Improved Synthesis of (Aminocarbene)chromium(0) Complexes with Use of C_8K-Generated $Cr(CO)_5^{2-}$. Multivariant Optimization of an Organometallic Reaction

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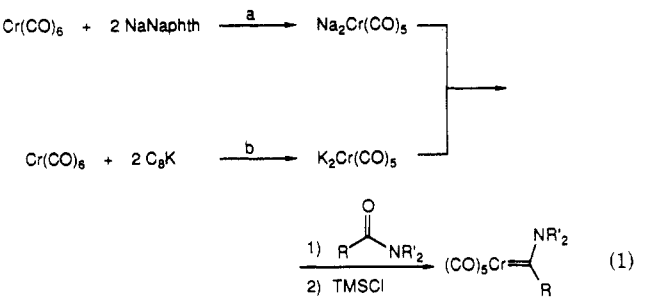
Potassium-graphite (C_8K) was an efficient reducing agent for the conversion of $Cr(CO)_6$ to $K_2Cr(CO)_5$. Reaction of a wide variety of amides with $K_2Cr(CO)_5$ produced in this manner gave good to excellent yields of (aminocarbene)chromium(0) complexes. Both the reaction procedure and purification of products were much more convenient than those for the previously developed sodium naphthalene procedure. The aminocarbene complex from 1-benzylpiperidin-2-one was formed in only 8% yield under standard conditions. Optimization studies changing one variable at a time (OVAT) increased this to only 32%. Application of multivariant optimization techniques rapidly increased this yield to 78%.

Introduction

Heteroatom-stabilized ("Fischer") chromium carbene complexes[1] continue to be extensively developed as useful reagents for organic synthesis.[2] In the past, most of the studies centered on the chemistry of alkoxycarbene complexes, and this area continues to be extensively exploited. More recently the related chemistry of aminocarbene complexes has begun to be explored, with substantial differences in reactivity patterns being observed. For example, (aryl)(alkylamino)carbene complexes underwent thermal reactions with alkynes to give indanones or aminoindenes,[3] while (alkyl)(alkenylamino)-, (alkyl)(aziridinyl), and (alkyl)(piperidinyl)carbenes produced bicyclic unsaturated lactams.[3c,4] More complex structures were produced when enynes were used as substrates.[5] (Alkyl)(amino)carbene complexes having α-hydrogens were homologated by α-deprotonation followed by alkylation with carbonyl compounds[6] or alkyl halides,[7] for ultimate use in organic synthesis. Aminocarbene complexes have also been N-acylated[8] and the resulting complexes converted to a number of unusual organic compounds. In these laboratories, photolytic reactions of aminocarbene complexes to produce amino-β-lactams[9] and α-amino acid esters[10] have been extensively developed.

Chromium aminocarbene complexes are most commonly prepared by exchange processes involving replacement of an alkoxy or acyloxy group from the corresponding oxocarbene by an amine.[11] This process is limited to the exchange of unhindered primary, and in some cases, secondary amines, and is restricted to those alkoxycarbene complexes accessible from ortholithium reagents.[12] We recently developed a general approach to (aminocarbene)chromium compounds utilizing the reaction of $Na_2Cr(CO)_5$, generated by the reduction of $Cr(CO)_6$ with sodium naphthalenide, with amides, followed by the addition of trimethylsilyl chloride (eq 1, path a).[13] This



(1)

reaction was quite general, and a wide variety of aminocarbene complexes were available by this method. A technical limitation of this procedure is the necessity of separating the product carbene from 2 equiv of naphthalene. In all cases, large amounts of silica gel were required for chromatographic purification, and with carbenes having large aliphatic groups, multiple separations were required to give pure product. To circumvent these problems, more easily separated reducing agents for chromium hexacarbonyl were sought.

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Potassium–graphite (C_8K) is easily prepared by simply heating the two components at 150–160 °C for a short time under an inert atmosphere. This heterogeneous reagent has been used to reduce a variety of organic compounds[14] and has been reported to reduce $Cr(CO)_6$ to the binuclear complex $K_2Cr_2(CO)_{10}$ at 25–40 °C in THF,[15] with graphite being the only byproduct. Although this binuclear complex is of no use for the preparation of aminocarbenes from amides,[9b] the ease of preparation of C_8K and the potential ease of separation of desired products from the residue of the reducing agent (graphite in this case) were sufficiently appealing to prompt attempts to use C_8K to reduce $Cr(CO)_6$ to $K_2Cr(CO)_5$ (eq 1, path b). The results of these studies are reported below.

