Carbon−Carbon Bond Formations Involving Organochromium(III) Reagents

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Contents

Alois Fürstner made his Ph.D. in 1987 at the Technical University of Graz, Austria, under the supervision of Prof. H. Weidmann. After postdoctoral research with Prof. W. Oppolzer at the Université de Genève, Switzerland, he completed his habilitation at the TU Graz in 1992. In 1993 he became group leader at the Max-Planck-Institut für Kohlenforschung in Mülheim, Germany, where he was appointed as a Director at the Institute and Scientific Member of the Max-Planck-Society in 1998. Since 1993 he has been lecturing at the University of Dortmund. He received a fellowship of the Fonds der Chemischen Industrie and was awarded the Leibniz Preis of the Deutsche Forschungsgemeinschaft. His research interests are focused on organometallic chemistry and catalysis and the application of these tools to natural product synthesis.

I. Introduction and Scope

The utility of chromium salts for organic synthesis was recognized during the last century, and the preparation of organochromium compounds was attempted early on. Among these pioneering studies, the famous experiments by Hein concerning the transmetalation of phenyl Grignard reagents with $CrCl_3$ in diethyl ether are most notable, although neither the available analytical methods nor the theoretical understanding of a chemical bond at that time permitted determination of the structure of the resulting bis(benzene)chromium species.[1] The correct interpretation of the π-bonding situation in this product and the missing link between σ-bond and π-bond arenechromium reagents were found much later in the mid 1950s.[2,3]

At about the same time, Anet and Leblanc were the first to prepare aqueous solutions of benzylchromium compounds by reaction of Cr(II) with benzyl chloride.[4] Subsequent kinetic and spectroscopic studies by Kochi et al. on this new and complementary approach to organochromium reagents have shown that the formal oxidative addition of Cr(II) into a C−X bond of a benzyl or alkyl halide proceeds by two consecutive single electron transfer (s.e.t.) events.[5,6] The fact that distinct (although rather short-lived) radical species precede the formation of organochromium(III) nucleophiles accounts for some of the peculiarities of Cr(II)-mediated additions of organic halides to various electrophiles.

A preliminary screening of the reactivity of benzylchromium and related reagents has been carried

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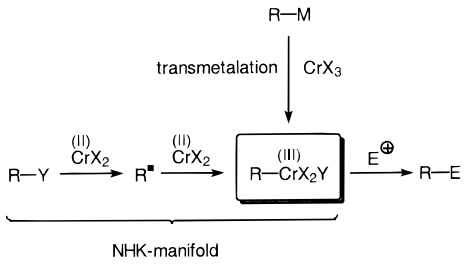
Scheme 1



out by the same authors, although it was a series of seminal papers authored by Nozaki and Hiyama et al. starting in 1977 that triggered an explosive development of this particular branch of organometallic chemistry. This group has demonstrated in great detail that Cr(II) readily inserts into allyl-, alkenyl-, alkynyl-, propargyl-, and aryl halides or sulfonates under *aprotic* conditions, giving rise to the corresponding organochromium(III) reagents, which are well behaved nucleophiles for selective organic transformations.[7−11] In 1986, Kishi et al.[12] and Nozaki et al.[13] independently and almost simultaneously discovered that traces of nickel salts exert a catalytic effect on the formation of the C−Cr(III) bond. This finding has significantly improved the reliability of these "one-pot Barbier type" addition reactions, and doping of $CrCl_2$ with catalytic amounts of Ni(II) became a standard trick for reactions involving less reactive substrates such as alkenyl and aryl halides or triflates.

As will become evident in more detail from the present review, Cr(II) or Cr(II)/Ni(II)-mediated reactions of this type are distinguished by a rather unique combination of chemical features. Most notable among them are (i) the broad range of substrates amenable to insertion of Cr(II) under mild conditions, accounting for the remarkably wide scope of this methodology; (ii) the pronounced chemoselectivity of organochromium intermediates for reactions with aldehydes as the electrophilic reaction partners; (iii) the strong driving force for such additions, which stems from the formation of highly stable O−Cr(III) bonds. This chemical incentive can be exploited to build up strain in the organic products; (iv) a superb compatibility with an array of different functional groups in *both* reaction partners, allowing to maintain various electrophilic groups intact within the organochromium nucleophiles; (v) a low basicity of organochromium(III) reagents; (vi) distinct stereochemical preferences, particularly in reactions of crotylchromium reagents; (vii) a simple setup and an excellent reliability even if applied to sensitive and polyfunctional compounds.

This unrivaled profile renders "Nozaki−Hiyama−Kishi" (NHK) reactions an indispensable tool for advanced organic synthesis, as witnessed, inter alia, by a rapidly growing number of applications to the total synthesis of target compounds of utmost complexity.

This review is meant to summarize the present state of the art of this and related chemistry.[14] It will also cover C−C bond formations with substrates other than organic halides or sulfonates involving a related Cr(II)−Cr(III) manifold. The data are organized according to the structure of the organochromium(III) reagents involved. Moreover, reactions of organochromium(III) species prepared by transmetalation routes are also included for comparative reasons. It should be noticed, however, that the transmetalation route, in contrast to the NHK protocol, usually does not allow to incorporate electrophilic sites into the organochromium nucleophile and is therefore less generally applicable. The literature is covered from 1977 (Nozaki's initial report)[7] to 1997. Some references dating from early 1998 are also included, although 1998 cannot be covered comprehensively.

It is emphasized that other prosperous fields of organochromium chemistry do not fall within the scope of this review. This refers in particular to addition polymerization reactions of terminal alkenes catalyzed by (supported) organochromium species[15,16] as well as to C−C bond formations involving either Fischer-type chromium carbenes, bis(arene) chromium compounds, or arene−$Cr(CO)_3$ complexes.[17] Simple reductions or reductive eliminations of functional groups induced by Cr(II), although preparatively highly useful, are also excluded,[18] as are papers dedicated to structural aspects of organochromium compounds.[19]

II. Chromium Salts and Setup of the Reactions

A. Stoichiometric Reactions

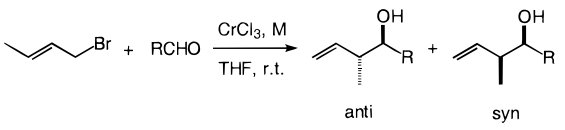
Anet and Leblanc have applied $Cr(ClO_4)_2$ for the preparation of benzylchromium reagents via oxidative addition.[4] For solubility reasons, however, the use of this salt is essentially confined to aqueous reaction media, e.g., as an excellent reagent for the cyclization of ω-unsaturated alkyl halides via alkyl-radical intermediates.[20]

With this limitation in mind, part of the success of Nozaki's work must be attributed to the fact that these authors introduced and systematically exploited $CrCl_2$ as the reagent for the preparation of organochromium reagents.[7−11] Because this salt is at least partly soluble in polar organic solvents, it has helped to expand the scope of organochromium chemistry to transformations requiring strictly anhydrous conditions. $CrCl_2$ is now by far the most widely used reagent for the preparation of organochromium reagents by oxidative addition.

$CrCl_2$ is a rather air-sensitive and hygroscopic pale gray powder which must be handled using Schlenk techniques. To ensure reproducible results, samples of high qualtity and purity should be used, whereas greenish lots may result in poor results or even in complete failure. $CrCl_2$ may either be purchased or can be prepared easily (in situ) from cheap $CrCl_3$ and various reducing agents.

