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Arylation of phosphoryl-stabilized carbanions with metal π-complexes of aryl chlorides and fluorides

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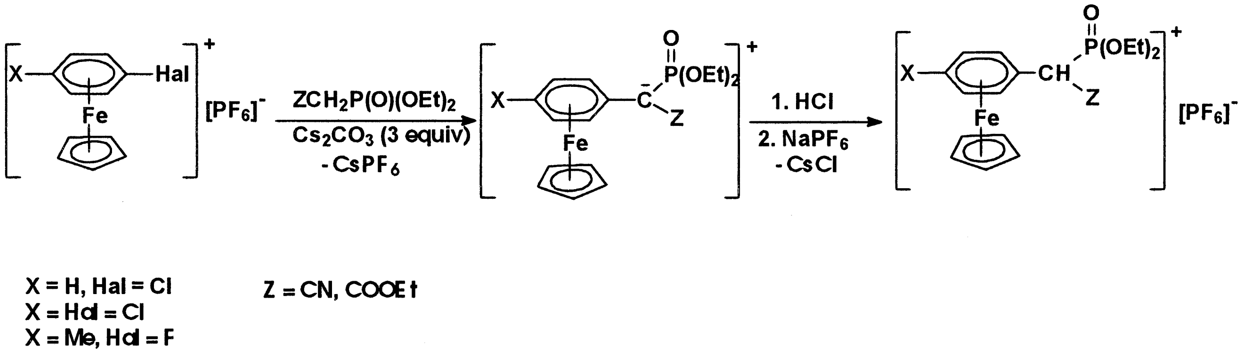
Abstract—The nucleophilic aromatic substitution of halogen in metal arene π-complexes η^6-(ArF)Cr(CO)$_3$ and [η^6-(ArHal)FeCp]$^+$ [PF$_6$]$^-$ (Hal = F,Cl) with phosphoryl-stabilized carbanions ZCH$_2$P(O)(OEt)$_2$ (Z = COOEt, CN) allows the synthesis of metal π-complexes of α-EWG-substituted arylmethylphosphonates in high yields. © 2001 Elsevier Science Ltd. All rights reserved.

Arylmethylphosphonates containing α-electron-withdrawing groups are expected to be versatile intermediate reagents for organic synthesis, Horner–Emmons reactions in particular, as well as potential biologically active compounds.[1] The most straightforward synthetic approach to arylmethylphosphonates is that based upon the nucleophilic substitution reaction of phosphoryl-stabilized carbanions with an aryl halide or its synthetic equivalent. However, reactions with simple aryl halides having no electron-withdrawing groups and therefore unreactive towards nucleophiles require some kind of activation. The arylation of stabilized carbanions can be promoted by copper species,[2] usually in stoichiometric amounts, by catalytic amounts of palladium complexes;[3] one can also use aryliodonium salts, arylbismuth and aryllead compounds[4] as efficient arylating agents. Unfortunately, each of these methods has a limited scope and usually works well only with specific CH-acids in a narrow range of pK_a. On the other hand, π-complexation of arene with a transition metal represents a different approach to its activation. In reactions with stabilized carbanions, the cationic arene complexes of iron have been investigated most extensively, the modified arene usually being liberated from the complex by vacuum pyrolysis.[5] Here we examine the potential of cationic and neutral aryl halide π-complexes in the arylation of α-EWG-substituted diethylmethylphosphonates ZCH$_2$P(O)(OEt)$_2$[Z = COOEt, CN, P(O)(OEt)$_2$].

Among π-coordinating fragments the CpFe$^+$-cation provides one of the most powerful activation effects, comparable to that of two nitro groups in 2,4-dinitrochlorobenzene.[6] The nucleophilic substitution reaction in CpFe$^+$-complexes of aryl halides with mono-phosphoryl-substituted carbanions (Z = COOEt, CN) (Scheme 1) can be performed under very mild conditions: at room temperature, in a solid–liquid sys-



Scheme 1.

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tem utilizing Cs_2CO_3 as a base for in situ generation of carbanion from the corresponding CH-acid (Table 1).[7] No phase-transfer agent is required. The use of CsF as a base is less efficient,[8] and at elevated temperatures leads to a gradual disappearance of the product, presumably as a result of a dephosphorylation reaction.[9]

Of the two CH-acids the stronger one, $CNCH_2P(O)(OEt)_2$ ($pK_a \approx 16$), was also the more reactive, allowing for shorter reaction times and the use of THF or MeCN instead of DMF as a solvent (entries 1, 3, 5 versus 2, 4, 6), which simplified the separation of the products. Methylendiphosphonate ($Z=P(O)(OEt)_2$), the weakest CH-acid in the triad ($pK_a=23$),[10] could not be arylated with aryl halide $CpFe^+$-complexes in the solid–liquid system. However, the reaction of a preformed carbanion of methylendiphosphonate (sodium salt, 2 equiv.) with chlorobenzene $CpFe^+$-complex in DMF (3 days) allowed us to obtain the nucleophilic substitution product in a moderate yield (entry 7).

The substitution products—$CpFe^+$-complexes of arylmethylphosphonates—are obtained in high yields (78–88%, Table 1) after acidification of the reaction mixture and addition of an excess of $NaPF_6$. The addition of a $[PF_6]^-$ salt is essential[11] since this anion is almost quantitatively precipitated in the course of reaction in the form of $CsPF_6$.