Results and Discussion

Heating potassium metal together with graphite under argon to 150 °C in a sand bath for 10–15 min with stirring produced the C_8K laminate, as evidenced by the change of color of the solid from the silver-gray of graphite to the metallic bronze color of the (pyrophoric) laminate. Addition of $Cr(CO)_6$ to a THF suspension of C_8K cooled to −78 °C followed by warming to 0 °C over the course of 3 h produced a silvery green slurry of the relatively insoluble $K_2Cr(CO)_5$ in a yellow-green solution. This suspension could be stored at −20 °C until use. Cooling this slurry to −78 °C, followed by adding the amide, warming to 0 °C, and stirring at that temperature until the slurry dissipated, cooling to −78 °C, followed by addition of trimethylsilyl chloride, and finally warming to room temperature produced the aminocarbene complex, which was easily purified by passing through a short plug of silica gel with 1:1 hexane–CH_2Cl_2 as solvent (Table I). The yields by this procedure were comparable to or better than those obtained with sodium naphthalenide as a reducing agent. This, coupled with the greater ease of purification, makes the C_8K method the procedure of choice.

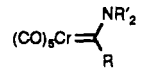
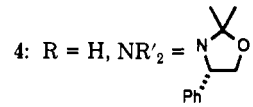
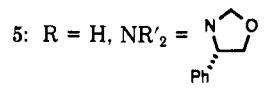
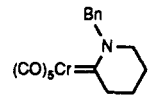
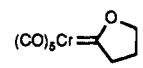
However, it was still not universally efficient. A particularly important example of this is entry 10 in Table I. This complex, derived from 1-benzylpiperidin-2-one, was central to a planned synthesis of pipecolic acid derivatives,[7b] and a high-yield synthesis of it was important. With use of the previously developed sodium naphthalenide procedure[13] the yield was only 8%. Attempts to optimize the yield by the traditional changing of one variable at a time (OVAT) increased it to only 18%. Changing from sodium to potassium naphthalenide under the improved conditions increased the yield to 32%, and virtually the same yield was obtained with C_8K. OVAT optimization at this stage led to no improvement.

The reason for this lies in the complexity of the reaction itself. The yield can and does depend on a number of different variables, and these variables are almost surely correlated rather than independent—that is, changing one variable will modify the influence of other variables in the reaction. If this is indeed the case, the OVAT approach will never lead to optimal yields. Instead procedures that make it possible to consider the *joint* influences of all variables *simultaneously* are required.[16] Such "multivariate" techniques are available[17] and are in common use in industrial situations but are rarely applied to fundamental research problems.

Rigorous multivariate optimization requires a full factorial analysis, wherein the response of the reaction to all variables is probed. The number of experiments required is 2^n, where n is the number of variables. However, with some foreknowledge of the relative importance of variables, from preliminary experiments, a "fractional factorial" design can be employed[18] and often leads to rapid improvement. Such a system was applied to the optimization of the synthesis of complex **10**.

Experience from attempted OVAT optimization suggested that a number of variables influenced the yield and that other variables could be kept constant. In this study the "constant" variables were chosen as follows: (1) ion pairing (with K^+ as counterion for the dianion); (2) THF as solvent; (3) TMSCl as electrophile; (4) use of 1.1 equiv of dianion vs amide. The variables that initially were considered most important (with levels at which they were studied given in parentheses) were (1) C, the concentration of the dianion (0.1 and 0.3 M) (2) A_T, the temperature of the reaction mixture after addition of amide (−35 and 0 °C), (3) A_t, the time allowed for the reaction between amide and dianion ($^1/_2$ and $1^1/_2$ h), (4) T_c, the equivalents of electrophile (2.2 and 4.0 equiv), (5) T_T, the temperature for reaction of the initial adduct with the electrophile (−35 and 25 °C), and (6) T_t, the time for the reaction between initial adduct and electrophile ($^1/_2$ and $1^1/_2$ h). With use of these six variables a fractional factorial design with eight

Table I. Synthesis of Chromium Carbene Complexes

carbene complex	yield, %[a] C_8K	yield, %[a] Na(naphth)
		
1: R = H, R′ = Me	93	84
2: R = Ph, R′ = Me	87	93
3: R = Me, R′ = Bzl	50	44
	96	93
4: R = H, NR′$_2$ =		
	63	
5: R = H, NR′$_2$ =		
6: R = Me, NR′$_2$ = 	54	78
7: R = o-ClPh, R′ = Et	50	
8: R = 3-furyl; R′ = Et	63	
9: R = H, R′ = Ph	35[b]	33[b]
12: R = $(CH_2)_{10}CH_3$, R′ = Me	74	
	78	8 (32)[c]
10		
	54[d]	42[d]
11		

[a] Yields are for isolated, purified complexes. [b] Prepared from the corresponding Vilsmeier's salt rather than the formamide. [c] Yield with use of potassium naphthalenide. [d] Prepared from reaction of the dianion with γ-chloropropionyl chloride.