Many literature data, at first sight, seem to indicate little differences in the performance of commercial $CrCl_2$ and that obtained by (in situ) reduction of $CrCl_3$. It is, however, advisable to pay some

Table 1. Influence of the Reducing Agent on Stereoselectivity[25]



R	$CrCl_3$/Zn		$CrCl_3$/Na(Hg)	
	Yield (%)	*anti:syn*	Yield (%)	*anti:syn*
c-C_6H_{11}	n.r.	n.r.	77	7.4:1
$PhSCH_2CH_2$	87	2.1:1	81.5	9.0:1
$AcOCH_2CH_2$	59	1.3:1	n.r.	n.r.
Ph	95	2.6:1	85	10.3:1
$PhCH_2$	80	1.4:1	n.r.	n.r.
$BnOCH_2CH_2$	n.r.	n.r.	75	15.9:1
PhCH=CH	80	1.4:1	91.4	4.7:1
n-$C_{11}H_{23}$	89	2.5:1	n.r.	n.r.
2-furyl	n.r.	n.r.	99	7.7:1
2-thienyl	n.r.	n.r.	93.2	6.6:1
3-pyridyl	n.r.	n.r.	71	5.5:1

attention to the provenance of the sample as well as to the proper choice of the reducing agent. In many cases, $LiAlH_4$ (originally used by Nozaki and Hiyama),[7] Zn, Na(Hg), or Mn are employed, but other reducing agents such as $LiBEt_3H$ may also be appropriate.[21] The use of electric current for similar purposes will be discussed in section II B. Noticeable differences in the outcome of the reactions must be expected in all cases in which the Lewis acidity of the admixed salts produced during the reduction step (LiCl, aluminum halides, $ZnCl_2$, etc.) affects the reactivity of acid sensitive substrates.[22−24] Moreover, admixed salts can alter the stereochemical course of NHK reactions, particularly with polyfunctional compounds in which chelation/nonchelation manifolds dictate the stereochemical outcome. As can be seen from a comparative study compiled in Table 1, the use of Zn as a reducing agent for $CrCl_3$ provides consistently lower anti:syn ratios than the use of Na(Hg).[25] Furthermore, some care must be taken with preparations of $CrCl_2$ employing $LiAlH_4$. It has been emphasized that the reduction of $CrCl_3$ with this particular reducing agent may remain incomplete, especially when carried out on a larger scale. Any unreacted $LiAlH_4$, however, will rapidly reduce the aldehyde substrate and must therefore lower the yields of the desired addition product.[25] This aspect also defines the optimum ratio between $LiAlH_4$ and $CrCl_2$ as 1:2, which should be carefully adhered to.[8]

In the same context, the reader is referred to a convenient synthesis of $CrCl_2(THF)_n$ ($n = 0-2$) from cheap $CrCl_3$ and metallic Cr powder as described by Jolly et al.[26] This reduction can be performed on a large scale and ensures that no extraneous metal salts contaminate the reagent. This preparation may help to standardize NHK-type reactions, although it has not yet been widely applied.

$CrBr_2$ prepared in situ from $CrBr_3$ and $LiAlH_4$ was found advantageous in reactions of certain organic bromides that are prone to Finkelstein exchange with the chloride ions of $CrCl_2$.[27,28] Some scattered reports on the use of CrI_2 can also be found in the literature, but no significant benefits have been ascribed to this reagent.[101]

$Cr(OAc)_2$ is a common reducing agent in organic chemistry for different types of functional groups[29] and has gained some popularity for dehalogenation reactions[18] as well as for the reaction cascades comprising the radical addition/organochromium reagent formations discussed in section X.

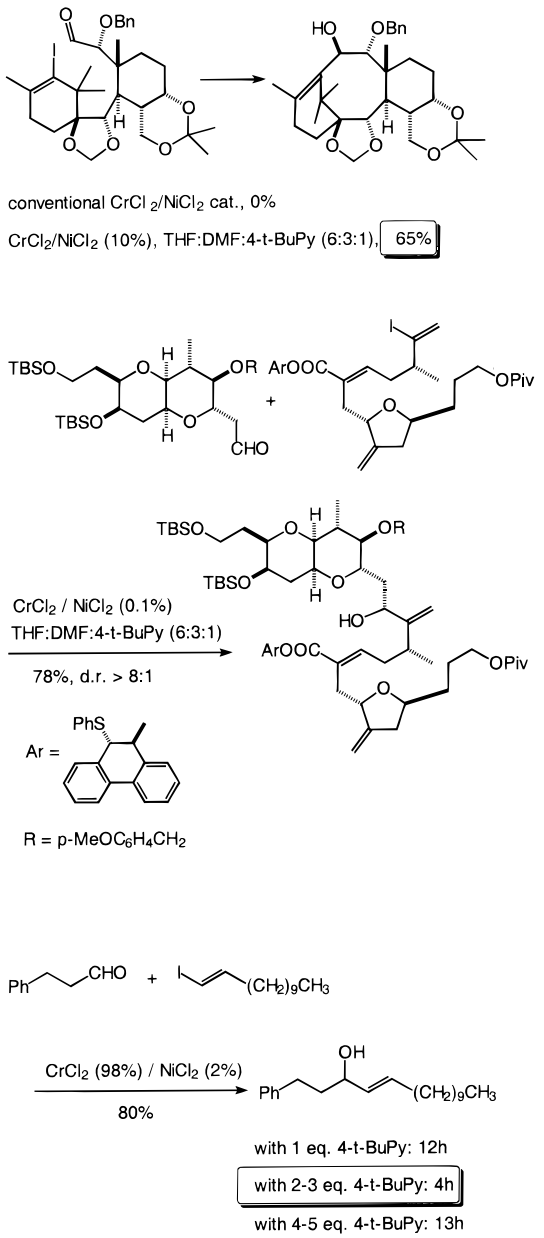
An important issue is the stoichiometry of NHK reactions. Cr(II) is a one-electron donor, and, therefore, 2 mol of the salt per 1 mol of organic halide (triflate, etc.) is required for the formation of any organochromium(III) nucleophile. In practice, however, Cr(II) is generally used in (large) excess. This is particularly true for intramolecular coupling reactions carried out under high dilution conditions, to increase the likelihood of reactive encounters of the substrate and the reagent. Examples using up to several hundred equivalents of $CrCl_2$ relative to the substrate have been reported.[30,31] Because chromium (as well as admixed nickel) salts are physiologically highly suspicious, it is clear that the development of catalytic versions of the NHK reaction is desirable. Section II B summarizes the current status in this field.

It is well established in the literature that the reduction power of Cr(II) and hence its propensity for oxidative insertion can be enhanced by complexation with donor ligands. Amines such as ethylenediamine and TMEDA have been studied in some detail.[32−34] It is therefore highly recommended to pay attention to the purification and drying of the solvents used in any kind of NHK reaction in order to get reproducible results. This is particularly true for reactions in DMF, as this solvent frequently contains traces of amine impurities. Amine-free DMF giving excellent and well reproducible results can be obtained, e.g., by distillation of predried DMF over a mixture of Desmodur-15 (a polyphenylisocyanate produced by Bayer AG) and dibutyl tinlaurate at 70−80 °C under reduced pressure.[35]

The ligand dependent redox potential of Cr(II) may also account for distinct solvent effects observed in many NHK reactions. In the original report of Hiyama and Nozaki et al.,[7] THF and DMF were tested as solvents. While reactions with allylic bromides or iodides were found to proceed in THF without incident, the latter medium was recommended for all applications to less reactive substrates (allyl chlorides, tosylates, etc.). This was ascribed to the fact that DMF dissolves the Cr(II) salt to a higher extent and likely modulates its reducing ability. Likewise, DMF or DMSO is usually employed for reactions of alkenyl and aryl halides (triflates) which also show a lower propensity for oxidative insertion of Cr(II). Kishi has mentioned that DMSO gives cleaner results at the expense of lower reaction rates,[36] although this observation may not be completely general.

