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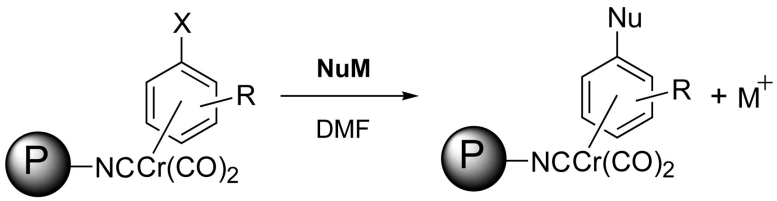

X= F, Cl
R= Cl, $CH(OEt)_2$, CHO, CH_3.

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Polymer-Supported Haloarene Chromium Dicarbonyl Isonitrile Complexes: A Study of Their Synthesis and Reactivity

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Different arene $Cr(CO)_3$ complexes were supported on a polystyrene isonitrile resin by photochemical-promoted replacement of a chromium carbonyl ligand by the NC group. The supported complexes proved to be stable and were successfully used for further transformations. In particular, the reactivity of dichlorobenzene complexes to different nucleophiles was investigated and found to be comparable with that of the parent $Cr(CO)_3$ complexes.

Metal-activated aromatic nucleophilic substitution (S_NAr) has been extensively studied in solution[1] and applied to the synthesis of different and multifunctionalized molecules. The alternative of performing such reactions using polymer-supported organometallic complexes[2] is of considerable interest because of its potential applications in combinatorial chemistry.

We[3,4] and other authors[5] have previously reported the chemistry of resin-bound chromium carbonyl carbene[3] and arene complexes[4−6] in which a chromium ligand was used to attach the organometallic moiety to the solid support. This is the most useful synthetic possibility for such complexes because the metal fragment acts as a traceless linker and, in principle, allows a number of decoration steps on the aromatic ring. Gibson[5] and then Rigby[6] extensively described the use of phosphine ligands to load a series of arene complexes onto a polystyrene resin and successfully carried out a series of reactions on different functions in a side chain of the complexed aromatic ring. However, because it is a donor ligand,[5a,7] a phosphine group considerably decreases the activation of the aromatic ring to the nucleophilic susbstitution induced by the metal carbonyl group, which is one of the most interesting aspects of such complexes and one that we wanted to investigate on solid phase. As reported in our preliminary communication,[4] we considered the isonitrile group a suitable ligand for anchoring the complex to the polymer and preserving the activation of the aromatic ring. The NC group is electronically very similar to a CO, and this is a basic prerequisite for maintaining reactivity in nucleophilic substitution reactions. In the same communication,[4] we described a preliminary study concerning the synthesis of polymer-supported fluorobenzene dicarbonyl isonitrile complex **3g** and its reactivity with sodium methoxide and other nitrogen nucleophiles (Scheme 1).

In this paper, we describe the synthesis and reactivity of a series of resin-bound dicarbonylisonitrile chromium chloro- and fluoroarene complexes **3a**−**h** (Scheme 2).

Results and Discussion

These complexes were prepared in good yields by means of a photochemically promoted ligand exchange from the parent $Cr(CO)_3$ complexes **1a**−**h** and isonitrile resin **2**. The latter was prepared from the commercially available hydroxymethylpolystyrene resin as previously described.[4] The best results were obtained from the direct photochemical exchange of a CO ligand of complexes **1a**−**h** with the tethered isonitrile **2**, in toluene at room temperature using a 125 W Hg vapor lamp.[8] The dark yellow resins **3a**−**h** were obtained in fairly good yields and completely characterized by IR, ^{1}H MAS NMR, and elemental analysis. Gel phase ^{19}F NMR was also made for compounds **3d**−**g**.

It is worth noting that because of the strong CO and NC absorptions, IR spectroscopy is an extremely useful and easy means of monitoring the reaction. In particular, the CO groups show two intense bands of about 1805−1930 cm^{-1}, whereas the absorption band of the NC function varies from 2122 cm^{-1} in resin **2** to 2050−2060 cm^{-1} for compounds **3a**−**h**. The reaction yields were determined on the basis of elemental analyses.