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experiments (2^{6-3}) was constructed (Table II).[17,19]

The average yield from these experiments was 46% (highest yield 58%), which should be compared to the 32% yield that was obtained from the OVAT procedure, but no conclusions could yet be made about the importance of the separate variables. In order to resolve this, a new fractional factorial design was constructed with eight new experiments complementing the first set of experiments (Table III). From this set of experiments a high yield of 61% was obtained with an average yield of 46%. Using the 16 experiments unambiguously showed the importance of the variables studied, with the variables most affecting the yield being the concentration of electrophile (higher yields with lower concentration), the time for the reaction between the initial adduct and electrophile (shorter time leading to higher yields), and the temperature and time for reaction between dianion and amide (higher temperature and longer time leading to higher yield). The concentration of the dianion did not significantly influence the reaction (Figures 1 and 2).

In order to confirm the significance of the variables, a number of experiments were designed outside the domain studied, moving in the direction suggested from the variables (steepest ascent approach; Table V).[18] When each of the variables influencing the reaction was extended in the direction of steepest ascent, only a 41% yield of product was obtained, indicating that at least one variable was extended too far. By retreat to an intermediate position (see Experimental Section for details), a 78% yield of complex **10** was obtained. The experiment was repeated with use of this final set of conditions, and a 77% yield of **10** was obtained, verifying the validity of the procedure.

Since full optimization to 100% was deemed unnecessary, no further optimization studies were carried out. Although the *specific* optimum conditions for the synthesis of complex **10** are unlikely to be general for the optimum synthesis of other difficult-to-prepare complexes, the knowledge gained about the importance and influence of reaction variables on yield should be generally applicable to all specific cases of this reaction class, making optimization in other systems considerably more efficient.

Experimental Section

General Procedure. Melting points were taken on a Mel-Temp apparatus and are uncorrected. A Bruker IBM-200 NMR spectrometer was used for the 200-MHz ^1H NMR spectra. The 270-MHz ^1H NMR and the 68-MHz ^{13}C NMR spectra were obtained on a Bruker IBM-270 NMR spectrometer. The 300-MHz ^1H NMR and 75-MHz ^{13}C spectra were obtained on a Bruker ACE 300 NMR spectrometer. NMR spectra were recorded in $CDCl_3$, and chemical shifts are given in parts per million relative to Me_4Si (0 ppm, ^1H) or $CDCl_3$ (77 ppm, ^{13}C). UV–vis spectra were obtained on a Varian DMS 80 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 1600 Series FT IR spectrophotometer. Electron impact and chemical ionization mass spectra were obtained on a VG Micromass Ltd. Model 16F spectrometer. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Column chromatography was performed with use of Alfa 70-μm silica gel as the stationary phase.

Solvents. Tetrahydrofuran (Mallinckrodt, AR grade) was predried over CaH_2 and distilled from benzophenone ketyl under a nitrogen atmosphere just prior to use. Hexane (technical grade) was distilled at atmospheric pressure. Methylene chloride was distilled over CaH_2 and stored over molecular sieves.

Reagents. The following reagents were purchased from the specific suppliers and used as received: chromium hexacarbonyl (Pressure Chemical), graphite (technical grade, Schaar and Co.), potassium (Mallinckrodt), chlorotrimethylsilane (Petrarch), 4-chlorobutyryl chloride (Aldrich), *N,N*-diphenylformamide (Aldrich), dimethylformamide (Aldrich), oxalyl chloride (Aldrich). The following amides were prepared according to literature procedures; **2**, **4**, **5**, **6**, **7**, **8**;[13] **3**, **10**.[7b] The amide **12** was prepared from the corresponding acid chloride and the appropriate amine by following the general procedure reviewed by Beckwith.[21] The Vilsmeier salt of **9** was prepared according to the literature procedure.[9b]

Preparation of Dipotassium Pentacarbonylchromate from Potassium–Graphite (C_8K) Laminate. Graphite (2.34 g, 195 mmol) was heated, while being stirred with a magnetic stirbar under argon, for 15 min at 150–160 °C in an Airless flask, in a sand bath. Potassium (0.95 g, 24.3 mmol) was added under argon, and the mixture was kept at 160 °C with stirring until the laminate had formed (10–15 min). The material was highly pyrophoric, necessitating cautious handling in thoroughly dried solvents. C_8K, the bronze color of which was indicative of its formation, was then cooled and suspended in 35 mL of anhydrous THF. C_8K (2.2 equiv) in THF was cooled to −78 °C, and $Cr(CO)_6$ (2.42 g, 11.0 mmol) was added under a positive flow of argon. The reaction mixture was stirred $^1/_2$ h at −78 °C and placed in an ice bath at 0 °C until the solution turned from a bronze-black color to a thick slurry of silvery green solids in a yellow-green solution. It was ready to use immediately or could be stored in the freezer for several days.

General Procedure for the Preparation of the (Aminocarbene)chromium Complexes. The Airless flask containing the $K_2Cr(CO)_5$, graphite residues, and THF was cooled to −78 °C under argon, and the amide (10 mmol) was added via syringe. The reaction mixture was stirred at −78 °C for $^1/_2$ h, warmed to 0 °C for 1 h (if solids other than graphite persisted, the mixture was warmed briefly to 25 °C to dissolve them), and cooled to −78 °C, TMSCl (30 mmol) was added, and this solution was stirred for $^1/_2$ h and warmed to 25 °C. Neutral Al_2O_3 (25 g) was added to absorb the product, and the solvent was removed under reduced pressure. Special care was taken to remove all of the THF at this stage. The resulting dry powder was chromatographed on a silica gel column (15–20 cm × 2 cm) with hexane–CH_2Cl_2 (1:1) as eluent to obtain the aminocarbene generally as the only product.