In many cases, solvent mixtures turned out to be advantageous. A notable example is the addition of alkenyl iodides (triflates) to aldehydes using *catalytic* amounts of $CrCl_2$ in combination with Mn(0) and

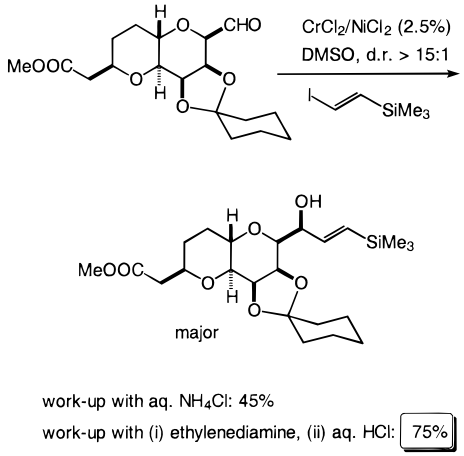
Scheme 2



TMSCl (cf. section II B);[35] in this particular case, a mixture of DME/DMF = 20/3 turned out to be optimal. Similarly, THF containing 1 equiv of DMF relative to $CrCl_2$ turned out to be best suited for $CrCl_2$-mediated olefination reactions of aldehydes with $Bu_3SnCHBr_2$ to afford (*E*)-configured vinylstannanes,[37] whereas 1,4-dioxane/THF = 6/1 is recommended for Takai−Utimoto olefination reactions of aldehydes with CHI_3 to afford (*E*)-configured vinyliodides with high selectivity.[38] It has also been described that the addition of alcohols such as i-PrOH as cosolvents can upgrade addition reactions involving organochromium(III) species.[39−41,154]

A particularly interesting and widely applicable modification of the standard reaction conditions was recently outlined by Kishi et al.[42] These authors play with the effect exerted by 4-*tert*-butylpyridine (2−5 equiv per Cr(II)), which significantly upgrades reactions of alkenyl halides mediated by $CrCl_2/NiCl_2$ cat. Specifically, this additive (i) seems to selectively solubilize the Cr(II), thus minimizing problems related to heterogeneous reaction mixtures, (ii) largely suppresses the undesirable homocoupling of the alkenyl halides, particularly in reactions requiring a high content of Ni(II),[42] and (iii) turned out to promote even those reactions which failed under conventional conditions as evident from the example related to a paclitaxel synthesis employing a tetrasubstitued alkenyl iodide as the substrate. The modified procedure has also significantly improved one of the key steps of a convergent synthesis of halichondrin B, a promising antitumor agent (Scheme 2) (cf. section III D).[43] In the same paper, Kishi et al. recommend a modified workup procedure which consists of the addition of a metal sequestering agent (e.g., aqueous ethylenediamine or aqueous sodium or potassium serinate) prior to extraction with aq HCl/ethyl acetate. This protocol results in a much better mass recovery as examplified by the reaction shown in Scheme 3.[42,67]

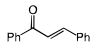
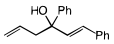
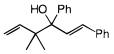
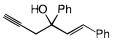
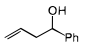
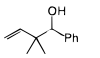
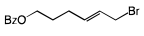
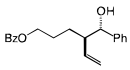
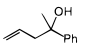
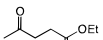
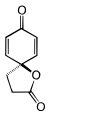
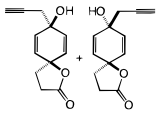
Scheme 3



Despite the popularity and widespread use of organochromium reagents in organic synthesis, very little work has been devoted to the use of chromium sources other than simple CrX_2 salts. A notable exception is a report by Wipf et al. claiming that the use of Ph_2Cr(TMEDA) leads to a unique rate enhancement and allows to perform NHK reactions at temperatures as low as −60 °C (Table 2).[44] The reagent is prepared immediately prior to use by adding PhMgBr (2 equiv) to a suspension of commercial $CrCl_2$ in THF in the presence of TMEDA (1 equiv) as a pale-brown, homogeneous solution. The authors state that no phenyl group transfer occurs under the reaction conditions, and that biphenyl is the major byproduct formed. Propargyl halides cleanly afford homopropargylic rather than allenylic alcohols under these conditions. This modified procedure was also recommended for 1,2-additions to enones, which are sometimes sluggish when carried out under conventional NHK conditions.[44]

The use of Cp_2Cr and $CpCrCl_2$ as mediators was launched during a study on NHK reactions catalytic in chromium[35] and will therefore be summarized in the following section.

Table 2. Ph_2Cr(TMEDA)-Mediated Additions of Organic Halides to Carbonyl Compounds Performed at −60 °C[44]

Carbonyl Compound	Halide	Product	Yield (%)
	allyl iodide		77
	prenyl bromide		83
	propargyl bromide		92
PhCHO	allyl iodide		86
	prenyl bromide		89
			60
PhCOMe	allyl iodide		76
	prenyl bromide		83
	propargyl bromide	 1.5 : 1	57

B. Chromium-Catalyzed Processes

The addition of an organochromium nucleophile to a carbonyl compound leads to the formation of a chromium alkoxide as the primary product. The high stability of the resulting O−Cr(III) bond serves as the thermodynamic sink that drives the conversion and can be used to compensate for considerable strain energy build up in the organic product. At the same time, however, the chromium alkoxide sequesters the metal salt and therefore renders NHK reactions catalytic in chromium a most difficult task.

As outlined in section II A, stoichiometric NHK reactions require 2 mol of Cr(II) per 1 mol of organic halide (triflate, etc.) for the formation of the nucleophile; in practice, however, Cr(II) is generally used in (huge) excess. Because of the toxicity of chromium and nickel salts, a catalytic version of the Nozaki−Hiyama−Kishi reaction is desirable.

Recent investigations by Fürstner et al. have addressed this issue.[35,45] The key feature of their modification consists of the silylation of the chromium alkoxide species initially formed by means of R_3SiCl, to release the metal salt from the organic product. The liberated Cr(III) can then be rereduced in situ to the active species by means of a stoichiometric and nontoxic reducing agent. Cheap, commercial Mn powder serves this purpose very well because it forms an efficient redox couple with Cr(III)[46] but does not react on its own with organic compounds.[47] Furthermore, the accumulating Mn(II) salts are essentially nontoxic and exhibit rather weak Lewis acidity.