The subsequent step was to investigate the reactivity and synthetic usefulness of these polymer-supported complexes in nucleophilic substitutions. As the reactivity of the corresponding unsupported isonitrile complexes in aromatic nucleophilic substitutions was completely unknown, an exhaustive study was first performed in solution.[9] These experiments proved that the reactivity of the aromatic ring

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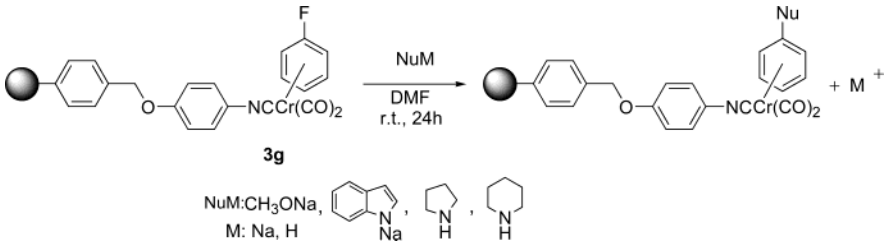
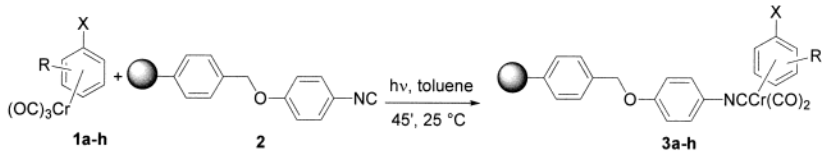
Scheme 1. Nucleophilic Substitution Reactions on Polymer-Supported Fluoro Benzene Complex



Scheme 2. Support of Haloarene $Cr(CO)_3$ Complexes **1a**−**h** on Isonitrile Resin **2**



			Y%
a:	X= Cl,	R= 2-Cl	63
b:	X= Cl,	R= 3-Cl	65
c:	X= Cl,	R= 2-CH(OEt)$_2$	66
d:	X= F,	R= 4-CH$_3$	67
e:	X= F,	R= 2-CH(OEt)$_2$	71
f:	X= F,	R= 2-CHO	92
g:	X= F,	R= H	70
h:	X= H,	R= H	68

Scheme 3. Nucleophilic Substitution Reactions on Polymer-Supported Haloarene Complexes

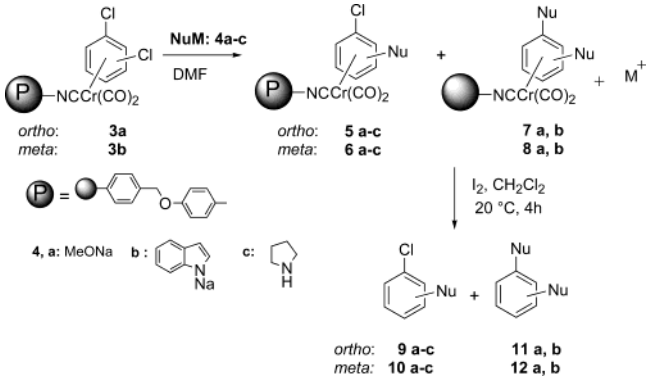


Table 1. Nucleophilic Substitution on *ortho*-Dichlorobenzene Resin **3a**

entry	nucleophile	*T* (°C)	*t* (h)	9, Y (%)[b]	11, Y (%)[b]
1	**4a**[a] (10 equiv)	35	8	**a**, 39	**a**, 10
2	**4b** (10 equiv)	35	8	**b**, 42	**b**, 18
3	**4c** (20 equiv)	35	10	**c**, 62	

[a] A 5.4 M solution in MeOH. [b] NMR yields.

is very similar to that of the analogous $Cr(CO)_3$ derivatives, a fundamental prerequisite for a solid phase application. On the basis of these results, we undertook a wide-ranging investigation of the reactivity of resin-bound haloarenes **3a**−**g** in aromatic nucleophilic substitutions.