Pentacarbonyl[(dimethylamino)methylene]chromium (1). The above procedure was used to produce 1.98 g (93%) of carbene **1**, as yellow crystals, from 623 mg (8.5 mmol) of dimethylformamide, 10 mmol of $K_2Cr(CO)_5$, and 25.5 mmol of TMSCl. This material was identical in all respects with that previously described.[13]

Pentacarbonyl[(dimethylamino)phenylcarbene]chromium (2). The above procedure was used to produce 1.97 g (87%) of carbene **2**, as yellow crystals, from 1.04 g (7.0 mmol) of *N,N*-dimethylbenzamide, 10 mmol of $K_2Cr(CO)_5$, and 21 mmol of TMSCl. This material was identical in all respects with that previously described.[13]

Pentacarbonyl[(dibenzylamino)methylcarbene]chromium (3). The above procedure was used to produce 1.29 g (50%) of carbene **3**, as a yellow oil, from 1.49 g (6.2 mmol) of *N,N*-dibenzylacetamide, 10 mmol of $K_2Cr(CO)_5$, and 18.6 mmol of TMSCl. This material was identical in all respects with that previously described.[7b]

Pentacarbonyl[((5*S*)-2,2-dimethyl-5-phenyl-1-aza-3-oxacyclopentyl)methylene]chromium (4). The above procedure was used to produce 4.3 g (96%) of carbene **4**, as a yellow solid, from 2.5 g (12.2 mmol) of the corresponding formamide, 13.4 mmol of $K_2Cr(CO)_5$, and 34 mmol of TMSCl. This material was identical in all respects with that previously described.[13]

Pentacarbonyl[((5*S*)-5-phenyl-1-aza-3-oxacyclopentyl)methylene]chromium (5). The above procedure was used to produce 0.18 g (63%) of carbene **5**, as a yellow solid, from 150 mg (0.8 mmol) of the corresponding formamide, 1.1 mmol of $K_2Cr(CO)_5$, and 2.5 mmol of TMSCl. ^1H NMR (270 MHz): δ 4.14 (dd, J = 7.6, 9.0 Hz, 1 H, OCH_2), 4.59 (dd, J = 6.9, 9.2 Hz, 1 H, OCH_2), 4.87 (t, J = 6.7 Hz, 1 H, NCHPh), 5.63 (s, 2 H, NCH_2), 7.15–7.43 (m, 5 H, ArH), 11.03 (s, 1 H, Cr=CH). ^{13}C NMR (75 MHz): δ 71.6 (OCH_2), 75.0 (NCHPh), 86.0 (NCH_2O), 127.4 (Ar), 129.5 (Ar), 129.6 (Ar), 135.8 (Ar), 217.0 (cis CO), 223.5 (trans CO), 260.3 (Cr=C). IR (film): ν 2057, 1908 cm^{-1}. UV–vis (11.7 mg/250 mL of hexane): λ_{max} 375 nm (ϵ = 11 375). MS (EI): m/z 355 (M^+ + 2), 354 (M^+ + 1), 353 (M^+), 325 (M^+ − CO), 297 (M^+ − 2CO), 269 (M^+ − 3CO), 241 (M^+ − 4CO), 213 (M^+ − 5CO). Anal. Calcd

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Table II. Fractional Factorial Design and Results for the Screening of Preliminary Variables

first series run no.	variable C	T_T	T_t	A_T	A_t	T_c	response % yield
1	−	−	−	+	+	+	55.9
2	+	−	−	−	−	+	41.2
3	−	+	−	−	+	−	43.5
4	+	+	−	+	−	−	57.9
5	−	−	+	+	−	−	35.8
6	+	−	+	−	+	−	44.9
7	−	+	+	−	−	+	38.6
8	+	+	+	+	+	+	52.7
calcd effect and mean	2.8	1.8	−3.3	4.2	2.9	0.8	46.3

Table III. Complement Fractional Factorial Design and Results for the Screening of Preliminary Variables

second series run no.	variable C	T_T	T_t	A_T	A_t	T_c	response % yield
1	−	−	−	−	−	−	49.4
2	+	−	−	+	+	−	60.9
3	−	+	−	+	−	+	49.9
4	+	+	−	−	+	+	36.8
5	−	−	+	−	+	+	50.9
6	+	−	+	+	−	+	31.6
7	−	+	+	+	+	−	42.8
8	+	+	+	−	−	−	45.0
calcd effect and mean	−2.3	−2.3	−3.3	0.4	1.9	−3.5	45.9

for $C_{15}H_{11}CrNO_6$: C, 51.00; H, 3.14; N, 3.97. Found: C, 51.12; H, 3.15; N, 4.00.

