Organochromium(III) Intermediates in Reductive Dimerizations and Reductive Metatheses of Organic Substrates by Novel Chromium(I) Reagents[1]

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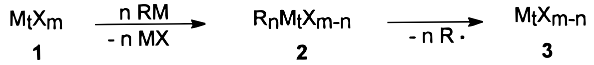
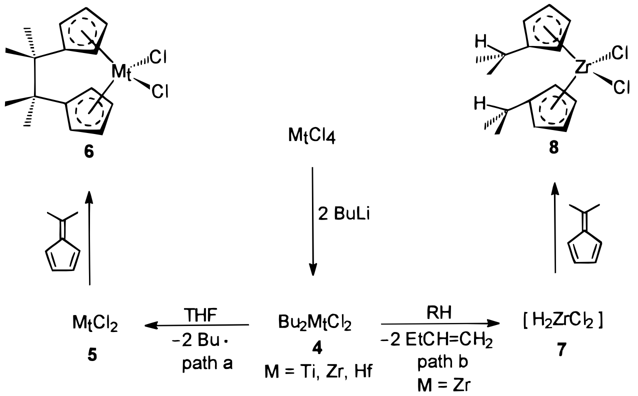
Summary: The novel reductants of empirical formulas CrCl and CrH (or its Bu_3Cr precursor) have been generated from $CrCl_3$ and either 2 equiv of butyllithium in cold THF or 3 equiv of butyllithium in hot toluene or THF, respectively. The CrCl reagent in THF readily effects the reductive dimerization of various aldehydes, ketones, acyl halides, α-halo ketones, and a gamut of benzylic halides, while CrH or its butylchromium(III) precursors in toluene bring about the reductive metathesis of polar bonds in carbonyl, epoxide, and nitro derivatives and, with nickel catalysis, in vinylic or aryl halides.

Recently we have shown that the interaction of transition metal salts (**1**) with main group metal alkyls can lead, via transition metal alkyl intermediates (**2**), to subvalent metal salts(**3**),[2] which are efficient and selective reducing agents for a broad array of organic substrates,[2,3] as well as suitable components with MAO for olefin polymerization catalysts[4] (Scheme 1). By this process, termed alkylative reduction,[2] reducing agents of the defined empirical compositions of $TiCl_2$,[2−4] $ZrCl_2$,[2] and $HfCl_2$[2] can be readily prepared in THF solution. The recently discovered, solvent-dependent kinetic stability of intermediates of type **2** now allows such partly alkylated metal salts to function as hydrometalating agents in hydrocarbons like toluene.[2,5] The convenient and versatile manner in which this solvent-dependent stability of $R_nM_tX_{m-n}$ (**2**) can be employed is illustrated for the selected synthesis of bridged or unbridged zirconocenes from the intermediate Bu_2ZrCl_2 (**4**) and the appropriate fulvene (Scheme 2). By conducting the butylation of M_tCl_4 in THF, the $Bu_2M_tCl_2$ (**4**) decomposes by reductive elimination at 25 °C to produce M_tCl_2 (**5**),[6] which effects the reductive dimerization of various fulvenes to produce *ansa*-metallocenes of titanium, zirconium, or hafnium (**6**) (path a).[7] Alternatively, if the intermediate $Bu_2M_tCl_2$ (**4**) is generated and allowed to react in a hydrocarbon like toluene,[8] it undergoes a *β*-hydride elimination and the transient H_2ZrCl_2 (**7**) hydrometalates the added fulvene to produce the unbridged zirconocene (**8**) in high yield (path b).[5] This arresting solvent effect holds great promise for the synthesis of both bridged and unbridged metallocenes,[5,7,9] as well as for the generation of selective reducing agents for organic synthesis.[2,3]

Scheme 1



Scheme 2



We now report the successful application of such alkylative reduction to chromium(III) salts and the observation of a similar solvent dependence on the alkylchromium intermediate. The interaction of 2 equiv of butyllithium with $CrCl_3$ in a THF medium at −78 °C with subsequent warming to 25 °C yielded a dark gray suspension, which was freed of all volatiles under reduced pressure.[10] The weight of the brown-black residue of **9** and its chlorine analysis by the Volhard method were consistent with the expected 1:2 mixture of CrCl and LiCl. By the IR analysis of **9** the only distinct absorptions were those of pure LiCl at 460 cm^{-1} and a strong new band at 478 cm^{-1}, which is assigned

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[1] Organic Chemistry of Subvalent Transition Metal Complexes. 18. Part 17: Eisch, J. J.; Owuor, F. A.; Shi, X. *Organometallics* **1999**, *18*, 1583.