We first studied the polymer-supported *ortho*- and *meta*-dichlorobenzene complexes **3a**,**b** in order to verify the possibility of substituting the two halogen atoms with different nucleophiles, as in the case of $Cr(CO)_3$ complexes.[10] Resins **3a**,**b** were reacted with an excess of nucleophiles **4a**−**c**[11] (Scheme 3 and Tables 1 and 2); the best results were obtained using dimethyl formamide (DMF) as the solvent at 35 °C for *ortho*-dichloro resin **3a** and at room temperature

Table 2. Nucleophilic Substitution on *meta*-Dichlorobenzene Resin **3b**

entry	nucleophile	*T* (°C)	*t* (h)	10, Y (%)[b]	12, Y (%)[b]
4	**4a**[a] (6 equiv)	20	6	**a**, 66	**a**, 22
5	**4b** (6 equiv)	20	15	**b**, 38	**b**, 53
6	**4b** (3 equiv)	20	15	**b**, 60	**b**, 30
7	**4c** (6 equiv)	20	48	**c**, 86	

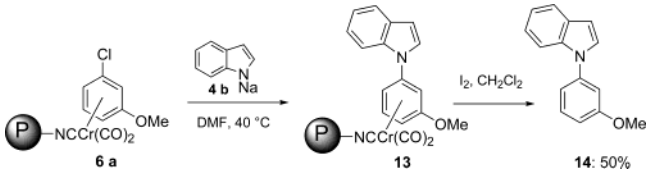
[a] A 5.4 M solution in MeOH. [b] NMR yields.

for *meta*-**3b**. The corresponding yellow resins **5**−**8** were isolated, and the reaction outcomes were evaluated after I_2 oxidative cleavage of the linker, which produced a mixture of monosubstituted **9** and **10a**−**c** and disubstituted **11** and **12a**,**b** arene derivatives (Tables 1 and 2). In the case of pyrrolidine **4c**, only monosubstituted compounds **9c** and **10c** were isolated.[12]

The results shown in Tables 1 and 2 demonstrate that the reactivity of polymer-bound haloarenes **3a**,**b** is in line with that of the corresponding $Cr(CO)_3$ complexes; i.e., the *meta*-supported complex **3b** was the most reactive. The *ortho*-resin **3a** required a slight heating (35 °C) and a higher amount of nucleophile, whereas the *meta*-**3b** reacted at room temperature and gave the corresponding *meta*-substituted chlorobenzene derivatives **10** and **12a**−**c** in higher overall yields. A variable amount of *ortho*-**11a**,**b** and *meta*-**12a**,**b** disubstituted arenes was also formed when using methoxide **4a** or indole anion **4b** (entries 1, 2 and 4, 5). In the case of *meta* complex **3b**, even the use of half of the amount of **4b** still gave disubstituted derivative **12b** (Table 2, entry 6). This high reactivity is comparable with that found for the corresponding $Cr(CO)_3$ complexes using **4b**.[13]

To validate the use of these polymer-supported complexes further, we investigated the reactivity of the derivatives bearing two different substituents on the aromatic ring by reacting the resin-supported *meta*-chloroanisole **6a** with the indole anion **4b** and pyrrolidine **4c**. Only the reaction with

Scheme 4. Reaction of Resin **6a** with the Indole *N*-Anion



4b was successful, and after the compounds were heated in DMF at 40 °C for 48 h, resin **13** was obtained (Scheme 4). The subsequent treatment of **13** with I_2 gave 1-(3-methoxyphenyl)indole **14** in 50% overall yield.

As a further example, we considered 2-fluoro benzaldehyde resin **3f** and its diethylacetal **3e**, in which the reactivity of both formyl and fluoro substituents can be exploited to achieve a number of derivatives. The reaction of acetal **3e** with nucleophiles **4a**−**d** (Scheme 5, path a) in DMF at room temperature gave resins **15a**−**d**. After I_2 treatment, arenes **16a**−**d** were obtained in rather good overall yields (46−75%). In particular, compound **16d**, which was obtained by means of substitution with sodium allyl alkoxide **4d**, is in principle a potential versatile intemediate for performing a number of intramolecular cycloaddition reactions leading to polycondensed heterocycles.[14]

