Accelerated Arene Ligand Exchange in AreneCr(CO_3) Complexes

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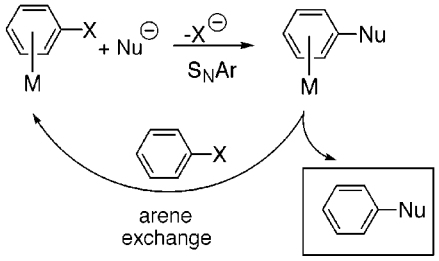
Activation of arene rings by complexation with metals through the pi system (π activation) is important in several processes such as arene hydrogenation and various coupling processes.[3] To achieve catalysis in such processes, arene ligand exchange must be facile. For example, a catalytic S_NAr process (Scheme 1)[4] might utilize the activation provided by $Cr(CO)_3$ but requires that an arene exchange step operate under similar conditions. Good yields are obtained in stoichiometric reactions of common nucleophiles with fluoro- and chloroarenes at moderate temperatures (25−50 °C),[5] but arene exchange is much less general and shows a high barrier[6] as well as unfavorable equilibrium for fluorobenzene exchanging with donor-substituted arenes.[7]

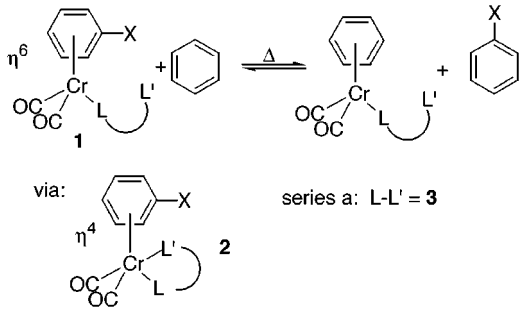
It has been noted that donor solvents[8] or a coordinating group in a side chain[9] on the arene ligand lower the barrier to exchange, but even in those cases the conditions are severe. The special case of a methyl acrylate ligand (L in benzene−$Cr(CO)_2L$), where arene exchange occurs at room temperature[10] suggests that much more powerful effects are possible by adjusting the nature of the ligand at the chromium.

We have been pursuing the concept that the CO ligand of an arene−$Cr(CO)_3$ complex can be replaced by a ligand which bears a second coordinating site (L′ in **1**). The group L′ is imagined to stabilize coordinatively unsaturated intermediates (e.g., as in **2**) *reversibly* and minimize irreversible side reactions of the $Cr(CO)_n$ unit during arene exchange.[11] A ligand which replaces a CO must be able to maintain the activation toward the S_NAr reaction; this process is sensitive to the electronic character of the replacement ligand (L)[5] (see Scheme 2).

Scheme 1. Catalytic S_NAr Process



Scheme 2. Role of a Pendant Ligand



Tris(pyrrolyl)phosphine (**A**) provides suitable activation[5] and is the basis for our first generation designs of L−L′ in **1**. As expected, complex **3A** (X = F) shows no arene exchange when heated in a sealed tube with benzene-d_6 for 17 h at 150 °C (Table, entry 1)[12] similar to the parent fluorobenzene-$Cr(CO)_3$ complex. We evaluated a soft pendant ligand (thioether) as L′ which could be installed easily on the pyrrolyl group and allow for a chelate ring during the exchange process. Lithiation of *N-tert*-butoxycarbonylpyrrole followed by quenching with MeSSMe and cleavage of the *t*BOC group gave 2-(methylthio)pyrrole in 80% yield.[13] Direct reaction of pyrrole with $MeSCH_2Cl$ in a toluene/water/K_2CO_3 mixture at 23 °C gave 2-(methylthiomethyl)pyrrole in 43% yield.[14] The readily available methyl 2-pyrrolylcarboxylate was also tested.

