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Modular Synthesis of Fluorous Trialkylphosphines

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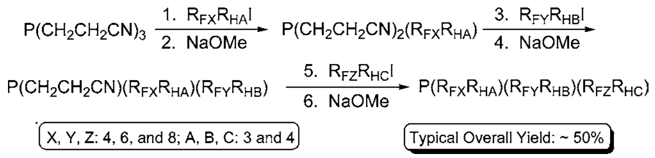
ABSTRACT



A modular synthetic protocol was developed for the preparation of fluorous trialkylphosphines with a different number of methylene spacers and various lengths of the fluorous ponytails $P[(CH_2)_AR_{FX}][(CH_2)_BR_{FY}][(CH_2)_CR_{FZ}]$ (A, B, C = 3 and 4; X, Y, Z = 4, 6, and 8).

Fluorous catalysts could offer facile product separation for many homogeneous catalytic reactions by temperature-dependent liquid−liquid[1] or solid−liquid[2] phase separation. Fluorous catalysts have been prepared by incorporating perfluoroalkyl group(s) or fluorous ponytails into the catalyst design.[3,4] Since one of the most frequently used ligands in transition metal catalysis are phosphines, various methods have been developed for the synthesis of fluorous phosphines.[5] In particular, fluorous mono- and polydentate trialkylphosphines could be very attractive ligands, as they coordinate very strongly to metals, an important property for long-term catalyst stability and metal recycling. Although the direct attachment of perfluoroalkyl groups to a phosphorus atom leads to fluorous phosphines,[5a,b,6] the strong electron-withdrawing effect of the fluorous ponytails decreases the electron density on the phosphorus center, resulting in limited coordination capability.[7] Therefore, the insertion of two or more methylene spacers between the phosphorus atom and the perfluoroalkyl groups is necessary to mitigate the electron-withdrawing effects.[4,5f,8]

Although one of the generally used methods for the preparation of fluorous trialkylphosphines involves the radical addition of PH_3[4,5e,f] or $R_{FX}(CH_2)_APH_2$[5f] (X = total number of carbon atoms of the perfluoroalkyl group, A = number of methylene groups) to perfluoroalkyl-alkenes, the other possibility is the coupling of $R_{FX}(CH_2)_AI$ with PCl_3 using the appropriate Rieke[9a,b] or Grignard reagents.[9c] We present here the first modular synthetic protocol that allows the complete control of the number of the methylene spacers and the length of the fluorous ponytails.

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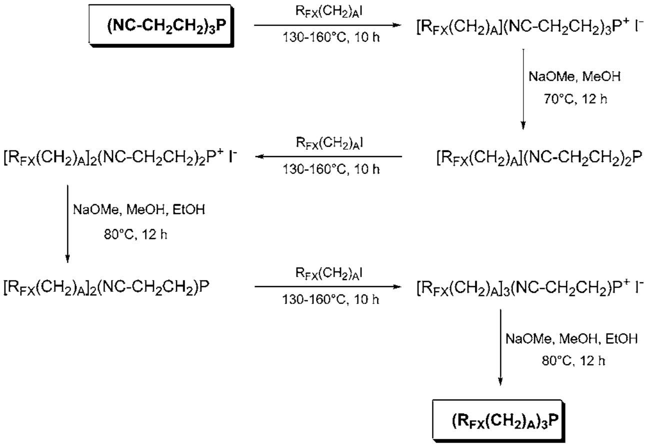
Table 1. Syntheses of Trialkylphosphines Containing Fluorous Chain(s)

number	$R^1(CE)_2P^a$; yield^b	$R^1R^2(CE)P$; yield^b	$R^1R^2R^3P$; yield^b
1	$(R_{F4}R_{H3})(CE)_2P$; 90.3	$(R_{F4}R_{H3})_2(CE)P$; 50.1	$(R_{F4}R_{H3})_3P$; 33.9
2	$(R_{F6}R_{H3})(CE)_2P$; 80.7	$(R_{F6}R_{H3})_2(CE)P$; 54.6	$(R_{F6}R_{H3})_3P$; 46.2
3	$(R_{F8}R_{H3})(CE)_2P$; 81.6	$(R_{F8}R_{H3})_2(CE)P$; 63.3	$(R_{F8}R_{H3})_3P$; 54.0
4	$(R_{F8}R_{H4})(CE)_2P$; 78.8	$(R_{F8}R_{H4})_2(CE)P$; 68.0	$(R_{F8}R_{H4})_3P$; 52.5
5	$(R_{F8}R_{H3})(CE)_2P$; 81.6	$(R_{F8}R_{H3})(R_{F8}R_{H4})(CE)P$; 66.4	$(R_{F8}R_{H3})(R_{F8}R_{H4})_2P$; 52.9
6	$(R_{F6}R_{H3})(CE)_2P$; 80.7	$(R_{F6}R_{H3})(R_{F8}R_{H3})(CE)P$; 57.3	$(R_{F6}R_{H3})(R_{F8}R_{H3})(R_{F8}R_{H4})P$; 46.8

[a] CE abbreviates the 2-cyanoethyl group and R_{HX} the $(CH_2)_X$ fragment. [b] Isolated overall yields, based on tris(2-cyanoethyl)phosphine.