The acetal function in compound **3e** can be easily hydrolyzed by treatment with a 10% PTSA solution in tetrahydrofuran (THF) (Scheme 5, path b), to give the resin-bound 2-fluorobenzaldehyde complex **3f**. This is an alternative route to the direct support of 2-fluoro benzaldehydeCr-$(CO)_3$ complex **1f** on resin **2**, as shown in Scheme 1. The reactivity of the formyl group in complex **3f** was then successfully tested in a reductive amination with 4-trifluoromethyl benzylamine in the presence of $NaBH(OAc)_3$ and gave resin **17** (path c) and, after cleavage, amine **18**. Furthermore, the direct substitution of the fluoro atom for pyrrolidine in benzaldehyde **3f** was also successful, giving resin **19** (path d) from which the corresponding 2-(1-pyrrolidinyl)benzaldehyde **20** was recovered in 68% overall yield after cleavage with air and sunlight. The reactivity of the formyl group (i.e., in reductive aminations) on resin 19 will be a matter of further investigations.

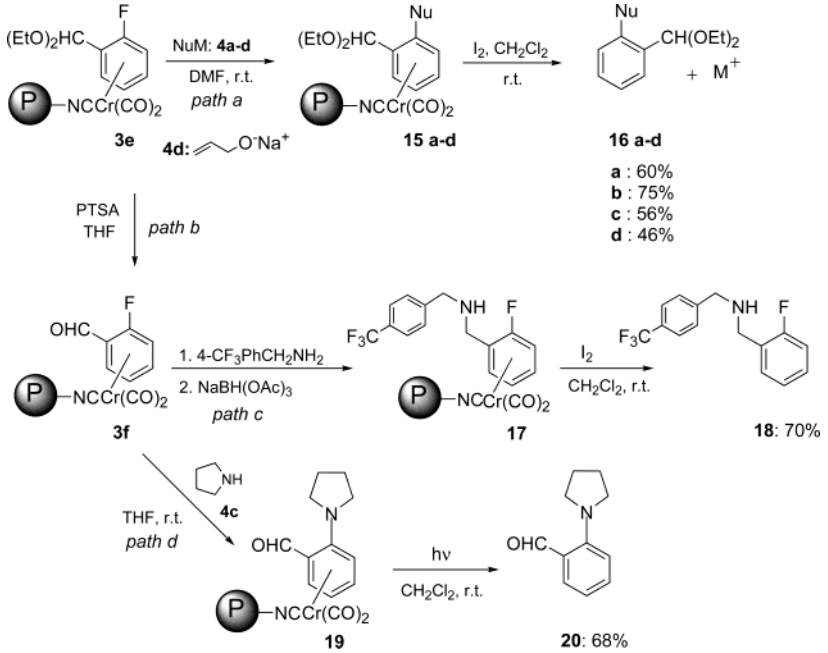
Conclusions. Different arene$Cr(CO)_3$ complexes were anchored to a polystyrene isonitrile resin by means of the photochemically promoted replacement of a chromium carbonyl ligand by the NC group. The use of the isonitrile group as a chromium ligand to anchor these complexes on the solid phase was successfully validated. It also proved to be effective in maintaining the aromatic ring reactivity typical of the parent $Cr(CO)_3$ complexes. The supported complexes proved to be stable and were used in a number of further transformations. In particular, the reactivity of dichlorobenzene complexes to different nucleophiles was investigated and found to be comparable with that of the corresponding $Cr(CO)_3$ complexes. In some cases, two different substituents were introduced on the same aromatic ring. We believe that these results are a good premise for further combinatorial chemistry applications.

Experimental Section

The reactions under nitrogen were performed using a standard vacuum line. THF was distilled from sodium benzophenone ketyl. The irradiation was carried out using a 125 W Hg vapor lamp (Philips). The ^1H and ^{19}F NMR spectra were recorded on a Bruker AC 300 and Bruker AMX 300, and the ^1H-MAS NMR spectra of resins were obtained in CD_2Cl_2 at 400 MHz using the Nano-probe. The IR spectra were recorded using a Perkin-Elmer FT-IR 1725X.

