomeric $(PNP)^+$ salts was conducted as shown in Scheme 2 from the aminophosphonium salt $[Ph_3PNH_2]^+ X^-$ (X = Br, Cl) **1**. Addition of *n*-Buli (2 equivalents) in hexane to a suspension of **1** in THF followed by treatment with Br_2 and addition of 1,2-dihydrophosphole (**2**)[17], 1,3,5-triaza-7-phosphaadamantane (**3**) (PTA)[18], triphenylphosphine (**4**), and 4,6,9-trimethyl-1,3,4,6,7,9-hexaaza-5-phosphatricyclo[3.3.1.$1^{3,7}$] decane (**5**) (THPA)[19,20] led respectively to the corresponding $(PNP)^+$ salts **8a–11a**. The structures were assigned on the basis of NMR data as well as X-ray diffraction studies for the salt **9a**. All complexes are air-stable solids. ^{31}P NMR spectra display two singlets at 51.7 and 20.7 ppm for the monocationic phospholene salt **8a**, two doublets at 21.5 and −27.9 ($^2J_{P,P} = 14.2$ Hz) ppm for the phosphoradamantane salt **9a**, one singlet for the symmetrical salt **10a** and two doublets at 4.45 and 21.1 ($^2J_{P,P} = 29.6$ Hz) ppm for **11a**. ^1H and ^{13}C NMR spectra and elemental analysis are in full agreement with the proposed structures. Additionally, X-ray diffraction studies on **9a** unambiguously confirm the structure of this salt (Figure 1). One unique feature of PTA **3** or THPA **5** is the ability to be chemoselectively protonated or alkylated at nitrogen β to phosphorus rather than at the phosphorus center.[20] In the case of the corresponding salts **9a** or **11a** alkylation at one of the three or six cyclic nitrogen atoms takes place easily with trifluoromethanesulfonate leading to the dicationic species **12a** or **13a** (Scheme 3). Alkylation with methyl iodide proceeds smoothly for **9a** affording the dicationic salt **12c** while no reaction is observed for **11a**.

Such a reaction induces in ^{31}P NMR a deshielding effect for the signals of the two phosphorus atoms from −27.9 to −18.6 (NPCN fragment) and from 21.5

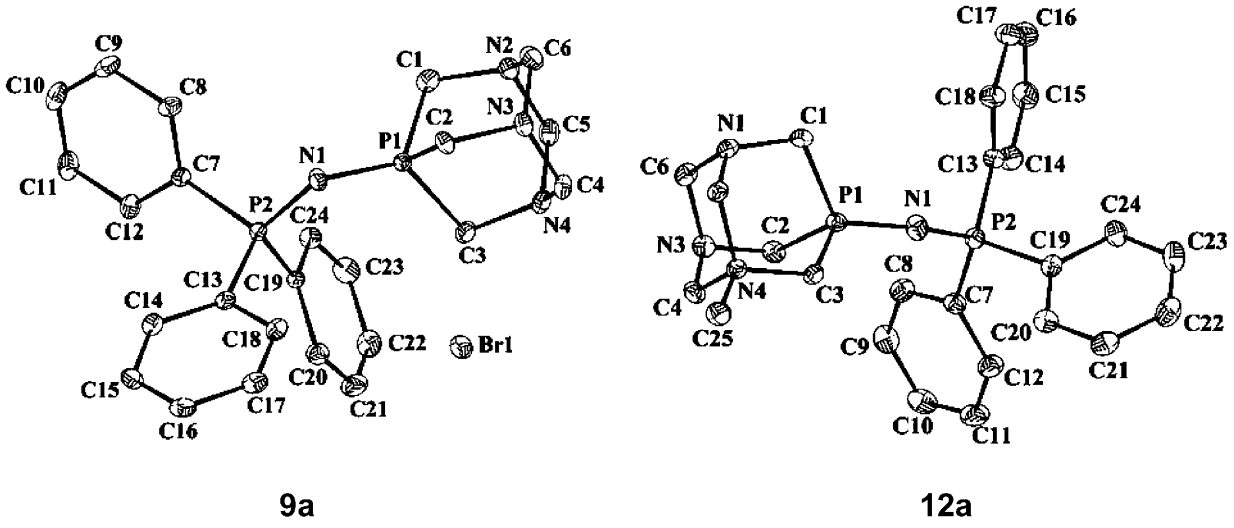
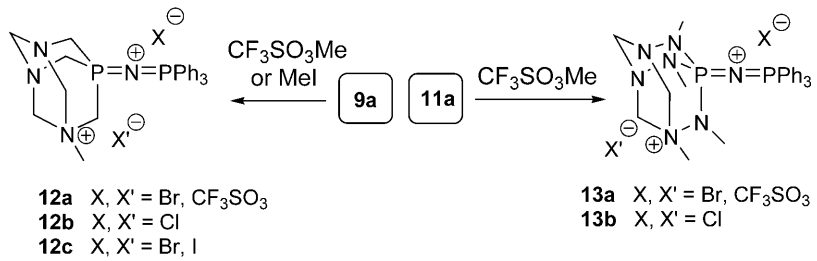


Figure 1. ORTEP diagram of the monosalt **9a** and of the disalt **12a**.

