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S_NAr Reactions with Fluoroarene-$Cr(CO)_2L$ Complexes, where L is a Potential Linker Ligand for Solid Phase Synthesis

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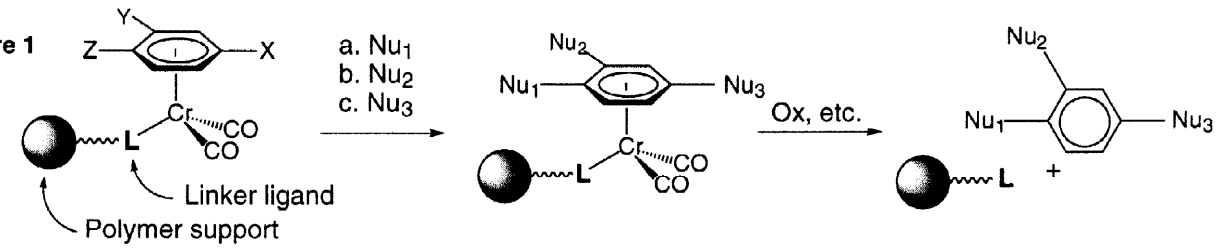
Abstract:

Fluoroarene-$Cr(CO)_2L$ complexes with L = CO, PPh_3, $P(OPh)_3$, P(pyrrolyl)$_3$, and P(pyrrolyl)$_2$(NMeBn) have been evaluated for rates of nucleophilic substitution by amines and other nucleophiles. While there is a strong effect on relative rates depending on nucleophile type and the electronic effects of L, the P(pyrrolyl)$_3$ and P(pyrrolyl)$_2$-(NMeBn) complexes show general reactivity comparable to the parent complexes, with L = CO.

Keywords: fluoroarene-chromium; P(pyrrolyl)$_3$; S_NAr; nucleophilic substitution

Introduction. We are interested in the polymer-bound metal-ligand system shown schematically in fig 1, which is the basis for creating libraries of aromatic compounds via multiple substitution at the arene ligand using solid phase organic synthesis. The chromium-ligand unit acts as the activating group[3] for the substitution reactions and as the linker to the polymer. In the role as linker, with easy oxidative or ligand exchange for detachment of the arene, the chromium-ligand unit is a special case of a "traceless linker."[4] Based on known reactivity of arene-$Cr(CO)_3$ complexes, reasonable leaving groups are Cl and F; likely nucleophiles are amines, and alkoxide, thiolate, and stabilized carbon anions. An effective process will have high yields and similar conditions for each substitution step.

Figure 1



From one study of the S_NAr substitution of amines with fluoroarene-$Cr(CO)_3$ complexes,[5] and numerous isolated observations,[3] it is not clear whether to expect rate-determining addition of the nucleophile (k_1, fig 2) or rate-determining loss of the halide from the anionic intermediate (k_2). The reverse of nucleophile addition is assumed to be faster than the addition ($k_{-1} > k_1$).[6] An electron-donor phosphine (L in **2**) is expected to decrease k_1 and increase k_{-1} and k_2. Little is known about the change in the S_NAr reactivity of arene-chromium complexes after replacement of a CO by another ligand. Previous results involving methoxide substitution for chloride suggest a rate-retarding effect for L = phosphine,[7] consistent with k_1

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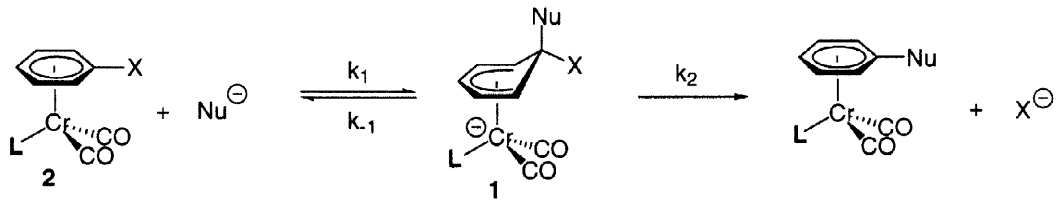
as the r.d.s., and contrasting with the mechanistic results for the case employing amine nucleophiles and complex **2** where L = CO and X = F.[5] Here we report preparative and spectroscopic (^{19}F NMR) studies to evaluate the effect of variations in the ligand L, the nucleophile, and the arene substituents on the S_NAr reactivity of fluoroarene-chromium complexes. The goal is identification of a system amenable to application in solid phase synthesis, with quantitative reactions under mild conditions.