The basic catalytic cycle for Nozaki−Hiyama−Kishi reactions employing CrX_n cat. (n = 2, 3), Mn (0), and a chlorosilane as the mediator is *formally* depicted in Scheme 4. It should be emphasized that this overall process does not imply that each individual step exactly follows the displayed order and rationale. Anyway, this catalytic setup turned out to be applicable to all types of Cr(II)-mediated reactions without compromising the yield, the chemo- and diastereoselectivity, or the compatibility with various functional groups.[35] Specifically it (i) applies to (functionalized) allyl-, alkenyl-, alkynyl-, and aryl halides as well as to alkenyl triflates as the substrates (Tables 3−5, Scheme 6); (ii) requires cocatalytic amounts of $NiCl_2$ when applied to alkenyl- and aryl halides but proceeds readily with undoped $CrCl_2$ in

Scheme 4

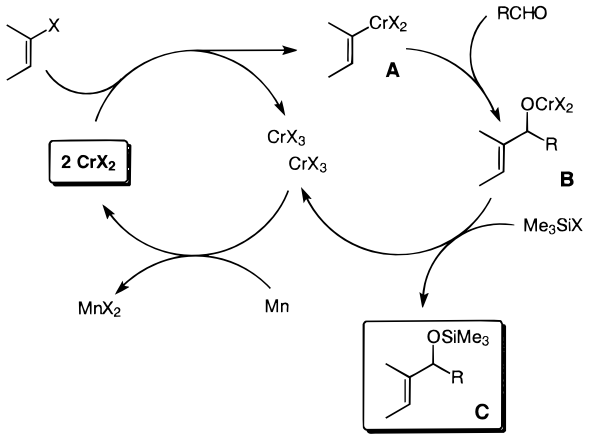
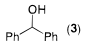
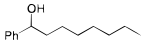
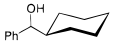
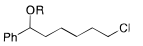
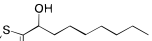
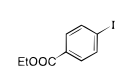
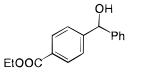
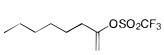
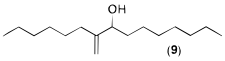
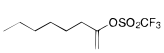
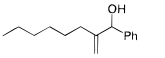
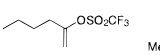
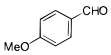
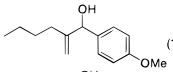
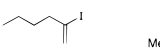
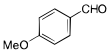
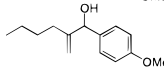
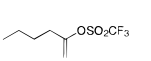
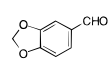
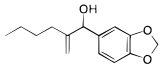
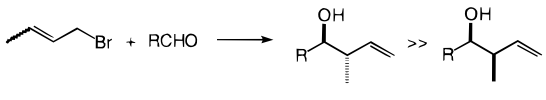


Table 3. Chromium-Catalyzed Reactions of Aryl Iodides, Alkenyl Iodides, and Alkenyl Triflates with Different Aldehydes[a] [35]

R-X	Aldehyde	Product	Yield (%) [b]	
			$ClMe_2SiR$ [c]	Me_3SiCl
PhI	PhCHO	 (3)	88	62
PhI	$CH_3(CH_2)_6CHO$	 (1a)	72	67
PhI	$C_6H_{11}CHO$	 (4)	71	
PhI	$Cl(CH_2)_5CHO$	 (5) R = Ac (6) R = H		66[c]
	$CH_3(CH_2)_6CHO$	 (7)	57	
	PhCHO	 (8)		57[d]
	$CH_3(CH_2)_6CHO$	 (9)		61
	PhCHO	 (10)		67
		 (11)		76
		 (11)		75
		 (12)		80

[a] All reactions were carried out with $CrCl_2$ (15 mol %, doped with cat. $NiCl_2$), Mn powder (4.2 mmol), aldehyde (2.5 mmol), R−X (5 mmol), chlorosilane (6 mmol) in DMF/DME (20/3) at 50 °C. [b] Refers to the product obtained after desilylation (aqueous Bu_4NF) of the crude mixture. [c] Refers to $ClMe_2Si(CH_2)_3$-CN as the silylating agent.

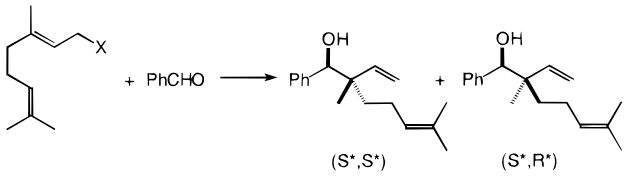
Table 4. Chromium-Catalyzed Reactions of Crotyl Bromide with Different Aldehydes[35]



anti *syn*

crotyl bromide	R	CrX_n cat.	Additives	Yield %	*anti : syn*
E	Ph	$CrCl_2$ (400 mol%)	---	100%	90 : 10
E	Ph	$CrCl_2$ (7 mol%)	Mn, TMSCl	79%	94 : 6
Z	Ph	$CrCl_2$ (7 mol%)	Mn, TMSCl	64%	90 : 10
E	Ph	$CrCl_3$ (7 mol%)	Mn, TMSCl	85%	91 : 9
Z	Ph	$CrCl_3$ (7 mol%)	Mn, TMSCl	74%	90 : 10
E	n-C_5H_{11}	$CrCl_2$ (400 mol%)	---	97%	96 : 4
E	n-C_5H_{11}	$CrCl_2$ (7 mol%)	Mn, TMSCl	84%	92 : 8
E	$(CH_2)_5COOMe$	$CrCl_3$ (7 mol%)	Mn, TMSCl	83%	92 : 8

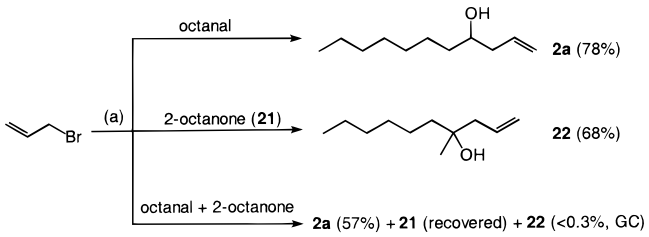
Table 5. Chromium-Induced Reactions of Geranyl Substrates with Benzaldehyde: Comparison between the Catalytic and the Stoichiometric Procedures[35]



X	$CrCl_2$	Additives	Yield	Diastereomeric ratio *S*,S* : S*,R**
$OP(O)(OEt)_2$	215 mol%	---	94% [a]	97 : 3
Br	7 mol%	Mn, TMSCl	79% [b]	94 : 6

[a] In DMPU as the solvent in the presence of LiI. [b] In THF as solvent.

Scheme 5



Key: (a) (i) $CrCl_2$ (7 mol%), Mn, TMSCl, THF, r.t.; (ii) H_2O

the case of allylic substrates; (iii) exhibits the usual preference for additions to aldehydes (Scheme 5); (iv) shows the very characteristic *stereoconvergent* path when applied to *γ-mono*substituted allylic halides; this propensity leads to the diastereoselective formation of anti configured homoallyl alcohols *independent* of the configuration of the starting material (Table 4) (cf. section VI C1); (v) shows the equally characteristic *stereodivergent* path in reactions with *γ,γ-di*substituted allyl halides (Table 5) (cf. section VI C1).