Reaction of 2-(methylthio)pyrrole with NaH followed by PCl_3 using a small excess of the 2-(methylthio)pyrrole produced tri-(2-methylthio)pyrrolylphosphine (**B**, 62% yield, colorless crystals, mp 76−77 °C). In a similar procedure but using Et_3N as base, reaction of di(pyrrolyl)chlorophosphine[15] with 2-(methylthio)-pyrrole produced di(pyrrolyl)(2-methylthio)pyrrolyl)phosphine (**C**, 59%, mp 45−46 °C). DMAP was the base of choice for conversion of 2-(methyl-thiomethyl)pyrrole to di(pyrrolyl)(2-(methylthiomethyl)pyrrole)phosphine (**D**, 37%, colorless oil) while NaH gave best results for 2-(methoxycarbonyl)pyrrole to di-(pyrrolyl)(2-(methoxycarbonyl)pyrrole)phosphine (**E**, 64%).[15]

Following the standard protocol,[16] the fluorobenzene−, and benzene−$Cr(CO)_3$ complexes (**3**, X = F, H; L = CO) were converted to the mono-cyclooctene analogues (**3**, L = cyclooctene) by replacement of one CO ligand under irradiation. Then thermal replacement of the cyclooctene with ligand **B**−**E** produced 1:1 complexes (for X = F, **3B**, and **3C**; for X = H, **3B**, **3C**, **3D**, **3E**.

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(2) Director, Princeton Small Molecule X-ray Facility.
(3) For examples with Cr complexes relevant to this work, see: Semmelhack, M. F., In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1992; Vol. 4, p 423.
(4) There are two examples of *catalytic* nucleophilic substitution with haloarene π complexes, with alkoxy replacing fluoride using a Rh(III) species [(a) Goryunov, L. I.; Litvak, V. V.; Shteingarts, V. D. *Zh. Org. Khimi* **1988**, *24*, 401. (b) Houghton, R. P.; Voyle, M.; Price, R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 925], and there are severe limitations which bring the mechanism into question. See: Eberson, L. *J. Mol. Catal.* **1983**, *20*, 27.
(5) For recent examples related to this work, see: Semmelhack, M. F.; Hilt, G.; Colley, J. H. *Tetrahedron Lett.* **1998**, *39*, 7683.
(6) (a) Muetterties, E. L.; Bleeke, J. R.; Wucherer, E. J.; Albright, T. A. *Chem. Rev.* **1982**, *82*, 499. (b) For a representative paper in the $Cr(CO)_3$ series and leading references, see: Traylor, T. G.; Stewart, K. J.; Goldberg, M. J. *J. Am. Chem. Soc.* **1984**, *106*, 4445.
(7) Arene exchange of fluorobenzene for benzene in the parent system, with (arene)$Cr(CO)_3$, is unfavorable with $K_{eq} < 0.1$. However, in excess PhF, the equilibrium can be driven to generate $PhFCr(CO)_3$ in 60% yield. [Mahaffy, C. A. L.; Pauson, P. L. *J. Chem. Res.* (S) **1979**, 126 and *J. Chem. Res.* (M) **1979**, 1752.] For the purpose of the S_NAr process in Scheme 1, it is required only that the equilibrium arene exchange be fast and that a sufficient concentration of $PhFCr(CO)_3$ be generated so that the (irreversible) substitution for F can proceed at a reasonable rate.
(8) Howell, J. S.; Yates, P. C.; Ashford, N. F.; Dixon, D. T.; Warren, R. *J. Chem. Soc., Dalton Trans.* **1996**, 3959.
(9) Traylor, T. G.; Stewart, K. J. *J. Am. Chem. Soc.* **1986**, *108*, 6977.
(10) Kundig, E. P.; Kondratenko, M.; Romanens, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 3146.
(11) A predominant side reaction is the irreversible oligomerization of the $Cr(CO)_n$ to give CO-bridged poly(metalcarbonyl) species.
(12) The Cr complex was heated in a sealed NMR tube with benzene-d_6 as a solvent. The tube was taken out of the oil bath and cooled to 23 °C, and the ^{19}F NMR spectra were taken at the appropriate time intervals.
(13) There is an earlier synthesis of 2-methylthiopyrrole: Nedolya, N. A.l; Brandsma, L.; Verkruijsse, H. D.; Trofimov, B. A. *Tetrahedron Lett.* **1997**, *38*, 7247**.** See Supporting Information for our preparation.
(14) This procedure was adapted from the preparation of 2-allylpyrrole: Wrackmeyer, B.; Schwarze, B. *J. Organomet. Chem.* **1997**, *534*, 181.
(15) See Supporting Information for preparation.
(16) Bernardinelli, G.; Cunningham, A. Jr.; Dupre, C.; Kundig, E. P.; Stussi, D.; Weber, J. *Chimia* **1992**, *46*, 126.