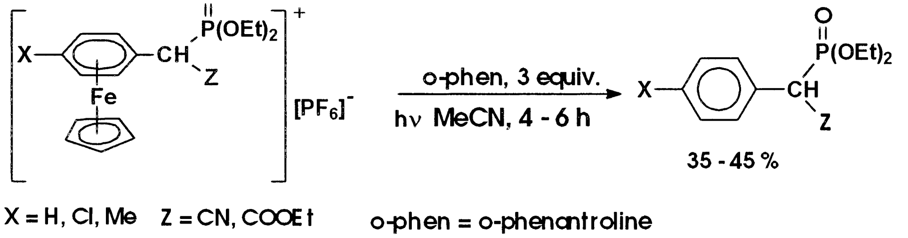
Decomplexation of $[\eta^6\text{-}\{ArCHZP(O)(OEt)_2\}FeCp]^+[PF_6]^-$ salts under pyrolytic sublimation conditions gave extremely poor yields of the free arenes (10–20%). Better, but still modest yields of the desired products (35–45%) were obtained in the reaction with 1,10-phenantroline under ambient light (Scheme 2).[12]

The lack of a general efficient method of recovering the free arene from the $[\eta^6\text{-}ArFeCp]^+[PF_6]^-$ complexes is a well-recognized problem. However, there is no such problem with $\eta^6\text{-}ArCr(CO)_3$ complexes, and their utility for the arylation of phosphoryl-stabilized carbanions (Z=CN, COOEt) was also examined. The $Cr(CO)_3$ complex of *p*-chlorotoluene failed to react with both methylphosphonates in the DMF/Cs_2CO_3 solid–liquid system, but did react with the preformed sodium salt of cyanomethylphosphonate in DMF at 60°C, yielding 75% of substitution product after 1.5–2 h. The more reactive $Cr(CO)_3$ complex of fluorobenz-

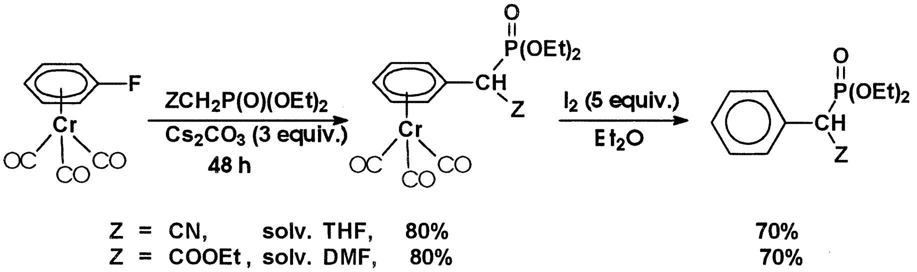
Table 1. The reactions of CH-acids $ZCH_2P(O)(OEt)_2$ ($Z=COOEt$, CN, $P(O)(OEt)_2$) with cationic complexes of aryl halides $[\eta^6\text{-}(p\text{-}XC_6H_4Hal)FeCp]^+[PF_6]^-$, 20°C, Cs_2CO_3, 3 equiv.

Entry	X	Hal.	Z	Solvent	Reaction time (h)	Product yield (%)
1	H	Cl	CN	DMF	1	80
				THF	24	78
2	H	Cl	COOEt	DMF	5	81
3	Cl	Cl	CN	MeCN	9	88
4	Cl	Cl	COOEt	DMF	20	84
5	Me	F	CN	THF	3	77
6	Me	F	COOEt	MeCN	20	83
7[a]	H	Cl	$P(O)(OEt)_2$	DMF	72	60

[a] The reaction with preformed $NaCH[P(O)(OEt)_2]_2$ (2 equiv.).



Scheme 2.



Scheme 3.

ene arylated these CH-acids at rt in the same solid–liquid system (Scheme 3). The products were isolated in good yields (80%) and demetallated with iodine (20°C) to give α-substituted phenylmethylphosphonates (isolated yield 70%).

In summary, the reaction of phosphoryl-stabilised carbanions with aryl halide transition metal π-complexes allows us to obtain α-substituted arylmethylphosphonates. However, we still have to find an efficient method for the demetallation of $CpFe^+$-complexes of arylmethylphosphonates.

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7. Typical experimental procedure: A mixture of $[\eta^6\text{-(ArHal)FeCp}]^+[PF_6]^-$ (1 mmol), CH-acid (1.1 mmol) and Cs_2CO_3 (3 mmol, dried under vacuum at 180°C) in 1.5 ml of DMF (or THF, MeCN) was stirred in the dark under argon. The actual solvent and reaction time are given in Table 1. The deep red reaction mixture was filtered through a Celite® pad into 0.2–0.4 ml of HCl (conc.), the Celite® filter was washed with acetone. The resulting solution was evaporated to 1–3 ml and poured into 3–5 ml of water containing $NaPF_6$ (1.5–2 mmol). The product was extracted with CH_2Cl_2, the combined extracts were evaporated to dryness. The residue was dissolved in 2–4 ml of acetone and the product was precipitated by the addition of 10–15–fold excess of Et_2O in the form of a brownish oil, solidifying into light-yellow foam upon vacuum drying.
8. With CsF, 20 and 40% yields were obtained for $CH_2(COOEt)P(O)(OEt)_2$ and $CH_2(CN)P(O)(OEt)_2$, respectively, in DMF after 7 h.
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