Figure 2



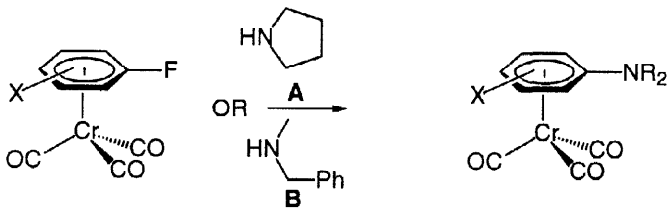
Results and Discussion. Table 1 displays the results of a series of kinetic determinations in DMF at 25 °C using ^{19}F NMR spectroscopy and fluoroarene-Cr(CO)$_3$ complexes.[8] The first four examples, **a-d**, show clearly the expected interplay of resonance and inductive substituent effects, consistent with k_1 as the r.d.s. The *p*-methoxy substituent, with a dominant electron donating effect, slows the rate by a factor of 15. The *m*-methoxy group has almost no effect, and the *o*-methoxy inductive withdrawing effect partially compensates for the resonance donor effect, leading to a rate decrease of only 2.7-fold. In **e**, the fluoro substituent is selectively replaced, and the *m*-chloro substituent has a rate-enhancing effect of 4.5. There is a remarkable variation in rate with amine structure, with pyrrolidine being faster by a factor of >100 compared to a simple primary amine (entry **f**) and compared to another secondary amine (entry **g**). Representative oxygen (**h**), sulfur (**i**), and carbon (**j**) nucleophiles show reactivity in the same range, with alkoxy being the faster by a factor of 13 over thiolate and a factor of 165 over malonate.

Table 1. Rate of Reaction of Fluoroarene Ligands with Nucleophiles.[10]

	Nucleophile	Arene-Cr(CO)$_3$ complex	Half Lifetime
a	Pyrrolidine	Fluorobenzene	67 sec
b	Pyrrolidine	2-Fluoroanisole	180 sec
c	Pyrrolidine	3-Fluoroanisole	65 sec
d	Pyrrolidine	4-Fluoroanisole	1010 sec
e	Pyrrolidine	3-Chlorofluorobenzene	15 sec
f	H_2NiPr	Fluorobenzene	9000 sec
g	HNMeBn	Fluorobenzene	11100 sec
h	NaOiPr	Fluorobenzene	20 sec
i	$NaSCH_2Ph$	Fluorobenzene	266 sec
j	$NaCH(CO_2Et)_2$	Fluorobenzene	3300 sec

Surprisingly few amines have been evaluated in reaction with chlorobenzene or fluorobenzene ligands.[9] Table 2 displays the results of preparative experiments with pyrrolidine (**A**) or N-methylbenzylamine (**B**) with fluorobenzene and isomeric fluoroanisoles at 23 °C. The isolated yields are uniformly high; the crude product was essentially as pure as the sample after simple chromatography.[10]

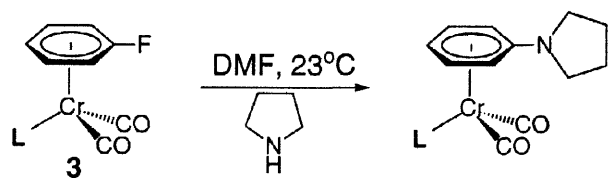
Table 2. Preparative Reactions of Amine Substitution for Fluoride.



Amine / Conditions	X	Yield
A / 2.2 mol-eq, 6h	H	98%
A / 2.2 mol-eq, 6h	2-OCH_3	96%
A / 2.2 mol-eq, 12h	3-OCH_3	95%
A / 4.0 mol-eq, 16h	4-OCH_3	97%
A / 2.2 mol-eq, 0.5h	3-Cl	97%
B / 2.2 mol-eq, 24h	H	98%
B / 2.2 mol-eq, 6h	3-OCH_3	89%
B / 2.2 mol-eq, 6h	4-OCH_3	88%
B / 2.2 mol-eq, 16h	3-Cl	91%