Resin-Supported Arene Complexes 3a−**h.** The photochemical ligand exchange was carried out in a 250 mL Pyrex vessel fitted with a water-cooled Pyrex finger. The UV source (Philips HPK 125 W Hg vapor lamp) was located inside the finger.[15] Nitrogen was bubbled through the reaction mixture during the photolysis. A 0.25 M toluene solution (10 mL) of arene chromium tricarbonyl **1a**−**h** (2.3 mmol, 3 equiv) and resin **2** (0.77 mmol, 1 equiv, load = 0.96) was irradiated

Scheme 5. General Reactivity of the Polymer-Bound 2-Fluorobenzaldehyde Complex



at room temperature. After 45 min, the reaction mixture was transferred to a 5 mL extract clean tube and filtered. The resin was then sequentially washed many times with toluene, DMF, MeOH, and CH_2Cl_2. The yellow resin **3a**−**h** was dried in a vacuum. The reaction yields were determined on the basis of elemental analyses.

Compounds. (**3a**) IR, ν_{max} (Nujol/cm^{-1}): 2136, 2054, 1996, 1932, 1884. ^{1}H MAS NMR (CD_2Cl_2): δ 5.18, 5.37 (Cr = 2.31%, load = 0.44, y = 63%). (**3b**) IR, ν_{max} (Nujol/cm^{-1}): 2136, 2060, 2009, 1930, 1894. ^{1}H MAS NMR (CD_2Cl_2): δ 4.91, 5.19, 5.33 (Cr = 2.68%, load = 0.51, y = 65%). (**3c**) IR, ν_{max} (Nujol/cm^{-1}): 2140, 2057, 2008, 1916. ^{1}H MAS NMR ($CDCl_3$): δ 1.23, 1.35 (CH_3CH_2O), 3.5, 3.7 (CH_3CH_2O), 4.9, 5.26, 5.4 (H arom + CH). Y = 66% 8 (after cleavage of the arene form the resin). (**3d**) IR, ν_{max} (Nujol/cm^{-1}): 2139, 2054, 2006, 1940, 1864. ^{1}H MAS NMR (CD_2Cl_2): δ 4.96, 5.18 (H arom). ^{19}F NMR (C_6D_6): δ −139.9 (Cr = 1.9%, load = 0.39, y = 67%). (**3e**) IR, ν_{max} (Nujol/cm^{-1}): 2136, 2058, 1945, 1915, 1877. ^{1}H MAS NMR (CD_2Cl_2): δ 1.21, 1.32 (CH_3CH_2O), 3.5, 3.8 (CH_3CH_2O), 4.90, 5.10, 5.26, 5.4 (H arom), 5.7 (CH). ^{19}F NMR (C_6D_6): δ −143.7 (Cr = 2.52%, load = 0.48, y = 71%). (**3f** (red resin)) IR, ν_{max} (Nujol/cm^{-1}): 2136, 2054, 1976, 1881, 1670. ^{1}H MAS NMR (CD_2Cl_2): δ 4.93, 5.19, 5.41, 5.92 (H arom), 9.84 (CHO). ^{19}F NMR (C_6D_6): δ −148.6 (Cr = 3.01%, load = 0.58, y = 92%). (**3g**)[4] IR, ν_{max} (Nujol/cm^{-1}): 2141, 2054, 2006, 1877. ^{1}H MAS NMR (CD_2Cl_2): δ 4.9, 5.1, 5.2, 7.37, 7.39 (load = 0.29). ^{19}F NMR (C_6D_6): δ −136.3. (**3h**) IR, ν_{max} (Nujol/cm^{-1}): 2139, 2061, 1993, 1904, 1864. ^{1}H MAS NMR (CD_2Cl_2): δ 5.15 (H arom) (Cr = 2.63%, load = 0.51, y = 68%).