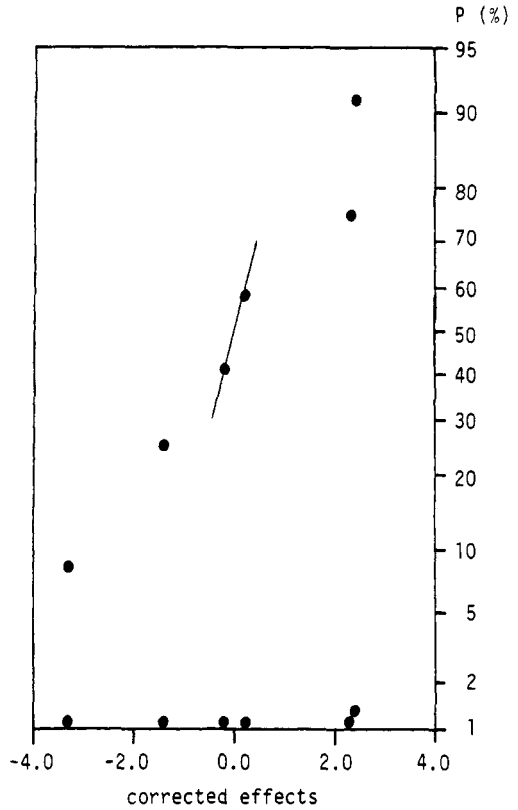
Pentacarbonyl(morpholinomethylcarbene)chromium (6). The above procedure was used to produce 1.21 g (54%) of carbene **6**, as yellow crystals, from 0.96 g (7.3 mmol) of morpholinoacetamide, 10 mmol of $K_2Cr(CO)_5$, and 22 mmol of TMSCl. This material was identical in all respects with that previously described.[13]

Pentacarbonyl[(2-chlorophenyl)(diethylamino)carbene]chromium (7). The above procedure was used to produce 1.33 g (49%) of carbene **7**, as a yellow solid, from 1.48 g (7.0 mmol) of *N,N*-diethyl-2-chlorobenzamide, 10 mmol of $K_2Cr(CO)_5$, and 21 mmol of TMSCl; mp 86–88 °C dec. ^{1}H NMR (300 MHz): δ 1.14 (t, J = 7.2 Hz, 3 H, CH_3), 1.56 (t, J = 7.2 Hz, 3 H, CH_3), 3.41 (q, J = 7.1 Hz, 2 H, NCH_2), 4.25 (dq, J = 14.2, 7.0 Hz, 1 H, NCH), 4.48 (dq, J = 14.2, 7.0 Hz, 1 H, NCH), 6.85 (dd, J = 1.4, 7.7 Hz, 1 H, ArH), 7.12 (dt, J = 1.5, 7.7 Hz, 1 H, ArH), 7.32 (m, 2 H, ArH). ^{13}C NMR (75 MHz): δ 13.8 (CH_3), 14.0 (CH_3), 49.1 (NCH_2), 54.2 (NCH_2), 121.9 (ArH), 123.4 (ArCl), 126.8 (ArH), 127.2 (ArH), 130.0 (ArH), 149.6 (Ar), 216.9 (cis CO), 223.7 (trans CO), 269.9 (Cr=C). IR (film): ν 2053, 1973, 1915 cm^{-1}.

Pentacarbonyl[(diethylamino)-3-furylcarbene]chromium (8). The above procedure was used to produce 1.65 g (62%) of carbene **8**, as a yellow solid, from 1.29 g (7.7 mmol) of *N,N*-diethyl-3-furancarboxamide, 10 mmol of $K_2Cr(CO)_5$, and 23 mmol of TMSCl; mp 45 °C. ^{1}H NMR (300 MHz): δ 1.17 (t, J = 7.2 Hz, 3 H, CH_3), 1.50 (t, J = 7.2 Hz, 3 H, CH_3), 3.57 (q, J = 7.1 Hz, 2 H, NCH_2), 4.31 (q, J = 7.1 Hz, 2 H, NCH_2), 6.15 (s, 1 H, 4′-furyl H), 7.10 (s, 1 H, 5′-furyl H), 7.42 (s, 1 H, 2′-furyl H). ^{13}C NMR (75 MHz): δ 14.4 (CH_3), 15.0 (CH_3), 48.7 (NCH_2), 54.5 (NCH_2), 106.5 (4′-furyl), 130.7 (5′-furyl), 137.6 (3′-furyl), 143.2 (2′-furyl), 217.3 (cis CO), 223.9 (trans CO), 266.7 (Cr=C). IR (film): ν 2053, 1907 cm^{-1}.