[2] Eisch, J. J.; Shi, S.; Alila, J. R.; Thiele, S. *Chem. Ber./Recl.* **1997**, *130*, 1175.

[3] Eisch, J. J.; Shi, X.; Lasota, J. *Z. Naturforsch.* **1995**, *50b*, 342.

[4] Eisch, J. J.; Pombrik, S. I.; Shi, X.; Wu, S. C. *Macromol. Symp.* **1995**, *89*, 221.

[5] Eisch, J. J.; Owuor, F. A.; Shi, X. *Organometallics* **1999**, *18*, 1583.

[6] The gas evolved from the decomposition of Bu_2ZrCl_2 into $ZrCl_2$ in THF solution was principally butane, an observation consistent with homolysis of the C−Ti bonds to produce butyl radicals, which would readily abstract H atoms from THF.

[7] Eisch, J. J.; Shi, X.; Owuor, F. A. *Organometallics* **1998**, *17*, 5219.

[8] Although the corresponding Bu_2TiCl_2 and Bu_2HfCl_2 derivatives are undoubtedly formed when $TiCl_4$ or $HfCl_4$ is treated with 2 equiv of butyllithium in toluene, the titanium mixture rapidly turns blue-green, signaling reduction to $BuTiCl_2$, and the hafnium mixture more slowly reacts with carbonyl derivatives as evidenced by a slower evolution of 1-butene.

[9] For the status of previously known methods of metallocene synthesis the following recent monograph can be consulted: Long, N. J. *Metallocenes—An Introduction to Sandwich Complexes*; Blackwell Science: Oxford, 1998; 285 pp.

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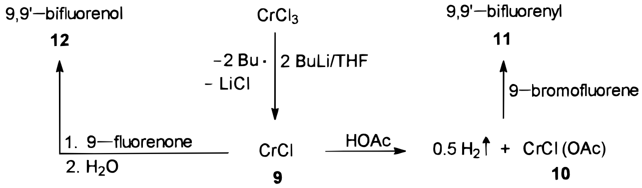
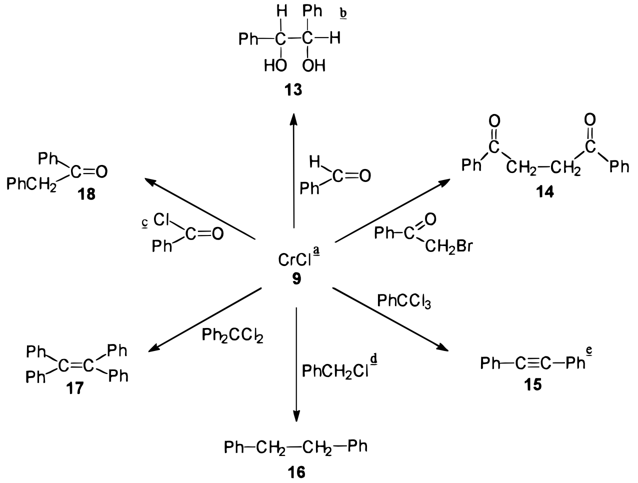
Scheme 3



to the Cr−Cl stretch.[11] From these observations we conclude that **9** is a physical mixture of LiCl and a chromium complex of empirical formula CrCl. Furthermore, the chromium(I) oxidation state of the chromium component in **9** is based upon the following observations: (1) treatment of **9** admixed with LiCl with glacial acetic acid produced 0.5 mol (±0.05 mol) of H_2 at STP, and the acetolysate thereby formed was able to couple 2 equiv of 9-bromofluorene to 9,9′-bifluorenyl (**11**) in over 40% yield (theoretical: 50%), corroborating the presence of chromium(II) (**10**), a one-electron reductant;[12a] (2) the brown solid gives a somewhat broadened ESR singlet with a g value of 2.00, consistent with the presence of a symmetrical ^{6}S state of a d^5 system,[12b] and (3) 1 equiv of **9** reacts with 2 equiv of 9-fluorenone to give upon hydrolysis 88% of 9,9′-bifluorenol (**12**) and 2% of 9-fluorenol, an observation in keeping with **9** functioning as a two-electron reductant (cf. Scheme 3). The foregoing chemical and spectroscopic measurements are in accord with the empirical formula of CrCl for this novel chromium reagent, but definitive conclusions about its state of aggregation and global structure must await an X-ray structure determination.