Scheme 4 suggest that one can start either from $CrCl_2$ or from $CrCl_3$ in catalytic amounts as the "pre-

Scheme 6

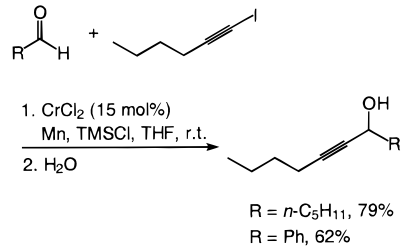


Table 6. Nozaki–Hiyama–Kishi Reactions Catalyzed by Cp_2Cr or $CpCrCl_2$·THF[a] [35]

R-X	Aldehyde	CrX_n cat.	Yield	*anti:syn*
allyl bromide	n-$C_7H_{15}CHO$	Cp_2Cr (2%)	73%	
allyl bromide	n-$C_7H_{15}CHO$	Cp_2Cr (1%)	76%	
allyl bromide	n-$C_7H_{15}CHO$	Cp_2Cr (0.5%)	62%	
(*E*)-crotyl bromide	PhCHO	Cp_2Cr (1%)	37% [b]	
(*E*)-crotyl bromide	n-$C_7H_{15}CHO$	Cp_2Cr (1%)	76%	77:23
(*E*)-crotyl bromide	n-$C_7H_{15}CHO$	$CpCrCl_2$·THF	92%	78:22
(*Z*)-crotyl bromide	n-$C_7H_{15}CHO$	Cp_2Cr (1%)	60%	65:35
(*E*)-crotyl bromide	$MeOOC(CH_2)_5CHO$	Cp_2Cr (1%)	76%	78:22
1-iodo-1-hexyne	n-$C_5H_{11}CHO$	Cp_2Cr (5%)	80%	
1-iodo-1-hexyne	n-$C_5H_{11}CHO$	Cp_2Cr (1%)	56%	
2-triflyloxy-1-octene	n-$C_7H_{15}CHO$	Cp_2Cr (9%) [c,d]	71%	
iodobenzene	n-$C_7H_{15}CHO$	Cp_2Cr (9%) [c,d]	59%	

[a] All reactions were carried out in THF at ambient temperature unless stated otherwise. [b] Together with 56% isolated yield of the pinacolization product 1,2-diphenyl-1,2-ethandiol. [c] The chromium catalyst was doped with $NiCl_2$. [d] In DME/DMF (20/3) at 50 °C.

catalyst" (Table 4).[35,45] Clearly, the latter salt is preferred for practical reasons as $CrCl_3$ is very cheap, insensitive to oxygen and moisture and therefore is much easier to manipulate. Finally, it has been shown that $CrCl_n$ cat. ($n = 2, 3$) can be replaced by Cp_2Cr cat. or $CpCrCl_2$ cat. These somewhat more electron-rich metal templates result in even better turn-over numbers and hence allow to lower the chromium catalyst loadings to as little as 1 mol %;[35,45] however, they are applicable only to reactions with aliphatic aldehydes (Table 6). Aromatic aldehydes undergo competing pinacol coupling in the presence of Cp_2Cr cat. (or $CpCrCl_2$ cat.), Mn(0), and TMSCl.[35]

Boeckman et al. have further extended the underlaying catalysis principle and applied it to highly stereoselective chromium-catalyzed additions of acrolein acetals to aldehydes (for the stoichiometric precedence, see section VI B).[48] The key to success in this specific application is the addition of catalytic amounts of NaI to the reaction mixture. This additive likely converts the TMSCl into TMSI which then transforms the acrolein acetals into α-iodo ethers; the latter react with the Cr(II). The overall process may be formally depicted as shown in Scheme 7. Note that this catalytic cycle implies that the MnI_2 or MnClI primarily formed must react with TMSCl to afford TMSI, otherwise the addition of *catalytic* amounts of NaI would not be sufficient to maintain the

Scheme 7

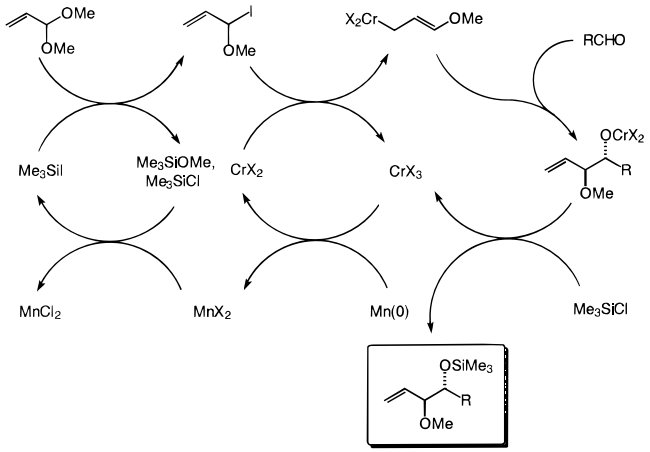
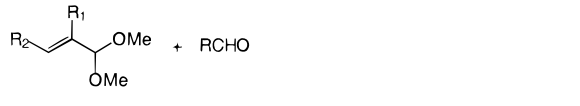
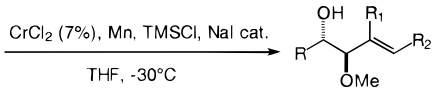


Table 7. Cr(II)-Catalyzed Additions of Acrolein Acetals to Aldehydes[48]





major isomer

R	R_1	R_2	Yield (%)	*anti:syn*
Ph	H	H	88	10.9:1
c-C_6H_{11}	H	H	93	8.4:1
n-C_3H_7	H	H	90	9.9:1
n-C_6H_{13}	H	H	92	10.1:1
i-C_3H_7	H	H	90	10.7:1
t-C_4H_9	H	H	86	1:1.5
i-Pr-CH=CH-	H	H	62	3.9:1
PhCH=CH-	H	H	61	4.5:1
Ph	Me	H	94	8:1
i-C_3H_7	Me	H	68	8.2:1
	H	H	46	20:20:1:1 [a]
	H	H	50	20:20:1:1 [a]

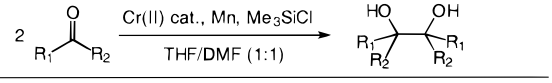
[a] 3,4-anti-4,5-syn:anti-anti:syn-anti:syn-syn.

process. Under these optimized conditions, the reaction turned out to be rather general, with the diol derivatives being formed with good to excellent anti selectivity (Table 7).[48]

Takai et al. have shown that Fürstner's conditions also allow to render the three-component coupling of a secondary or tertiary alkyl iodide, a 1,3-diene, and an aldehyde catalytic in $CrCl_2$.[49] This unconventional reaction, relying on an interesting interplay of radical and anionic species, is discussed in more detail in section VI A.

The basic catalytic principle outlined by Fürstner et al.[35,45] also enables chromium-catalyzed pinacol coupling reactions. These authors had already noticed that Cr(II)-catalyzed reductive coupling processes may compete with the formation of the organochromium reagents if electron withdrawing substituents render the aldehyde substrates prone to s.e.t. events. This behavior is particularly pronounced if $CrCl_3$ cat.