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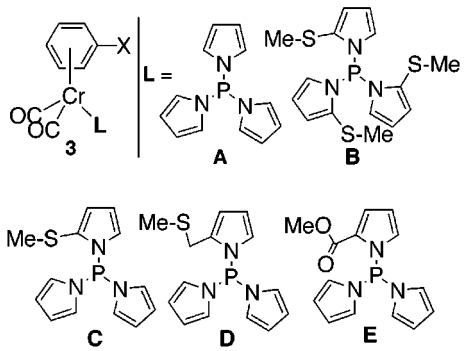
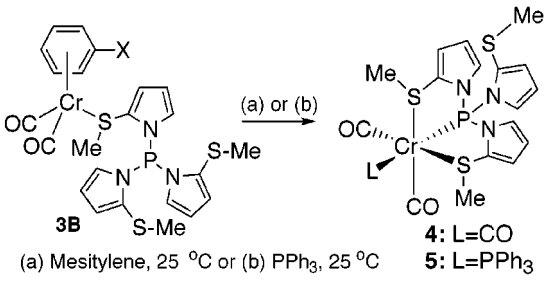


Complexes **3B** (X = F, H) were unstable toward loss of the arene ligand, even during chromatography on SiO_2. They were tentatively characterized by NMR (primarily ^{19}F, ^{31}P) as having the coordination of the sulfur unit (Scheme 3).[17] Warming **3B** (X = F) at 60 °C in mesitylene as solvent in attempted arene exchange led to loss of the fluorobenzene ligand and isolation of complex **4**, in low yield. This result suggested that the fluorobenzene ligand is lost easily but coordination by the mesitylene is not favorable. Using triphenylphosphine, the complex **5** was obtained.[18]

In contrast, the mono(methylthio) ligand, **C**, attaches to the chromium through phosphorus (**3C**, X = H; and **3C**, X = F), and this ligand has been carefully evaluated.[19] An X-ray diffraction study revealed two closely related conformations in the crystal for **3C**, X = H, with the sulfur atom poised about 4 Å from the Cr.[20] Arene exchange proved to be strongly accelerated by the methylthio group. When dissolved in benzene-d_6, the fluorobenzene ligand underwent conversion to the complex of benzene-d_6 (**6**) with a half-life time of 44 min at 60 °C (Scheme 4, Table 1, entry 2).[21] The corresponding benzene complex (**3C**, X = H) exchanged cleanly with benzene-d_6 but now with a half-life time of 7 h at 70 °C and 2 h at 80 °C (entry 3, 4). On a preparative scale, complex **3C**, X = F, was dissolved in benzene and heated at 80 °C to produce complex **3C**, X = H, in 94% yield. We attribute the rate difference for **3A**, X = F ($t_{1/2}$ > 17 h at 150 °C), and **3C**, X = F ($t_{1/2}$ = 44 min at 60 °C), to the stabilizing effect of the pendant methylthio group on the coordinatively unsaturated intermediates involved in arene exchange.