Pentacarbonyl[(diphenylamino)methylene]chromium (9). The Vilsmeier salt was prepared as previously described[20] from the formamide and 2 equiv of oxalyl chloride. Vilsmeier's salt (2.5 g, 10 mmol) and 10 mmol of $K_2Cr(CO)_5$ gave 1.7 g (35%) of carbene **9** as a yellow solid. This material was identical in all respects with authentic material.[20]

Optimization of the Synthesis of Pentacarbonyl[2-benzyl-2-azacyclohexylidene]chromium (10). The optimization procedure briefly discussed in the text was done in the following manner. A first series of experiments (fractional factorial design) was run with use of the combination of highs and lows shown in Table II. The variables and the highs (+) and lows (−) were as follows: concentration of chromium dianion (C), (+)



order number of effects (i)	1	2	3	4	5	6
corrected effects from full factorial	-3.3	-1.4	-0.2	-0.2	0.2	2.4
identity of effects	T_t	T_c	T_T	C	A_T	A_t
$P = \frac{100\,(i - 1/2)}{6}$	8.3	25.0	41.7	58.3	75.0	91.7

Figure 1. Normal plot of main effects (corrected).

Table IV. Full Factorial Design of the Four Influencing Variables (Obtained from the Screening Experiments)

variable T_t	A_T	A_t	T_c	response % yield
−	−	−	−	49.4
+	−	−	−	45.0
−	+	−	−	57.9
+	+	−	−	35.8
−	−	+	−	43.5
+	−	+	−	44.9
−	+	+	−	60.9
+	+	+	−	42.8
−	−	−	+	41.2
+	−	−	+	38.6
−	+	−	+	49.9
+	+	−	+	31.6
−	−	+	+	36.8
+	−	+	+	50.9
−	+	+	+	55.9
+	+	+	+	52.7

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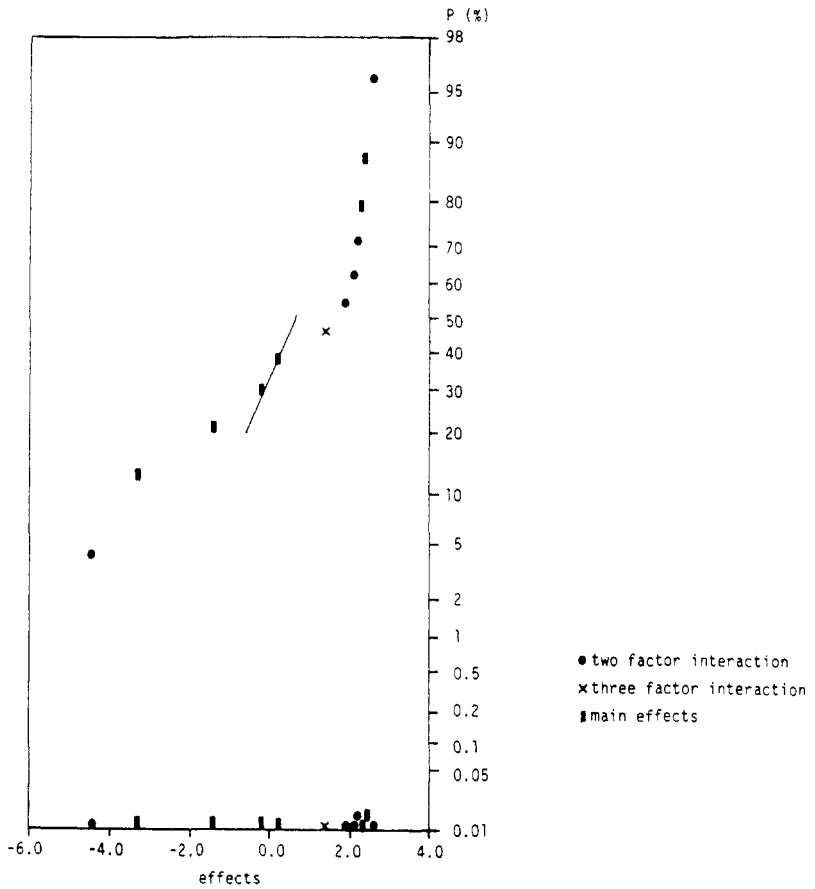
(21) Beckwith, A. L. J., Zabicky, J., Eds. *The Chemistry of Amides*; Interscience: New York, 1970; pp 73–185.



order number of effects (i)	1	2	3	4	5	6	7	8	9	10	11	12
corrected effects from full factorial	-4.4	-3.3	-1.4	-0.2*	+0.2*	1.4	1.9	2.1	2.2	2.3	2.4	2.6
identity of effects	T_tA_T	T_t	T_c	T_T	C	$T_tA_tT_c$	A_tT_c	T_tT_c	A_TA_t	A_T	A_t	T_tA_t
$P = \frac{100(i - 1/2)}{12}$	4.2	12.5	20.8	29.2	37.5	45.8	54.2	62.5	70.8	79.2	87.5	95.8

Full factorial normal plot with main effects, two factor and three factor interactions.

*Not from full factorial.