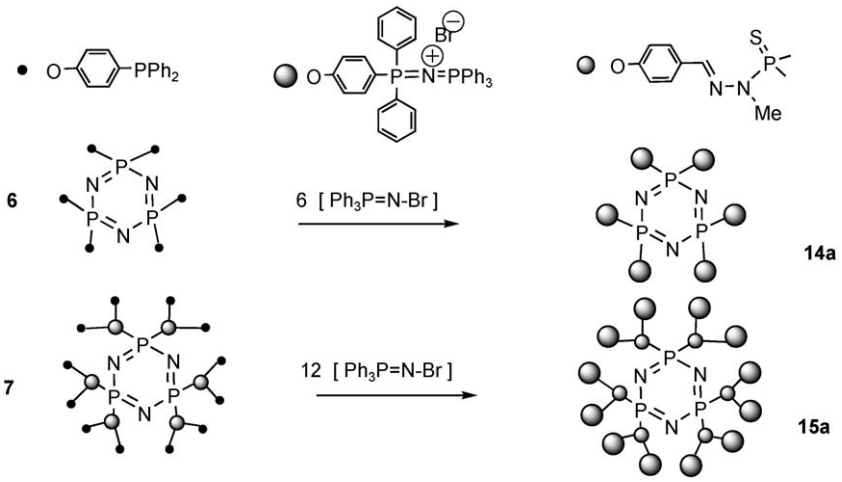


Scheme 3. Synthesis of dicationic (PNP) salts **12a–c**, **13a**, **13b**.

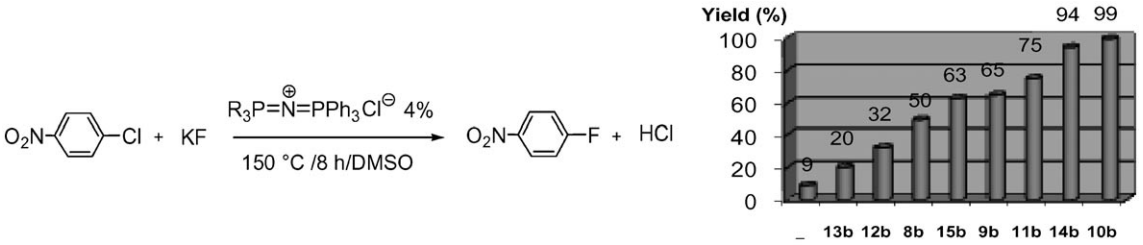
to 27.8 (PPh_3 unit) ppm with disappearance of the initial doublets observed for **9a** on behalf of two singlets for **12a**. The ^{1}H NMR spectrum of **12a** shows a new doublet at 2.94 ($^3J_{H,P}=3.1$ Hz) ppm corresponding to the methyl group linked to a intracyclic nitrogen atom, while the formation of N-CH_3 unit is corroborated in ^{13}C NMR by the presence of a singlet at 48.6 ppm. An ORTEP diagram of such a structure is shown in Figure 1. Two main features can be emphasized: lengthening of the cyclic N–C bonds around the alkylated nitrogen atom and a slight opening of the $P_1N_1P_2$ angle (143.7° for **12a**, 138.9° for **9a**).