Our approach is based on the alkylation of 2-cyanoethyl-substituted phosphines[10] with $R_{FX}(CH_2)_AI$[11] resulting in a phosphonium iodide followed by the removal of a 2-cyanoethyl group by sodium methoxide,[10] yielding 3-methoxypropionitrile and the corresponding phosphine (Scheme 1).

Scheme 1. Synthetic Protocol Leading to Fluorous Trialkylphosphines; X = 4, 6, and 8; A = 3 and 4



A completely fluorous phosphine could be obtained by performing three consecutive alkylation/dealkylation steps. For example, the reaction of neat 1-iodo-3-perfluorooctylpropane ($R_{F8}(CH_2)_3I$) and $P(CH_2CH_2CN)_3$ resulted in $[R_{F8}(CH_2)_3P(CH_2CH_2CN)_3]^+I^-$ in almost quantitative isolated yield, as the ^{31}P NMR spectrum of the crude reaction mixture in acetone-d_6 showed only one peak at 38.7 ppm. The key parameter to achieve high yields is the vigorous stirring of the initial biphasic reaction mixture at 130 °C. Furthermore, when the reaction mixture starts to solidify (after 1−2 h), the temperature should be increased to 160 °C. $R_{F8}(CH_2)_3I$ is used in 50−70% excess to function also as a solvent; otherwise at the end of the reaction the mixture turns into solid even at 160−180 °C. The alkylation of $P(CH_2CH_2CN)_3$ with $R_{F4}(CH_2)_3I$, $R_{F6}(CH_2)_3I$, and $R_{F8}(CH_2)_4I$ was also performed, and the yields of the corresponding phosphonium salts varied from 98.7% to 99.2%. These salts are air-stable white powders with high melting points (which are higher with longer fluorous ponytails, as expected) and are insoluble in fluorous solvents, apolar organic solvents, diethyl ether, and dichloromethane but soluble in acetone and acetonitrile.

The dealkylation of $[R_{F8}(CH_2)_3P(CH_2CH_2CN)_3]^+I^-$ was triggered by sodium methoxide in methanol at 70 °C. The isolated yield was typically 80 ± 2% after 12 h, irrespective of the length of the perfluoroalkyl-alkyl chain. Formally this reaction is a nucleophilic substitution on the C-atom of the 2-cyanoethyl group neighboring the phosphorus atom, facilitated by the strong electron-withdrawing effect of the nitrile group. The phosphine serves as the leaving group, and the product is the 3-methoxypropionitrile. The $R_{FX}(CH_2)_3P(CH_2CH_2CN)_2$ compounds are colorless liquids (R_{F4}) or white powders (R_{F6} and R_{F8}), soluble in dichloromethane and acetone, slightly soluble in diethyl ether, insoluble in fluorous solvents even at 70−80 °C, and stable in air at room temperature.

The incorporation of the second fluorous chain was carried out in a similar fashion, resulting in the corresponding $\{[R_{F8}(CH_2)_3]_2P(CH_2CH_2CN)_2\}^+I^-$ typically in 90−98% yield. These white salts are also air-stable, and their solubility is similar to that of monoperfluoroalkyl-alkyl derivatives. According to in situ ^{31}P, ^{19}F, and ^1H NMR investigations, we could observe only one type of phosphonium salt in the crude reaction mixture, indicating the irreversible formation of the phosphonium salts.

The removal of the next 2-cyanoethyl group from the phosphorus center was also carried out with sodium methoxide in the 2:1 mixture of methanol and ethanol at 80 °C. The $[R_{FX}(CH_2)_3]_2P(CH_2CH_2CN)$ compounds were obtained in 75−85% yields. They are soluble in dichloromethane and acetone and, in the case of ponytails longer than perfluorobutyl, in fluorous solvents. The R_{F8} derivatives can be stored in closed vials for weeks without significant level of oxidation, but the substances with shorter perfluoroalkyl chains show considerable air sensitivity. Nevertheless, all workup performed under air resulted in the formation of less than 1% phosphine oxides (measured by ^{31}P NMR).