Figure 2. Normal plot of the full factorial design on four variables (A_T, A_t, T_t, T_c) plus the addition of variable effects for C and T_T that are not influencing the reaction.

0.3 M, (-) 0.1 M; temperature after addition of amide (A_T), (+) 0 °C, (-) -35 °C; time after addition of amide (A_t), (+) $1^1/_2$ h, (-) $^1/_2$ h; temperature after addition of TMSCl (T_T), (+) 25 °C, (-) -35 °C; time after addition of TMSCl (T_t), (+) $1^1/_2$ h, (-) $^1/_2$ h; number of equivalents of TMSCl vs amide (T_c), (+) 4.0 equiv, (-) 2.2 equiv. In all of these experiments a $^1/_2$-h time period was used to equilibrate the reaction mixture when it was cooled to -78 °C.

To obtain true values for the main effects of each variable (separate from two-factor and three-factor interactions), a second set of experiments was designed that would subtract the multivariable interactions from the first series of experiments. This second series of experiments was established by the use of generators[18] to complement the first set. This provided values for the main effects of each of the variables without requiring the running of a full factorial study for all six variables. These are shown in Table III. The results of these two series of experiments are displayed in the normal plot (Figure 1). In a normal plot, the point clustered around 0.0 indicate that those points do not influence the reaction, while points that deviate the most from 0.0 significantly influence the reaction. Two variables (C, T_T) were shown to not influence the reaction, while the remaining four had some influence (A_T, A_t, T_t, and T_c). A full factorial design could be obtained by utilizing the results of the two series of experiments already run for the four influencing variables. This is shown in Table IV, and the normal plot (Figure 2) shows the two-factor and three-factor interactions of these four variables. The best yield of carbene at this point was 61%.

A third series of experiments was run with use of a steepest ascent approach.[18] The variable changes and results are shown in Table V. The best yield was reproduced to obtain a 77–78% yield of carbene **10**. The optimized reaction sequence consisted of adding 0.190 g (1.0 mmol) of 1-benzylpiperidin-2-one to a precooled (-78 °C) solution of THF (3.5 mL) and 1.1 mmol of $K_2Cr(CO)_5$, stirring for $^1/_2$ h, warming to -17 °C for 1 h, cooling to -78 °C for $^1/_2$ h, and then adding 0.4 mL (3.1 mmol) of TMSCl and continued stirring for $^1/_2$ h at -78 °C. When the mixture was warmed to 25 °C, 2.5 g of neutral Al_2O_3 was added, followed by removal of solvent under reduced pressure and chromatography on silica gel to produce 0.25 g (78%) of carbene **5** as yellow crystals. This material was identical in all respects with that previously described.[7b]

Table V. Steepest Ascent Approach[a]

third series run no.	variable					response
	A_T, °C	A_t, h	T_c, equiv	T_T, °C	T_t, h	% yield
1	+17.5	1	1.3	−78	0	45.9
2	−17.5	2	1.3	−78	0	23.2
3	+17.5	2	1.3	−78	0	41.0
4	+35	$2^1/_2$	1.3	−78	0	37.0
5	+17.5	1	3.1	−35	1	63.3
6	+17.5	1	2.2	−78	0	52.6
7	0	$1^1/_2$	2.2	−78	0	3.5
8	−17.5	1	3.1	−78	0	77.7
9	−17.5	1	3.1	−78	0	72.1
10	+17.5	1	3.1	−78	0	77.1

[a] C was equal to 0.3 M in all cases.

Pentacarbonyl[2-oxacyclopentylidene]chromium (11). To a precooled (−78 °C) suspension of $K_2Cr(CO)_5$ (5 mmol) in THF (100 mL) under argon was added 4-chlorobutyryl chloride (0.705 g, 5 mmol) dropwise. The reaction was warmed to room temperature slowly overnight. After the mixture was filtered through Celite, the solvent was removed under reduced pressure, resulting in a dark brown solid. Purification by column chromatography (silica gel, 5% Et_2O–hexane) yielded the desired carbene as a yellow solid (0.710 g, 54%). This material was identical in all respects with that previously described.[12]

Pentacarbonyl[(dimethylamino)undecylcarbene]chromium (12). *N,N*-Dimethylundecylamide (910 mg, 4.0 mmol) was added to 48 mmol of $K_2Cr(CO)_5$ in 20 mL of THF at −78 °C, and the resulting mixture was stirred at that temperature for 1.25 h, warmed to 0 °C and stirred for 1 h, and cooled to −78 °C and stirred for 1.5 h. Trimethylsilyl chloride (12.0 mmol) was added, and the mixture was stirred at −78 °C for an additional $^1/_2$ h. After the mixture was warmed to room temperature, addition of Al_2O_3, removal of solvents, and column chromatography (silica gel; 1:1 hexane–CH_2Cl_2), 1.19 g (74%) of complex **12** was obtained as a pale green oil. ^{1}H NMR (270 MHz): δ 0.88 (t, J = 7.0 Hz, 3 H, CH_3), 1.19–1.24 (m, 18 H, CH_2), 3.03 (t, J = 7.8 Hz, 2 H, =CCH_2), 3.30 (s, 3 H, NCH_3), 3.82 (s, 3 H, NCH_3). ^{13}C NMR (67.9 MHz): δ 14.0 (CH_3), 22.7 (CH_3), 24.8 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 31.9 (CH_2), 41.8 (=CCH_2), 52.8 (NCH_3), 53.3 (NCH_3), 218.0 (cis CO), 223.2 (trans CO), 277.8 (Cr=C). IR (film): ν 2855, 2051, 1907 cm^{-1}. MS (EI): m/z 403 (M^+), 375 (M^+ − CO), 347 (M^+ − 2CO), 291 (M^+ − 4CO), 263 (M^+ − 5CO).