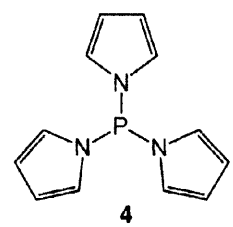
In evaluating candidates for the linker ligand, L in fig. 1, phosphorus-based ligands offered convenience and well-established patterns of steric and electronic effects on reactivity of attached ligands.[11] The series of complexes shown in Table 3 was prepared from the corresponding arene-$Cr(CO)_3$ complexes by initial photochemical formation of the arene-$Cr(CO)_2$(cyclooctene) derivative,[12] followed by thermal replacement of cyclooctene by the ligand of choice.[13] The trimethylphosphite complex[12,14] was unstable and decomposed during purification and further reactions. The tris(pentafluorophenyl)phosphine complex reacted with pyrrolidine by rapid substitution[15] for the *p*-fluoro substituents of the phenyl groups on the phosphorus, which complicates the use of this phosphine for further development. The other complexes were tested for relative reactivity, in comparison with fluorobenzene-$Cr(CO)_3$, again using ^{19}F NMR in DMF at 23 °C with excess amine (Table 3).

Table 3. Ligand Effects on the Rate of Substitution by Pyrrolidine



L	Half Lifetime
a. PPh_3	>> 48.0 h
b. $P(OPh)_3$	6.1 h
c. $P(Pyr)_3$	91 sec
d. $P(Pyr)_2$(NMeBn)	33.6 min

The triphenylphosphine ligand (in **3a**) strongly inhibits substitution; even with the amine as solvent on a preparative scale at 50 °C, no conversion was detected. Triphenylphosphite (in **3b**), a less electron donating ligand, restores useful reactivity and the fluorobenzene ligand undergoes substitution with pyrrolidine in DMF at 23 °C about 3800 times slower than fluorobenzene-$Cr(CO)_3$ under similar conditions. Unlike simple aminophosphines, tris(pyrrolyl)phosphine [$P(Pyr)_3$ in **4**] is relatively stable toward cleavage of the N-P bond and shows a relatively strong electron withdrawing effect, nearly comparable to CO.[16] This is consistent with rapid substitution for fluoride in complex **3c** under the standard conditions (15 mol-eq pyrrolidine, DMF) with a half lifetime of 91 sec, only 1.4 times slower than the parent fluorobenzene-$Cr(CO)_3$ complex. While one can imagine tethering **4** to a solid support (as **L** in fig 1), we developed an alternative, **5**, involving a benzylmethylamino substituent on phosphorus.[17] The benzylamino group in **5** mimics the



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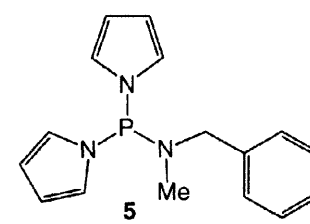

5

benzylamino side chain on a well-known Merrifield resin derivative.[18] and is a model for future linker ligands. Table 4 displays preparative results with complexes **3b-d**.

Table 4. Preparative Reactions with Substituted Fluoroarene-Cr(CO)$_2$L Complexes

AreneCr(CO)$_2$L	Amine	Conditions	Yield
3 b	Pyrrolidine	neat, 23 °C,48 h	96%
3 c	Pyrrolidine	15 mol-eq, 25 °C[a]	87%
3 d	Pyrrolidine	4 mol-eq, 23 °C, 1 h	83%

(a) The product was isolated from combined ^{19}F NMR samples.

Summary. The preparative and kinetic results indicate that S$_N$Ar reactions on tris(pyrrolyl)phosphine-modified fluoroarene-chromium complexes proceed rapidly and with high efficiency, appropriate for the development of solid phase versions for combinatorial synthesis. We are investigating the reactivity of polymer-supported analogs of the fluoroarene-Cr(CO)$_2$PPyr$_2$(NBnMe) system, where the Bn group is part of a polystyrene chain.[19]