Scheme 4



[a] The included products were obtained upon hydrolytic workup in nonoptimized yields under reaction conditions specified in Table 1. [b] With aldehydes and unsymmetrical ketones, the racemic isomer was always the major product, the racemic:meso ratio ranging from 2.5:1.0 to 6:1. [c] Some benzil was also formed. [d] When this homocoupling was conducted in the presence of 1 equiv of 9-fluorenone, up to 10% of the product was 9-benzyl-9-fluorenol, evidence for the organometallic intermediate, $PhCH_2CrCl_2$, formed from **9** by oxidative addition. [e] No trace of hexaphenylbenzene formed; in fact, this alkyne proved completely inert to **9** in refluxing THF or octane.

Although there have been numerous and extensive reports upon the applications of chromium(II) and chromium(III) reagents in organic synthesis,[13] the present finding represents, to our best knowledge, the first discovery of the great and variegated value of chromium(I) reagents for the selective formation of carbon−carbon and carbon−hydrogen bonds.[14] The unpurified CrCl (**9**) produced from $CrCl_3$ in THF can be used for a wide variety of reductive dimerizations in high yield, such as those portrayed in Scheme 4 and listed in Table 1. Three observations support the intermediacy of organochromium complexes in these reductive dimerizations: (1) the preponderance of the racemic isomer over the meso isomer in the homocoupling of aldehydes or unsymmetrical ketones;[2] (2) the isolation of 9-deuterio-9-fluorenol as the byproduct formed from the reaction of 9-fluorenone with an excess of **9** and after workup with DOAc; and (3) the formation of 9-benzyl-9-fluorenol when the homocoupling of $PhCH_2Cl$ was attempted in the presence of 9-fluorenone.[15]

In contrast with the reactivity of **9** to polar, unsaturated organics, the CrCl complex undergoes reductive metathesis with C−X, C−O, and C−N linkages only slowly. However, such sluggish reactivity can be compensated effectively by the addition of catalytic amounts of nickel(II) salts to the preformed CrCl in THF, thereby generating the actual nickel(0) catalyst[16] (Table 2). An alternative, equally effective method of accelerating such reductive metatheses consists of producing butylchromium(III) reagents by treating a suspension of $CrCl_3$ in hot toluene with 2 or 3 equiv of butyllithium, thereby generating Bu_nCrCl_{3-n} ($n = 2$ or 3), which have sufficient kinetic stability in toluene to act as hydro-

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(10) Separate condensation of the volatiles from THF gave a liquid which decolorized Br_2 in CCl_4 and whose IR spectrum exhibited absorptions at 1639 cm^{-1} (C═C) and 3040 cm^{-1} (═C−H) expected from the presence of 1-butene. The 10−40 ppm region of the ^{13}C spectrum supported the presence of butane.

(11) This assigned frequency for the Cr−Cl stretch in CrCl is appropriately less than that stretch of 494 cm^{-1} reported for $CrCl_2$, and such lowering of the frequency is consistent with the lower nuclear charge. No IR peaks indicative of free or coordinated THF could be observed, nor any absorption in the 1500−1600 cm^{-1} region attributable to a metal−hydrogen stretch. The physical mixture of CrCl + 2LiCl can slowly be freed of LiCl by Soxhlet extraction of the CrCl from the mixture by a long-term extraction with a THF−toluene pair, but such purification is unnecessary for efficient reduction of various organic substrates.

(12) (a) The presence of **10** in the acetolysate was confirmed by adding 9-bromofluorene and obtaining a 42% yield of 9,9′-bifluorenyl (theoretical 50%). The reagent, $CrCl_2$, is such a known radical reductant in the Nozaki−Kishi−Hiyama reaction (Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349). Further leading references on chromium(II)-mediated organic syntheses: Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3180. Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. Jubert, C.; Nowotny, S.; Kornemann, D.; Antes, I.; Tucker, C. E.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 6384. (b) The authors are indebted to Professor David C. Doetschman of this Department, who assisted us in performing such ESR measurements and interpreting the results with the facilities of the NSF Regional Center for Pulsed EPR and Photochemical Studies, of which he is the director.

(13) (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1.

(14) Reductive coupling of benzylic halides has been achieved previously with chromium(0) complexes such as $Cr(CO)_3(NH_3)_3$: Wey, H. G.; Butenschön, H. *Chem Ber.* **1990**, *123*, 93.

(15) The intermediates suggested by these chemical trapping experiments, namely, an oxachromacyclopropane, from 9-fluorenone (Ar_2C═O) and **9**, and $PhCH_2CrCl_2$, from $PhCH_2Cl$ and **9**, would account for the isolation of 9-dideuterio-9-fluorenol from the former reaction after treatment with DOAc and for the formation of 9-benzyl-9-fluorenol from the latter reaction after reaction with 9-fluorenone.