Table 8. Chromium-Catalyzed Pinacol Coupling Reactions



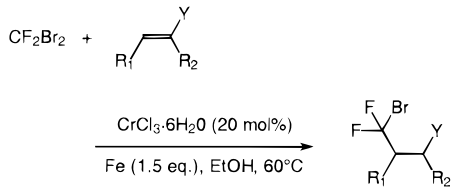
R_1	R_2	CrX_n (mol%)	Yield (%)	*dl/meso*	Ref.
Ph	H	$CrCl_3$ (5)	74	38:62	50
		$CrCl_3$ (1)	70	47:53	50
		Cp_2Cr (5)	77	48:52	50
p-MeC_6H_4	H	$CrCl_3$ (5)	70	53:47	50
p-ClC_6H_4	H	$CrCl_3$ (5)	65	51:49	50
p-BrC_6H_4	H	$CrCl_3$ (5)	60	54:46	50
p-$AcOCC_6H_4$	H	$CrCl_3$ (5)	70	50:50	50
p-$MeOOCC_6H_4$	H	$CrCl_2$ (7)	73	n.r.	35
2-furyl	H	$CrCl_3$ (5)	51	50:50	50
Ph	Me	$CrCl_3$ (5)	57	48:52	50
		Cp_2Cr (3)	60-67	52:48	50

is replaced by the more electron rich metal templates Cp_2Cr or $CpCrCl_2$.[35] As an extension of these observations, Boland et al. have recently described an efficient method for effecting pinacol coupling reactions of aromatic carbonyl compounds catalytic in Cr(II) (Table 8).[50] Thus, a combination of either $CrCl_3$ cat. or Cp_2Cr cat. with Mn powder and TMSCl in DMF/THF as the preferred solvent mixture provides good to excellent yields of the desired diols and turned out to be compatible with various functional groups in the substrates. Replacing TMSCl by more bulky chlorosilanes had a negative effect on the rate and yield of the reaction but resulted in an improved dl:meso ratio. This observation was interpreted in terms of a direct participation of the chlorosilane in the dimerization step, most likely by silylating the ketyl radicals initially formed to afford silylalkoxy radical intermediates. In the absence of the Cr(II) catalysts, the pinacolization was either slow or did not occur at all, whereas reduction of the aldehydes to the corresponding alcohols then became a serious side reaction.[50]

A chromium-catalyzed version of the Takai–Utimoto olefination employing *gem*-dihalides, $CrCl_3$ cat., and Sm/SmI_2 (instead of Mn powder) as the stoichiometric reducing agent will be outlined in section XI.[51] In close analogy, a redox couple comprising $CrCl_3 \cdot 6H_2O$ cat. and Fe powder as the stoichiometric reducing agent in ethanol as the solvent of choice effects a practical hydrobromodifluoromethylation reaction of electron-deficient alkenes via 1,4-additions of dibromodifluoromethane to the substrates (Table 9). Control experiments made sure that Fe powder, in the absence of $CrCl_3$, does not induce this transformation. It is assumed that $CrCl_2$ formed in situ is the actual coupling agent.[52]

In all of the above-mentioned protocols, the active Cr(II) species are regenerated via chemical redox couples with Mn, Sm, or Fe. Obviously, electrochemistry may constitute an attractive alternative. In this context, Grigg et al.[53] devised an electrochemically driven NHK reaction catalytic in $CrCl_2$ (ca. 10 mol %) (Table 10). The current density turned out to be a critical parameter and must be carefully controlled. Furthermore, it was shown that $LiClO_4$ used as the supporting electrolyte simultaneously acts as the

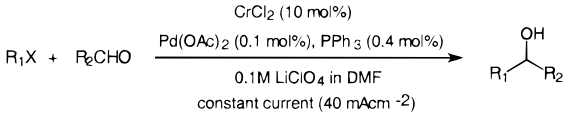
Table 9. Chromium-Catalyzed Hydrobromodifluoro methylation of Electron-Deficient Alkenes[52]



R_1	R_2	Y	Product	Yield (%)
H	H	COOEt	$BrCF_2CH_2CH_2COOEt$	72
H	H	COOMe	$BrCF_2CH_2CH_2COOMe$	75
H	H	COOH	$BrCF_2CH_2CH_2COOH$	64 [a]
H	H	$CONH_2$	$BrCF_2CH_2CH_2CONH_2$	72
H	Me	COOEt	$BrCF_2CH_2CH(Me)COOEt$	80
Me	H	COOEt	$BrCF_2CH(Me)CH_2COOEt$	43
H	H	CN	$BrCF_2CH_2CH_2CN$	62
H	H	COMe	$BrCF_2CH_2CH_2COMe$	60
Cyclohex-2-en-1-one			3-bromodifluoromethyl-cyclohexanone	18

[a] In THF instead of EtOH as the solvent.

Table 10. Chromium-Catalyzed NHK Reactions under Constant Current Conditions[53]



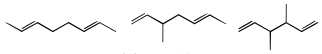
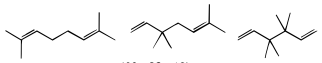
X	R_1	R_2	Yield (%)
Br	2-propenyl	Ph	69
Br	2-propenyl	2-naphthyl	55
Br	2-propenyl		62
I	Ph	Ph	66
I	Ph	2-naphthyl	54
Br	Ph	Ph	57
Br	Ph	2-naphthyl	51

oxophilic mediator of the catalytic cycle, making TMSCl unnecessary. This electrochemical version uses Pd(0) (formed in situ from $Pd(OAc)_2$ and PPh_3) as a cocatalyst.[53]

Griggs study was preceded by reports of Steckhan et al.[54] who accomplished the reductive coupling of benzylic and allylic halides with catalytic amounts of $CrCl_2$ that is constantly regenerated at an electrode surface (Table 11). Control experiments have shown that the substrates are not dimerized directly in an electrochemical step under the conditions used (glassy carbon cathode, −0.4 V vs Cd/Hg reference electrode), but that the presence of $CrCl_2$ as a catalyst is essential. Similar electrochemical modifications were also used for simple Cr(II)-induced C−X bond reductions.[18c,55]

Finally, a catalytic variant of Cr(II)-mediated radical cyclizations of α-bromo acetals to substituted tetrahydrofuran derivatives should be mentioned, which also relies on the electrochemical regeneration of the active chromium species (alternatively, $LiAlH_4$ may be used for the same purpose, although this setup requires a relatively large amount of chromium acetate (33 mol %) in order to achieve satisfactory yields).[56] These results are assessed in more detail in section X.

Table 11. Chromium-Catalyzed, Electrochemically-Driven Dimerization of Organic Halides[54]

Substrate	Product	Yield (%)
benzyl bromide	1,2-diphenylethane	60
α,α-dibromotoluene	stilbene (*E*:*Z* = 85:15)	51
trichlorotoluene	1,2-diphenylacetylene	30
3-bromocyclohexene		77
1-bromo-2-butene	 (43 : 46 : 11)	78
1-bromo-3-methyl-2-butene	 (60 : 28 : 12)	81

III. Alkenylchromium(III) Reagents

A. Exploratory Studies

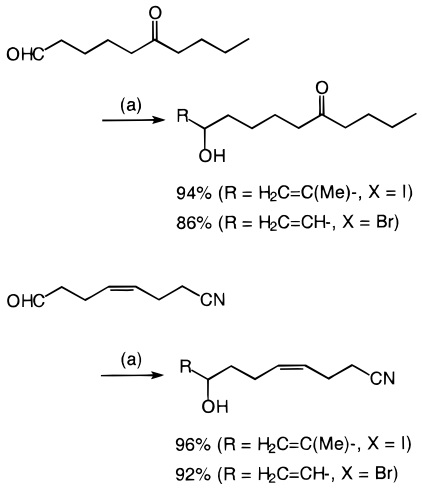
In 1983, Nozaki et al. reported a first in-depth investigation on the addition of alkenyl halides to aldehydes mediated by $CrCl_2$ (Table 12).[10] This pioneering study revealed many of the salient features of this transformation: Thus, good to excellent results were obtained in all cases, provided that a slight excess of the halide (ca. 2 equiv) and of the chromium salt (≥4 equiv) is used in DMF as the preferred solvent. Iodoalkenes were found to be significantly more reactive than the corresponding bromoalkenes. The configuration of the double bond is retained during the reaction in the case of disubstituted and (*E*)-configured trisubstituted haloalkenes, whereas (*Z*)-configured trisubstituted alkenyl halides provide (*E*)-allyl alcohols. Moreover, the excellent chemoselectivity of this reaction was pointed