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Registry No. 1, 38893-15-1; 2, 30971-68-7; 3, 117041-11-9; 4, 112044-06-1; 5, 129174-67-0; 6, 112044-04-9; 7, 129174-69-2; 8, 129174-69-2; 9, 112068-79-8; 10, 124685-64-9; 11, 54040-15-2; 12, 129174-70-5; C_8K, 12081-88-8; $Cr(CO)_6$, 13007-92-6; $K_2Cr(CO)_5$, 107799-34-8; dimethyl formamide, 68-12-2; *N,N*-dimethylbenzamide, 611-74-5; *N,N*-dibenzylacetamide, 10479-30-8; (*S*)-2,2-dimethyl-4-phenyl-3-oxazolidinecarboxaldehyde, 112043-98-8; (*S*)-4-phenyl-3-oxazolidinecarboxaldehyde, 129174-66-9; morpholinoacetamide, 1696-20-4; *N,N*-diethyl-2-chlorobenzamide, 10345-79-6; *N,N*-diethyl-3-furancarboxamide, 73540-76-8; diphenylformamide, 607-00-1; 1-benzylpiperidin-2-one, 4783-65-7; 4-chlorobutyryl chloride, 4635-59-0; *N,N*-dimethyldodecylamide, 3007-53-2.

Reactions of the Cyanomethyl Complex $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(CH_2CN)$ and Ylide Complex $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(CH_2P(p\text{-tol})_3)]^+PF_6^-$ with *n*-BuLi/TMEDA: Generation, Stereospecific Alkylation, and Basicity of Transition-Metal-Substituted Carbanions and Ylides

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Reaction of the cyanomethyl complex $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(CH_2CN)$ (**2**) with *n*-BuLi/TMEDA (THF, −78 °C) and then $CH_3OSO_2CF_3$ stereospecifically gives (*SR,RS*)-$(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(CH(CH_3)CN)$ ((*SR,RS*)-**4**, 75%). Reaction of PPN^+CN^- and the ethylidene complex *sc*-$[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(=CHCH_3)]^+PF_6^-$ (*sc*-**8**) gives the opposite diastereomer, (*SS,RR*)-**4** (91%). The former reaction proceeds, as assayed by ^{31}P NMR spectroscopy and deuterium labeling, via the initial formation (ca. 2:1) of carbanions $Li^+[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(CHCN)]^-$ (**5**) and $(\eta^5\text{-}C_5H_4Li)Re(NO)(PPh_3)(CH_2CN)$ (**6**); **6** isomerizes to **5** thermally (−78 °C, 2.5 h) or upon addition of $CH_3OSO_2CF_3$. Complex **5** is the first observable transition-metal-substituted carbanion (IR (cm^{-1}): ν_{CN} 1980; ν_{NO} 1597) and is also stereospecifically alkylated by *n*-C_4H_9I. Equilibration reactions show the C_α acidity of **2** (THF) to be less than that of CH_3CN and comparable to that of CH_3CH_2CN. Reactions of (*SR,RS*)/(*SS,RR*)-**4** and *n*-BuLi/TMEDA give only cyclopentadienyl ligand lithiation. Reactions of the ylide complex $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(CH_2P(p\text{-tol})_3)]^+PF_6^-$ with *n*-BuLi/TMEDA (THF, −24 °C) and then $CH_3OSO_2CF_3$ (−78 °C) stereospecifically give (*SS,RR*)-$[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(CH(CH_3)P(p\text{-tol})_3)]^+PF_6^-$ ((*SS,RR*)-**16**, 83%). This transformation proceeds, as assayed by ^{31}P NMR spectroscopy, via the ylide $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(CH{=}P(p\text{-tol})_3)$. An authentic sample of (*SS,RR*)-**16** is prepared from *sc*-**8** and $P(p\text{-tol})_3$ (90%).

Organic reactive intermediates—e.g., carbanions, carbocations, radicals, carbenes—have been the focal point of innumerable studies over many years. There has been a roughly parallel development of the chemistry of transition-metal alkyl complexes. Surprisingly, little attention has been given to the generation of reactive intermediates

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