(16) Nickel(0) complexes readily cleave, via oxidative addition, a wide variety of C−S, C−X, C−N, C−O, and even C−C bonds; for a leading reference to the extensive literature, cf.: Eisch, J. J.; Aradi, A. A.; Lucarelli, M. A.; Qian, Y. *Tetrahedron−Symposium-in-Print* **1998**, *54*, 1169.

Table 1. Reductive Dimerizations of Various Unsaturated Organic Substrates by Chromium(I) Chloride, CrCl (9), in THF

substrate[a]	ratio (S:**9**)	product	yield, %
benzaldehyde	1:2	PhCHOH−CHOHPh[b]	93
	2:1	PhCHOH−CHOHPh[c]	87
acetophenone	2:1	PhCMeOH−CMeOHPh[d]	46
benzophenone	1:1 or 2:1	$Ph_2COH-COHPh_2$[e]	10
9-fluorenone	2:1	9,9′-bifluorenol[f]	98
benzyl chloride	1:2	$PhCH_2-CH_2Ph$	95
PhCHMeBr	2:1	PhCHMe-CHMePh[g]	81
9-bromofluorene	2:1	9,9′-bifluorenyl[h]	96
α,α′-dichloro-*o*-xylene	2:1	1,2,5,6-dibenzocyclooctane[i]	40
$PhCHCl_2$	1:2	PhCH═CHPh[j]	80
Ph_2CCl_2	1:3	$Ph_2C=CPh_2$	98
$PhCCl_3$	1:1	$PhCCl_2-CCl_2Ph$[k]	58
$PhCCl_3$	1:3	PhC≡CPh[l]	100
α-bromoacetophenone	2:1	1,4-diphenyl-1,4-butanedione[m]	79
benzoyl chloride	2:1	1,2-diphenylethanone[n]	64
1,1-diphenylethene	1:2	2,2,3,3-Tetraphenylbutane[o]	33

[a] Reactions conducted in THF at 25 °C or at reflux for 12−24 h or 3−4 h, respectively; yields not yet optimized. [b] Racemic:meso ratio of 2.6:1.0; 1% $PhCH_2OH$. [c] Racemic:meso ratio of 6.0:1.0; <1% $PhCH_2OH$. [d] Racemic:meso ratio of 3.0:1.0; 4% PhMeCHOH. [e] Also 1% Ph_2CHOH; in Et_2O products were $Ph_2COH-COHPh_2$ (26%), Ph_2CHOH (34%), and $Ph_2C=CPh_2$ (1%). [f] Also 2% 9-fluorenol. [g] Racemic:meso ratio of 1:1; <1% PhEt. [h] Also 4% fluorene. [i] Other oligomers with and without benzocycloalkane rings formed. [j] A 19:1 mixture of *E* and *Z* isomers. [k] Also 33% recovered $PhCCl_3$. [l] No trace of hexaphenylbenzene; in fact, separate reactions of PhC≡CPh and **9** in refluxing THF or in PhMe gave no cyclotrimer. [m] Also 3% PhMeC═O. [n] Less than 1% of benzil or benzoic acid. [o] Also 2% Ph_2CHCH_3.

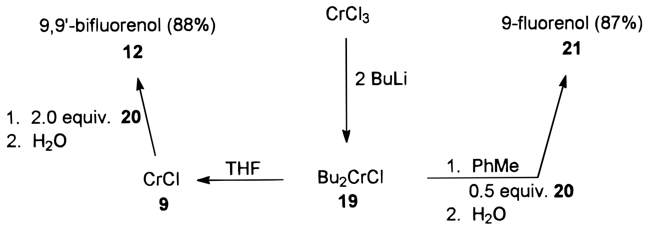
Table 2. Reductive Metatheses of Various Carbon−Heteroatom Linkages with Nickel-Catalyzed CrCl (9) Reagents in THF or with Dibutylchromium(III) Chloride (19) in Toluene

substrate	product	yield, %
Chromium(I) Chloride (**9**) Catalyzed by Nickel in THF[a]		
2-bromobiphenyl (no Ni)	biphenyl	20
2-bromobiphenyl (5% Ni)	biphenyl	92
4-bromotoluene (no Ni)	toluene	0
4-bromotoluene (5% Ni)	toluene	84
iodobenzene (no Ni)	benzene	1
iodobenzene (5% Ni)	benzene	95
Dibutylchromium(III) Chloride in Toluene[b]		
9-fluorenone	9-fluorenol	87
4-bromotoluene	toluene	90
benzalaniline	*N*-benzylaniline	95
styrene oxide	2-phenylethanol	98
benzonitrile[c]	benzaldehyde	75
dibenzothiophene	biphenyl	60
4-nitrobenzophenone[c]	4-aminobenzophenone	64