Nucleophilic Substitution Reactions on *ortho*-Dichloro and *meta*-Dichloro Resins 3a,b. General Procedure. Under a nitrogen atmosphere, the appropriate nucleophile **4a**−**c** (6−20 equiv; see Tables 1 and 2; the indole anion was generated as described below; see also ref 9) was added to resin **3a** or **3b** (0.770 g, 0.594 mmol, 1 equiv) previously swollen in dry DMF (4.5 mL). The mixture was gently stirred at 35 °C in the case of **3a** or at room temperature in the case of **3b**. The reaction solution was then drained, and the resins **5**−**8** were sequentially washed with 5 mL of DMF, MeOH, and DCM (eight times) and then dried in a vacuum. *Ortho*-substituted resins: IR ν_{max} (Nujol/cm^{-1}) (**5a** + **7a**) 2061, 2006, 1891; (**5b** + **7b**) 2047, 1951, 1864; (**5c**) 2068, 2009, 1928. *Meta*-substituted resins: IR ν_{max} (Nujol/cm^{-1}) (**6a** + **8a**) 2052, 1915, 1875; (**6b** + **8b**) 2053, 1942, 1875; (**6c**) 2061, 1939, 1866.

General Procedure for Cleavage from the Solid Support. Cleavage with I_2. Products **9**−**12** were released from the solid support by swelling resins **5**−**8** in CH_2Cl_2 (10 mL) and treating them with a 0.1 M CH_2Cl_2 solution of I_2 (1.1 equiv). After the products were stirred for 4 h at room temperature, the brown polymer was filtered and washed with CH_2Cl_2 (8 × 5 mL). The combined organic phases were washed with an aqueous solution of $Na_2S_2O_3$ and then dried over Na_2SO_4 and evaporated. The residue was taken up with diethyl ether (5 mL) and filtered over a pad of Celite and evaporated. The crude mixture contained, as indicated by NMR spectroscopy, compounds **9**−**12** and a minor unidentified hydrocarbon and aromatic contaminants, possibly fragments of the polystyrene resin. A filtration over a little pad of SiO_2 provided **9**−**12** as analytically pure material. All spectroscopic data of the obtained arenes were consistent with those reported in the literature.[9,10,16]

Photochemical Cleavage. Alternatively, the CH_2Cl_2 suspension of the resin can be exposed to air and sunlight for 24 h under stirring. The polymer was filtered and washed with CH_2Cl_2 (8 × 5 mL). The combined colorless organic phases were dried over Na_2SO_4, filtered over a pad of Celite, evaporated, and treated as reported above.

Nucleophilic Substitution of the Indole Anion (4b) on Resin 6a. A 0.8 M DMF solution of indole (0.963 mmol, 10 equiv, 1.2 mL) was added dropwise to a slurry of NaH (55% suspension in oil, 11 equiv) in dry DMF (1 mL) at 0 °C.[9] After 10 min, this suspension was added through a cannula to resin **6a** (0.096 mmol, 1 equiv), which was swollen in dry DMF (1.5 mL). The mixture was gently stirred at 40 °C for 6 h and then overnight at room temperature. Methanol (0.5 mL) was added to the mixture, the reaction solution was drained, and the resin was sequentially washed with DMF, MeOH, and DCM (12 × 8 mL). Resin **13** was then dried in a vacuum. IR ν_{max} (Nujol/cm^{-1}): 2052, 1941, 1907, 1867. Cleavage with I_2 followed by a preparative plate chromatography gave a fraction containing a mixture of 1-(3-methoxyphenyl)-1*H*-indole[15] **14** (50% overall yield) and unreacted 3-cloroanisole (22%).

Nucleophilic Substitution Reactions of 4a−**d on Resin 3e.** The reactions were carried out following the general procedure reported above, and yellow resins **15a**−**d** were obtained. IR ν_{max} (Nujol/cm^{-1}) (**15a**) 2034, 1942, 1901, 1860; (**15b**) 2054, 1915, 1881, 1864; (**15c**) 2055, 2000, 1952, 1864; (**15d**) 2027, 1901−1860. I_2 cleavage from the resins and purification were run as reported in the general procedure and afforded analytically pure arenes **16a**−**c**. Compound **16d** was purified by preparative plate chromatography (CH_2Cl_2), which caused hydrolysis of the acetal function, and the corresponding 2-allyloxy benzaldehyde was isolated.The spectral and analytical data were consistent with the assigned structure for **16a**,**c** and with those reported in the literature for **16b**,**d**.[10,11b]