As in the case of the monosalt **9a**, the P_1N_1 and N_1P_2 bond distances [1.569(3) and 1.582(3) Å in **9a**, 1.565(3) and 1.583(3) Å in **12a**] clearly indicate a strong delocalization of the charge along the $P_1N_1P_2$ fragment. In order to extend the scope of the use of $(PNP)^+$ salts in Halex reaction, we investigated the possibility to prepare dendrimers bearing $(PNP)^+$ salts on their surface. Indeed the role of dendritic catalysts has been the subject of a lot of investigations as pointed out by the number of reviews published within the last two years[21–36] because such nano-objects combine a unique set of characteristics due to their tailored size, their perfectly well-defined structures, a very high local catalyst concentration on their surface, the possibility to easily recover them and to reuse them without significant loss of activity. For this purpose, dendrimers **6** and **7** of generation 0 and 1, respectively, were prepared according to a method reported by one of us.[37] The corresponding dendritic salts **14a** and **15a** (Br as counter-anion) incorporating six or twelve $(PNP)^+$ units were obtained in excellent yield (82–85%) by the same method which allows us to prepare the salts **8a**–**11a** (Scheme 4). Their formation is monitored by ^{31}P NMR with disappearance of the singlet due to the terminal triphenylphosphine units in **6** on behalf of doublets at 23.8 (OC_6H_4PN) and 24.8 ($NP(Ph)_3$) ppm with $^2J_{P,P}=5.2$ Hz for **14a**. Similarly, the disappearance of the singlet due to terminal phosphine of **7** is observed simultaneously with the appearance of two doublets at 23.9 and 24.7 ($^2J_{P,P}=5.9$ Hz) for **15a.** Treatment of **14a** and **15a** with AgCl leads to **14b** and **15b** (Cl as counter-anion).

Having in hands a number of monocationic and multicationic PNP molecules we investigated their properties as catalysts in the Halex reaction and more precisely for the transformation of 4-chloronitrobenzene to 4-fluoronitrobenzene, a very important molecule for an industrial point of view. We performed the



Scheme 4. Synthesis of dendritic salts **14a** and **15a** (**a**: counter-anion is Br^-). The corresponding $(PNP)^+$ chlorides **14b** and **15b** are obtained by halide exchange (**b**: the counter-anion is Cl^-).

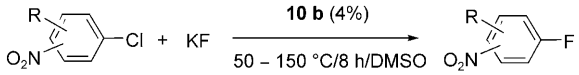


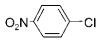
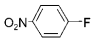
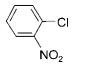
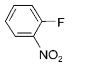
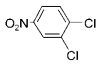
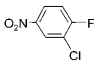
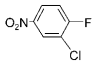
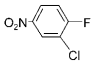
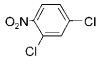
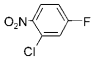
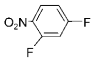
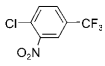
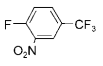
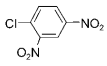
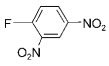
Scheme 5. $(PNP)^+$-catalyzed fluorination of 4-chloronitrobenzene.

tests in DMSO which is very often the solvent of choice to promote this type of catalyzed fluorination. The preliminary experiments showing that chlorides salts were apparently more efficient we decided to perform all the studies with them. They are obtained from **8a–11a**, **12a,c**, **13a–15a** *via* simple bromide-chloride, iodide-chloride and sulfonate-chloride exchanges (the description of the exchanges is given in Experimental Section). First experiments were conducted in DMSO with $(PNP)^+$ salts (4% mol.) at 180 °C, that is to say the usual conditions for Halex reactions. The first run performed with **10b**, giving quantitative yield after 8 h, we then decreased the temperature to 150 °C, a temperature which was previously never successfully used and which prevents catalysts and substrates from degradation. It can be mentioned that the Halex reaction conducted without catalyst at 150 °C is extremely slow (9% after 8 h). In marked contrast the reactions performed with the monocationic derivatives **8b**, **9b**, **11b** led to satisfactory results: 50 to 75% of fluorination of 4-chloronitrobenzene after 8 h (Scheme 5). Surprisingly, since we were expecting a better solubilization of the fluorine anion, the dicationic $(PNP)^+$ salts **12b** and **13b** appeared to be not effective at this temperature (while no apparent degradation of the salts could be observed).

More interesting are the results obtained starting from the dendritic salt **14b** as well as the monomer **10b**: the transformation is close to 100%. This can be considered as the best result reported so far for such experimental conditions including results reported with other charged species as Ph_4P^+, R_4N^+, or $(CNC)^+$ compounds.[13,14] A negative dendritic effect is observed with the dendrimer of generation 1, **15b**: in this case, the 4-fluoronitrobenzene is obtained in 63% yield only. These encouraging results prompted us to investigate the catalytic activity of the most efficient system, that is to say the monomer **10b**, for the Halex reaction involving diversely substituted nitrobenzene derivatives (Table 1). Worth noting is that the $(PNP)^+$ salt (**14b**), although a little bit less efficient, is however also interesting taking into account the possibility to re-use it several times *via* a simple filtration (work is in progress in this field). Several key features can be emphasized i) fluorination of the *ortho*-chloronitrobenzene, a reaction usually difficult to perform because of steric hindrance due to the nitro group in *ortho* position, occurs at 150 °C with 85% yield (entry 3), ii) monofluorination of 3,4-dichlonitrobenzene is quantitative and totally selective on chlorine in *para* position (entry 4): this opens new perspectives for the selective functionalization of fluorinated aromatic derivatives diversely substituted, a very important class of compounds in the field of health,[1] iii) in marked contrast, full nucleophilic substitution of the 2,4-dichloronitrobenzene is the main reaction leading to the difluorinated aromatic compound in 80% yield after 8 h ; only 10% of the monofluorinated one is detected (entry 6), iv) quantitative yield of fluoro-2,4-dinitrobenzene is obtained at 150 °C as well as at 110 °C. Remarkably the reaction also occurs at 50 °C