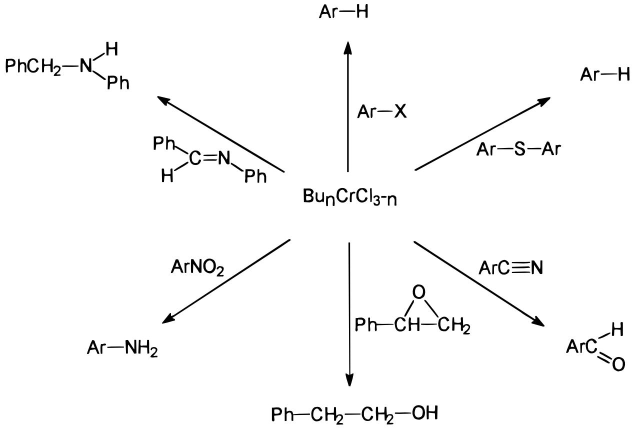
[a] Catalyst: nickel(II) acetylacetonate (5% of the millimoles of $CrCl_3$ employed). [b] The $CrCl_3$ suspended in toluene was treated with 2 molar equiv of BuLi and the resultant mixture heated at reflux for 2 h to yield a gray suspension; the substrate was added and the reduction conducted at 25 °C (superscript *c*) or at reflux (no superscript).

chromating agents via olefin elimination (cf. behavior of $Bu_2M_tCl_2$ (**4**) depicted in Scheme 2).[5,17] Evidence for the presence of Bu_2CrCl (**19**) in toluene can be readily grasped from Scheme 5: the bimolecular reduction of 9-fluorenone (**20**) by **9** in THF is essentially completely switched over to monomolecular reduction by hydrochromation via **19** in toluene.[18] The butylchromium(III) generated in toluene can be utilized (with or without Ni(0) catalysis) to achieve a wide variety of reductive metatheses (Scheme 6 and Table 2).

Scheme 5



Scheme 6



In conclusion, the interaction of $CrCl_3$ with 2 equiv of butyllithium in THF has been shown to provide a convenient and straightforward source of chromium(I) chloride,[19] a highly selective reductive dimerization agent for aldehydes, ketones, acyl halides, α-halo ketones, and diverse allylic halides and, when accompanied by nickel(II) catalysts, a most useful reagent for the monomolecular reductive metathesis of certain C−X, C−O, C−N, and N−O bonds. By the simple variant of conducting the interaction of $CrCl_3$ and butyllithium (1:2 or 1:3) in toluene, kinetically stable Bu_nCrCl_{3-n} intermediates can be generated which are capable of cleaving C−E or C═E bonds by chromium hydride transfer.

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(17) When the reaction of a fine suspension of $CrCl_3$ with 2 or 3 equiv of butyllithium was conducted in warm toluene, gray suspensions were formed with little gas evolution, observations consistent with the formation of Bu_2CrCl or Bu_3Cr, respectively. Further heating of such suspensions of Bu_3Cr at reflux in toluene led to the evolution of 1-butene and butane and a darkening of the suspended solid toward black. Acetolysis of such black solids generates principally 1.0−1.5 equiv of H_2, consistent with the presence of Cr and/or CrH, respectively (F. A. Owuor). In unpublished work we have further ascertained that such CrH can be stabilized and isolated as a complex with LiH (cf. ref 2). The relative importance of Bu_3Cr, Bu_2CrCl, and CrH in effecting the reductive metatheses depicted in Scheme 6 and cited in Table 2 has not yet been determined.

(18) Accompanying the formation of 88% of 9,9′-bifluorenol (**12**) in THF was only 2% of 9-fluorenol (**21**). Conversely, in toluene the 87% yield of 9-fluorenol (**21**) contrasted with 1% of **12**.

(19) It should be noted that the potential of CrCl for effecting the reductive dimerization of fulvenes for the production of *ansa*-chromocenes (cf. ref 7) is currently being evaluated in this laboratory: Eisch, J. J.; Owuor, F. A.; Wang, J. Unpublished studies. For a previous *ansa*-chromocene synthesis: Schwemlein, H.; Zsolnai, K. L.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1983**, *256*, 285.