References and Notes

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5 Bunnett, J. F.; Hermann, H. *J. Org. Chem.*, **1971**, *36*, 4081.
6 Anionic intermediates related to **1** can be generated by addition of highly reactive nucleophiles ($k_1 > k_{-1}$), and are stable in the absence of a leaving group at the position. For a discussion, see reference 3.
7 For one example with chlorobenzene, involving L = PPh$_3$ and P(nBu)$_3$ showing no reaction with sodium methoxide, see: Ogata, I.; Iwata, R.; Ikeda, Y. *Nippon Kagaku Zasshi*, **1969**, *90*, 1156.
8 Integral areas of the signal due to fluoride on the starting fluoroarene ligand were determined relative to an internal standard, α,α,α–trifluorotoluene, which was shown to be inert under the typical reaction conditions. Using a large excess of nucleophile, pseudo-first order conditions were demonstrated. For the example of pyrrolidine and fluorobenzene-Cr(CO)$_3$, the plot of ln (integral area) vs time gave a straight line with R = 0.99934 over 90% reaction (28 data points). The solvent was DMF and the arene complexes were typically at ca 0.05 M. In parallel preparative experiments, the yields were shown to be >95%.
9 Pyrrolidine, piperidine, and n-butyl amine were used by Bunnett in the kinetic study.[5] See also preparative studies with (a) pyrrolidine and benzylamine/fluoroarenes, see: Gilday, J. P.; Widdowson, D. A. *Tetrahedron Lett.*, **1986**, *27*, 5525; (b) morpholine/fluorobenzene, see: Mahaffy, C. L.; Pauson, P. A. *J. Chem. Res.*, **1979**, 128.
10 Representative procedure for the nucleophilic substitution on fluoroarene-chromium-tricarbonyl complexes: In a 50-mL round bottom flask under argon, fluorobenzene-chromium-tricarbonyl (50 mg, 0.21 mmol) was dissolved in 2 mL of dry DMF and pyrrolidine (2.2 mol-eq, 34 mg, 0.47 mmol) was added all at once. The mixture was stirred for 6 h at 23 °C and the volatiles were removed by rotary evaporation. The residue was chromatographed (SiO$_2$, hexanes/ethyl acetate = 4/1 as eluent). The yellow band was collected and the solvent removed to yield the product (60 mg, 0.21 mmol, 98%) as a yellow solid.
11 (a) The electronic effects can be assessed by the effect on the IR stretching frequency for a CO in the same ligand sphere. See: Poulton, J. T.; Sigalas, M. P.; Folting, K.; Streib, W. E.; Eisenstein, O.; Caulton, K. G. *Inorg. Chem.*, **1994**, *33*, 1436. (b) The steric effects have been evaluated in terms of the cone angle for the ligand. See: Tolman, C. A. *Chem. Rev.*, **1977**, *77*, 313.
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13 The yields for the thermal replacement of the cyclooctene ligand are as follows: L = PPh$_3$ 95%; P(OPh)$_3$ 96%; P(OMe)$_3$ 83%; P(C$_6$F$_5$)$_3$ 49%; P(Pyr)$_3$ 76%; P(Pyr)$_2$(NMeBn) 67%.
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16 For discussion and leading references, see: Moloy, K. G., Petersen, J. L. *J. Am. Chem. Soc.*, **1995**, *117*, 7696.
17 This phosphine can be synthesized in a one pot procedure in good yields: A 100-mL Schlenk flask is charged with pyrrole (freshly distilled, 1.59 mL, 1.54 g, 22.9 mmol) and triethylamine (6.39 mL, 4.64 g, 45.9 mmol) in 65 mL THF under argon atmosphere and the mixture was cooled to -78 °C. Trichlorophosphine (1 mL, 1.574 g, 11.5 mmol) was added slowly, the mixture stirred for 15 min at -78 °C, allowed to reach ambient temperature over 1 h and subsequently heated to 60 °C. After 24 h, 1 mol-eq N-benzyl methyl amine (1.48 mL, 1.39 g, 11.5 mmol) was added and the mixture stirred for another 24 h at 60°C. The white precipitate is filtered off and washed with THF. The volatiles are distilled off and the residue is taken up in hexanes and the solution is filtered once more. The solvent is evaporated and the residue was subjected to column chromatography (SiO$_2$, n-heptane) whereafter 2.98 g (92%) of the phosphine are obtained as colorless liquid.
18 For a recent application, see: Chatterjee, S.; Pedireddi, V. R.; Rao, C. N. R. *Tetrahedron Lett.*, **1998**, *39*, 2834.
19 We wish to acknowledge financial support in the form of a BASF postdoctoral fellowship to GH.