Table 12. Addition of Alkenyl Halides to Aldehydes Mediated by $CrCl_2$. Exploratory Studies[10]

Alkenyl halide	Aldehyde	t (h)	Yield (%)
2-Iodopropene	PhCHO	0.25	100
	$C_8H_{17}CHO$	0.25	100
2-Bromopropene	PhCHO	3	77
	$C_8H_{17}CHO$	3	62
1-Iodocyclohexene	PhCHO	3	79
	$C_8H_{17}CHO$	0.5	93
	Me_2CHCHO	17	72
1-Iodo-1-phenylethene	PhCHO	5.5	89
	$C_8H_{17}CHO$	7	83
Vinyl bromide	PhCHO	15	80
	$C_8H_{17}CHO$	1.5	77
(*E*)-PhCH=CHBr	PhCHO	1	82 [a]
(*Z*)-PhCH=CHBr	PhCHO	1	78 [a]
	PhCHO	3	91 [b]
	PhCHO	3	90 [b]

[a] Configuration of the double bond retained. [b] Affords the (*E*)-configured allyl alcohol exclusively.

Scheme 8



(a) RX, $CrCl_2$, DMF, r.t.

out, which allows to distinguish rigorously between aldehydes and ketones, esters or nitriles, etc. (Scheme 8). The addition of alkenylchromium(III) reagents to cyclohexanone occurred only at elevated temperature (50 °C) and in rather poor yield (22%). Finally, these authors found that 2,2-diiodopropane may replace 2-iodopropene as an isopropenyl donor.[10]

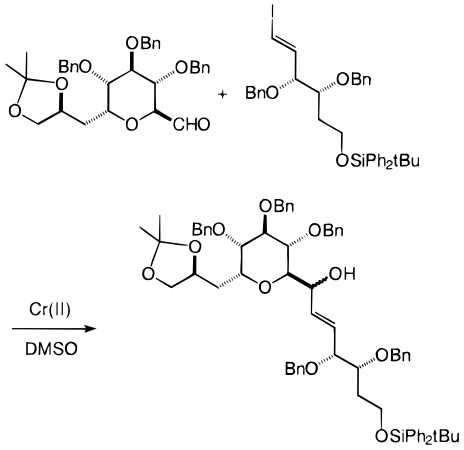
B. Palytoxin

One of the highlights in organochromium chemistry is Kishi's seminal work on the total synthesis of palytoxin, i.e., the toxic principle isolated from marine soft corals of the genus *Palythoa*. This monumental endeavor not only illustrates the applicability of NHK reactions to target compounds of utmost complexity, but also led to fundamental insights into the basics of organochromium chemistry in general.[57]

In early model studies, the formation of the C.7−C.8 bond of palytoxin was identified as a particularly challenging task. Whereas aldol and Wittig approaches were found impractical, the addition of alkenyl iodides to aldehydes mediated by $CrCl_2$ gave encouraging results, because these coupling reactions turned out to be compatible with the required polyfunctional and rather sensitive substrates. Despite this promising selectivity profile, however, the yields were erratic, depending much on the batch and source of $CrCl_2$ used.[36,57] A detailed analysis showed that this inconvenience can be solved by adding catalytic amounts of $NiCl_2$ (usually 0.1−1% w/w) to the $CrCl_2$ salt.[12] Under these conditions, the reactions turned out to be very well reproducible and high yielding (Table 13). However, it is recommended to keep the amount of this additive low to avoid competing homocoupling of the iodoolefins. Most likely, $NiCl_2$ is first reduced to Ni(0) or Ni(I) by $CrCl_2$, which then oxidatively inserts into the halide. Transmetalation of the resulting organonickel species by Cr(II) or Cr(III) leads to the desired organochromium intermediate and regenerates $NiCl_2$. $Pd(OAc)_2$ exerts a similar effect, but this additive was markedly less studied.[53,57d] The reactions proceed well in DMF, DMF/Me_2S, or DMSO, with the latter leading to slower but somewhat cleaner conversions. In parallel work, the group of Prof. Nozaki has also reported beneficial effects of Ni(II) cat. on chromium-mediated C−C-coupling reactions.[13] Based on these fundamental studies, the doping of $CrCl_2$ with catalytic amounts of Ni(II) salts became a standard recipe for all reactions involving alkenyl- and aryl halides.

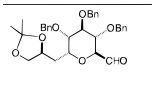
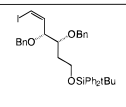
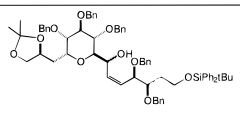
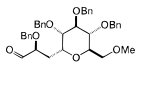
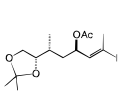
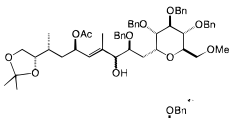
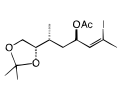
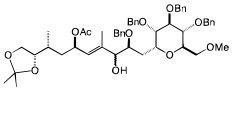
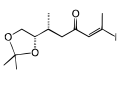
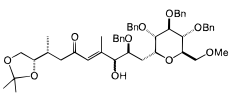
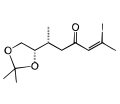
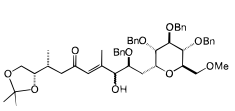
Importantly, Cr(II)/Ni(II)-mediated reactions of disubstituted alkenyl halides are distinguished by the fact that the geometry of the starting olefin is

Table 13. Model Studies on Palytoxin: Ni(II)-Effect on Chromium-Mediated Coupling Reactions[12]



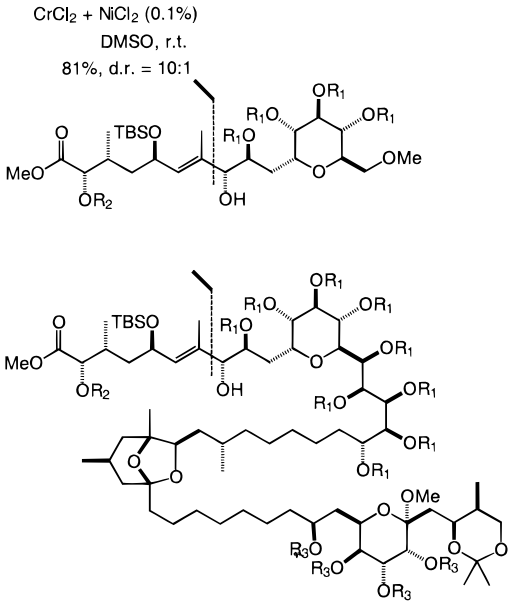
Aldehyde (eq.)	Halide (eq.)	Reagent	Yield (%)	d.r.
1	1.5	$CrCl_2/NiCl_2$ (0.1%) (1.5eq.)	55	1.3:1
1	1.5	$CrCl_2/NiCl_2$ (0.1%) (3eq.)	60	1.3:1
1	3	$CrCl_2/NiCl_2$ (0.1%) (6eq.)	71	1.3:1
1	10	$CrCl_2/NiCl_2$ (0.1%) (10eq.)	80	1.3:1
1	1.5	$CrCl_2/Pd(OAc)_2$ (0.1%) (3eq.)	54	1:1
1	3	undoped $CrCl_2$	0-80	1.3:1