The last fluorous chain was incorporated into the molecules similarly to the previous ones in 80−90% yield. All of the $\{[R_{F8}(CH_2)_3]_3PCH_2CH_2CN\}^+I^-$ compounds were obtained as

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[10] Grayson, M.; Keough, P. T.; Johnson, G. A. *J. Am. Chem. Soc.* **1959**, *81*, 4803.

[11] $R_{F4}(CH_2)_3I$, $R_{F6}(CH_2)_3I$, $R_{F8}(CH_2)_3I$, and $R_{F8}(CH_2)_4I$ can be prepared by the radical addition of the appropriate $R_{FX}I$ to allyl alcohol or to 3-buten-1-ol, reduction of the resulted iodo-hydroxy compound to the corresponding alcohol with Bu_3SnH, and conversion of the hydroxy group to an iodine group with KI in the presence of H_3PO_4/P_2O_5.[5f]

air-stable white powders with high melting points. The final step of the synthetic protocol involves a dealkylation step performed similarly to the second dealkylation in the 1:1 mixture of methanol and ethanol in high yields. Because the final product fluorous phosphines are all soluble in fluorous solvents, we used a methanol/FC-72 fluorous biphasic extraction during the workup. The isolated fluorous phosphines are air-sensitive off-white powders (R_{F8}) or slightly yellow oils (R_{F4}, R_{F6}).[12]

It should be emphasized that the "intermediate" phosphines and phosphonium iodides containing at least one 2-cyanoethyl group can serve as useful building blocks for subsequent functionalization and immobilization. A great advantage of this procedure is that the expensive perfluoroalkyl-alkyl iodides can be recycled almost quantitatively after the workup procedures of the alkylation steps.[13] Our procedures also offer a much safer approach to the synthesis of alkylphosphines by eliminating the use of the highly toxic PH_3, an important consideration for academic laboratories. Finally, we have developed a modular synthetic protocol for the synthesis of fluorous alkylphosphines that allows the complete control of the number of the methylene spacers and the length of the fluorous ponytails, thus providing a library of ligands with slightly different reactivities for homogeneous transition metal catalysis.

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Supporting Information Available: Detailed experimental procedures and NMR data of each compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) **General Procedure for the Alkylation of Phosphines.** The appropriate phosphine (27 mmol) and perfluoroalkyl-alkyl iodide (46 mmol) was placed into a round-bottomed flask, closed with a stopcock, clamped, and heated with vigorous stirring at 130 °C for 1 h and then at 160 °C for 10 h. After cooling to 35 °C, 50 mL of CH_2Cl_2 was added to the yellowish-brown solid, and the mixture was finely powdered in a mortar and filtered through a Büchner funnel. Washing with 2×50 mL of CH_2Cl_2 and drying in vacuo gave the corresponding phosphonium salt as a white or off-white powder. **General Procedure for the Dealkylation of Phosphonium Salts.** The appropriate phosphonium salt (27 mmol) was weighted into a heavy-walled round-bottomed flask and treated with NaOMe (30% w/w solution in methanol, 54 mmol) and MeOH (28 mL, <0.1% water). For the second dealkylation the molar ratio was changed to 17 mmol of phosphomium salt, 34 mmol of NaOMe, 12 mL of MeOH, and 6 mL of EtOH, and for the last dealkylation the ratio was 9 mmol of phosphomium salt, 18 mmol of NaOMe, 7 mL of MeOH, and 7 mL of EtOH. The flask was closed with a stopcock, clamped, and heated to the adequate temperature with vigorous stirring. The initial mixture turned into solution after about 30 min. After 12 h the reaction mixture was cooled to room temperature and evaporated to dryness using rotary evaporator combined with water-vacuo. The brown residue was then suspended in 100 mL of water and filtered through a Büchner funnel. The remaining solid was suspended again in 50 mL of water, filtered, dissolved in 250 mL of $CHCl_3/CH_3OH$(10:1), and dried over desiccated $MgSO_4$. The solution was then filtered and evaporated to dryness, and the residue was finally dried in vacuo (80 °C, 0.05 mbar), giving the corresponding phosphine. In the case of the last dealkylation step, the fluorous biphasic workup procedure was preferred strictly under nitrogen. After the crude reaction mixture was cooled to room temperature, O_2-free methanol and FC-72 were added to the mixture. The extraction at 30 °C was followed by a further amount of O_2-free FC-72. All fluorous phases were combined, and the solution was evaporated to dryness at atmospheric pressure. Drying in high vacuum at 80 °C gave the corresponding fluorous phosphine. For detailed experimental data see Supporting Information.

(13) The excess of the perfluoroalkyl-alkyl iodide is dissolved in dichloromethane after filtration from the phosphonium salt. After removal of the dichloromethane by rotary evaporation, the residue can be distilled to recover the pure alkylating agent, perfluoroalkyl-alkyl iodide.