Table 1. $(PNP)^+$-catalyzed fluorination of aromatic chlorides.[a]



Entry	Ar–Cl	T [°C]	Ar–F	Yield [%][b]
1		150		99 (93)
2		125		50
3		150		85 (76)
4		150		100 (91)
5		150		5
6		150	 	10 80 (68)
7		150		72 (65)
8		150		100
9		110		100
10		50		70

[a] This reaction of S_NAr type is not efficient with non-activated aromatic chlorides (bearing electron donating substituents.

[b] GC yields determined with 1,3-dimethoxybenzene as internal standard (isolated yields in bracket).

leading to the final species in 70% yield (after 8 h at this temperature): to our knowledge such conditions are among the mildest ever reported for Halex reactions (entries 8–10).

In conclusion, a unique family of monomeric to dendritic, and monocationic to multicationic (PNP) compounds have been prepared and fully characterized. Preliminary catalyst tests on Halex reactions of industrial interest show that some of them are efficient catalysts allowing one to increase the yield and the chemoselectivity of the reactions which are performed in some cases in the mildest conditions reported up to now. Extension of the studies of the catalytic properties of these $(PNP)^+$ salts as well as the design and use as catalysts of functionalized monomeric and dendritic $(PNP)^+$ salts of higher generations are under active investigation.

Experimental Section

Synthesis of Triphenylphosphiniminophosphonium Chloride 10b

At −15 °C under dry nitrogen, a solution of *n*-butyllithium (1.6 M in hexane, 19.90 mL, 31.87 mmol) was added dropwise to a suspension of triphenylaminophosphonium chloride (**1b**) (5.00 g, 15.94 mmol) in anhydrous THF (80 mL) in order to form Ph_3PNLi. Upon addition, the mixture was stirred for 2 h at −15 °C. In the same time, a solution of hexachloroethane (3.77 g, 15.94 mmol) in THF (15 mL) was added dropwise to a solution of triphenylphosphine (**4**) (4.18 g, 15.94 mmol) in THF (15 mL) at 25 °C, and the mixture was stirred for 2 h. The latter was added dropwise at −15 °C to the solution of Ph_3PNLi. After return to room temperature, the mixture was stirred for 4 h. It was then filtered and the beige residue obtained was diluted in dichloromethane (150 mL) and washed three times with an aqueous solution of sodium chloride (10%, 50 mL). The organic layer was dried with sodium sulfate, filtered and evaporated. Finally, the beige residue was dissolved in a dichloromethane/methanol mixture (7/3, v/v, 20 mL) and precipitated with diethyl ether (200 mL). Upon filtration and rinsing with diethyl ether, **10b** was obtained as a white solid; yield: 6.09 g (67%); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.35$–7.44 (m, 24 H), 7.60–7.63 (m, 6 H); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 21.7$ (s, 2 P); ^{13}C NMR (62 MHz, $CDCl_3$): $\delta =$ 134.3 (s, 6 C, C-*p*), 132.5 (m, 12 C), 130.1 (m, 12 C), 127.3 (dd, $^3J_{P,C} = 1.9$ Hz, $^1J_{P,C} = 107.7$ Hz, 6 C, C-*o*).

General Procedure for Halex Reaction

After standard cycles of evacuation and back-filling with dry and pure nitrogen, 4-chloronitrobenzene (300 mg, 1.9 mmol), potassium fluoride (143 mg, 2.86 mmol), phase-transfer catalyst (0.076 mmol) and dimethyl sulfoxide (0.4 mL, 5.7 mmol) were charged in a Schlenk tube and heated at ±150 °C for 8 h. After cooling, 5 mL of distilled water were added and the mixture was extracted three times with 5 mL of dichloromethane. Organic layers were combined, dried with sodium sulfate, filtered and analyzed *via* gas chromatography. The yield was determined using 1,3-dimethoxybenzene as a standard (results of Scheme 5).

Supporting Information

Detailed experiments and characterisation of isolated products are available in the Supporting Information.

Acknowledgements

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