Scheme 3. Tricoordination with Ligand **B**



Scheme 4. Arene Exchange in Benzene-d_6

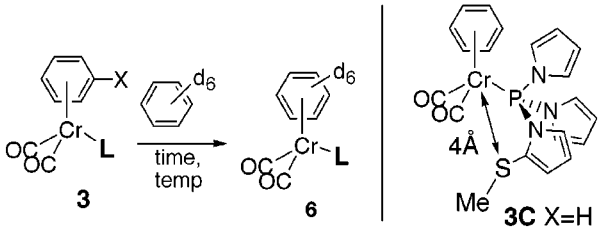


Table 1. Rates of Arene Exchange with Complexes **3**

entry	X	L	$t_{1/2\,(min)}$	temp (°C)
1	-F	**3A** (H)	>1000	150
2	-F	**3C**, (SMe)	44	60
3	-H	**3C**, (SMe)	420	70
4	-H	**3C**, (SMe)	120	80
5	-H	**3D**, (CH_2SMe)	1620	70
6	-H	**3E**, (CO_2Me)	26	70

The corresponding ester side chain was somewhat more effective. Complex **3E** (X = H) gave exchange with C_6D_6 with a half-life time of 26 min at 70 °C (entry 6). In preliminary experiments, the complex of the higher homologue ligand **D** (complex **3D**, X = H), which would have a six-membered chelate ring, shows a half-life time of about 27 h at 70 °C in benzene-d_6, somewhat slower compared to **3C**, X = H (entry 5). Work is in progress to define fully the steric and electronic properties which influence arene exchange in these systems.

Acknowledgment. We thank Drs. Istvan Pelczer and Carlos Pacheco for assistance with the NMR studies and Dr. Dorothy Little for Mass Spectrometry service.

Supporting Information Available: Procedures for the preparation and characterization of compounds **B**, **C**, **E**, **3C** (X = F), **3C** (X = H), **3E** (X = H), **4** and **5**; the ORTEP diagrams, X-ray procedures and tables for **5** and for **3C** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) ^{19}F NMR (470 MHz) peak at −141.5 ppm consistent with the S-bound complex ^{32}P NMR (202 MHz) peak at 59.7 ppm consistent with the S-bound complex.

(18) Characterized by spectroscopic data and an X-ray diffraction study. See Supporting Information.

(19) Characterization of **3C**, X = H: ^{1}H NMR (500 MHz, benzene-d_6) δ 1.92 (s, 3H), 4.41 (d, J^3_{PH} = 2.4 Hz, 6H), 5.73 (td, J_1 = 2.8 Hz, J_2 = 1.6 Hz, 1H), 6.03 (dt, J_1 = 3.2 Hz, J_2 = 1.2 Hz, 1H), 6.23−6.28 (m, 5H), 6.88−6.92 (m, 4H) ppm. ^{13}C NMR (125 MHz, benzene-d_6) δ 21.7, 111.8 (d, J^3_{CP} = 4.5 Hz), 112.7 (d, J^3_{CP} = 5.9 Hz), 118.9 (d, J^3_{CP} = 3.2 Hz), 124.6 (d, J^2_{CP} = 6.6 Hz), 130.5 (d, J^2_{CP} = 9.8 Hz), 236.2 (d, J^2_{CP} = 27 Hz) ppm. ^{31}P NMR (162 MHz, benzene-d_6) δ 173.5 ppm. MS (+FAB, nitrobenzyl alcohol): *m*/*z* 461 (17%), 395 (21%), 355 (42%), 327 (100%), 307 (81%), 289 (42%). IR (CH_2Cl_2 soln): 1055 (s), 1181 (s), 1444 (s), 1866 (s), 1925 (s), 2925 (m).

(20) The ORTEP diagram and relevant tables are included in the Supporting Information.

(21) In an NMR tube were put complex **3C,** X = F (20 mg, 0.040 mmol), trifluorotoluene (2 μL, as internal standard), and benzene-d_6 (1 mL), and the solution was subjected to three freeze−pump−thaw cycles, after which the tube was sealed under vacuum. The NMR probe was preheated to the chosen temperature, and the tube was put in. A series of ^{19}F NMR spectra were collected. Disappearance of the starting material and appearance of free fluorobenzene were followed via integration of the corresponding peaks. These numbers were related to internal standard and plotted against time in a logarithmic scale to yield straight lines from which half-life time was calculated.