Hydrolysis of the Acetal Function in Resin 3e. Resin **3e** (0.210 g, 0.11 mmol, 1 equiv) was swollen in THF (1 mL). The mixture was deoxygenated with bubbling nitrogen, and then toluene-4-sulfonic acid (10% mol) was added and the mixture was gently stirred at room temperature for 2 h. The color of the resin changed from yellow to red, the solution was drained, and resin **3f** was washed twice with an aqueous solution of $NaHCO_3$ and then several times with MeOH and CH_2Cl_2. The obtained resin was compared with that obtained with the direct support of 2-fluoro benzaldehyde (Scheme 1).

Reductive Amination of Resin 3f. Under a nitrogen atmosphere, resin **3f** (0.200 g, 0.11 mmol, 1 equiv) was swollen in dry CH_2Cl_2 (1.5 mL), after which *p*-trifluoromethylbenzylamine (0.065 mL, 0.44 mmol, 4 equiv) was added. The mixture was gently stirred at room temperature for 1 h, and then, a solution of $NaBH(OAc)_3$ (0.22 g, 0.995 mmol, 9 equiv) in dry CH_2Cl_2 (1.5 mL) was added. The

mixture was gently shaken for 18 h at room temperature, before the reaction was quenched with MeOH and drained. The resin was sequentially washed with DMF, MeOH, and CH_2Cl_2 (several times). Yellow resin **17** was dried in a vacuum. IR ν_{max} (Nujol/cm^{-1}) 2056, 1950, 1915, 1878. ^{1}H MAS NMR ($CDCl_3$): δ 3.57, 3.94 (CH_2N), 4.93, (H aromCr) 7.49, 7.56 (arom). ^{19}F NMR (C_6D_6): δ −61.9 (CF_3), −143.1; N = 1.01%, Cr = 1.48%. The treatment of **17** with I_2 gave, after preparative plate chromatography (CH_2Cl_2), amine **18** in 68% overall yield. ^{1}H NMR (C_6D_6): δ 2.11 (bs, 1H, NH), 4.06 (s, 4H, CH_2N), 7.2−7.6 (m, 4H arom), 7.8 (AB sist., 4H arom). ^{19}F NMR (C_6D_6): δ −62.5 (CF_3), −119.25. Elemental analysis: C, 63.52%; H, 4.61%; N, 4.95. $C_{15}H_{13}F_4N$ requires C, 63.60%; H, 4.61%; N, 4.95%.

Reaction of Formyl Resin 3f with Pyrrolidine. Under nitrogen atmosphere, resin **3f** (0.250 g, 0.138 mmol, 1 equiv) was swollen in dry DMF (1.5 mL), after which pyrrolidine (0.230 mL, 2.765 mmol, 20 equiv) was added. The mixture was gently stirred at room temperature for 24 h. The solution was drained, and the resin was sequentially washed with DMF, MeOH, and CH_2Cl_2 (several times), and then dried in a vacuum. After photochemical cleavage from the resin, 1-(2-formylphenyl)pyrrolidine **20**[18] was recovered almost analytically pure in 73% overall yield. ^{1}H NMR (C_6D_6): 2.1 (m, 4H, CH_2), 3.5 (m, 4H, CH_2N), 6.9−7.8 (m, 4H arom), 10.19 (CHO).

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(8) For in-solution reactions, the photochemical exchange of a CO for RNC gave the best results using a two-step protocol via cyclooctene as a labile intermediate ligand.[6b,9]

(9) Results to be published; also reported in a poster presentation at the *3rd International School of Organometallic Chemistry*, 9−13 September 2001, Camerino, Italy. For example, fluoro,[4] *ortho*-, and *meta*-dichlorobenzene dicarbonyl 2,6-dimethylphenylisonitrile complexes reacted with alkoxydes, carbanions, indole, and acetone oxime anions under very mild conditions (DMF, 20−35 °C).

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