Table 14. Model Studies on Palytoxin: Retention versus Inversion of the Configuration of the Starting Alkenyl Iodides[12]

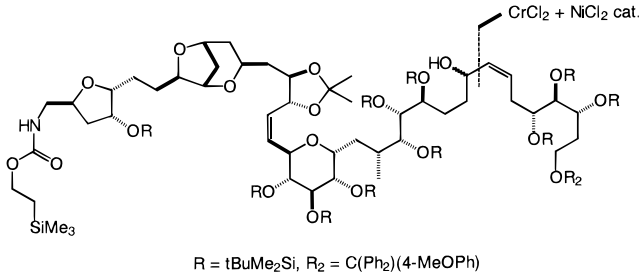
Aldehyde	Halide	Product	[a]	Yield %
			A	0-60
			B	58
			A	0-64
			B	86
			A	0-15
			B	15
			A	0-63
			B	82
			A	0-20
			B	28

[a] Method A: using undoped $CrCl_2$ (excess). Method B: using $CrCl_2/NiCl_2$ (0.1 mol %) (10 equiv).

Scheme 9



Scheme 10

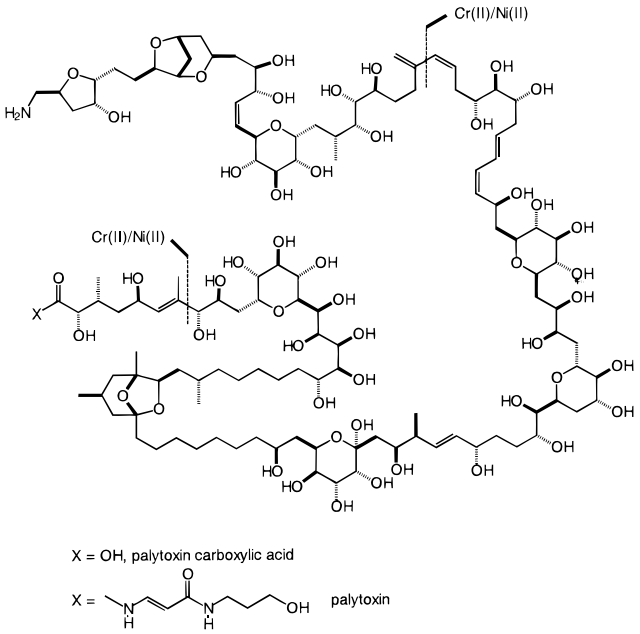


retained during the C−C bond formation. In contrast, trisubstituted iodoolefins, independent of their configuration, afford (*E*)-configured allyl alcohols (Table 14). Notwithstanding this stereochemical convergence, (*Z*)-configured substrates generally provide lower yields.[12]

Another important observation during the palytoxin project concerns the subtle influence of the protecting groups in allylic position to the vinyliodide function on the efficiency and stereoselectivity of the NHK reactions. In particular, substrates bearing allylic R_3SiO substitutents react much more efficiently than those with BnO groups (Schemes 9 and 10). Moreover, by switching from Me_3SiO- to the more bulky $tBuMe_2SiO$- (TBSO-) group, the stereochemical outcome can be vastly improved.[36,57]

On the basis of these important insights gained during extensive model studies, the chromium methodology served twice as a key step during the total synthesis of palytoxin carboxylic acid for the formation of the C.7−C.8 and the C.84−C.85 bonds (Scheme 11).[58]

Scheme 11

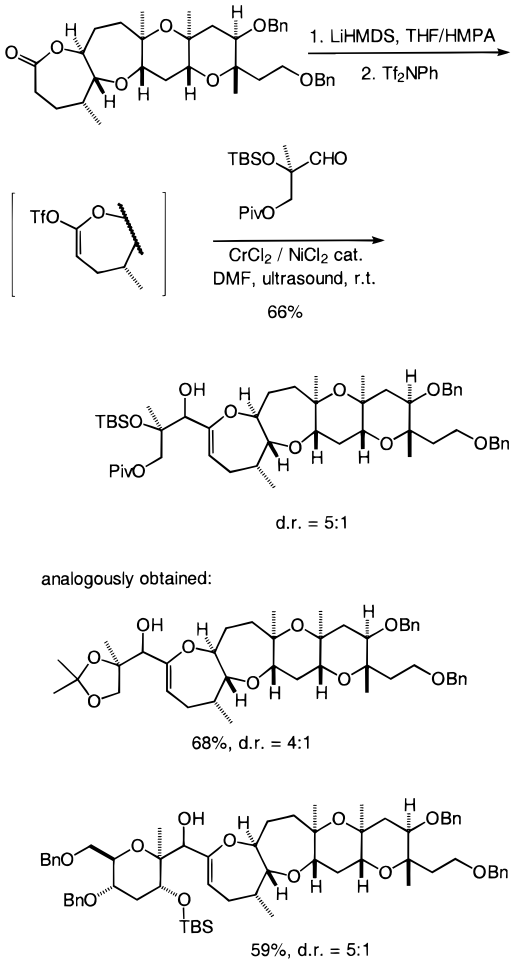


C. Functionalized Alkenyl Halides and Alkenyl Triflates

The overwhelming precedence of the palytoxin project encouraged many other research groups to venture into Cr(II)/Ni(II)-mediated coupling reactions. As a result, many applications to advanced organic synthesis have been described, including an impressive number of key steps of natural product syntheses. The scope of this valuable transformation was further increased when it was recognized that alkenyl triflates may substitute alkenyl halides as the starting materials (Table 15).[13] They are readily prepared via the enolization of carbonyl compounds or upon addition of TfOH to alkynes; therefore, this modification denotes an important extension of the NHK reaction in structural terms. DMF or mixtures of DMF/THF are again the preferred reaction media. A detailed and checked procedure describing the reaction of 1-hexylethenyl triflate with 3-phenylpropanal is available.[59] The propensity of alkenyl triflates to insert Cr(II)/Ni(II) is similar to that of alkenyl bromides but distinctly lower than the reactivity of alkenyl iodides.[60] Importantly, they also react cleanly in the catalytic setup employing $CrCl_2$ ($NiCl_2$) cat., Mn(0), and TMSCl.[35] Vinylmesylates activated by adjacent electron-withdrawing groups can also be used, although they tend to give lower yields and have not yet been investigated in full detail.[62]

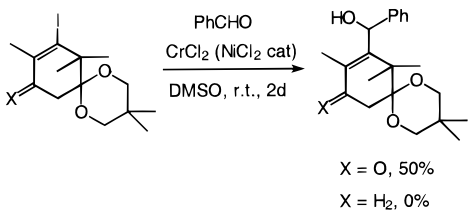
A further extension has been developed by Nicolaou et al. who describe for the first time the use of lactone-derived enoltriflates in NHK reactions. These substrates are prepared in situ by preparation and quenching of the lactone enolate with Tf_2NPh. The performance of this new methodology becomes evident from its successful implementation into the total synthesis of brevetoxin B (Scheme 12).[61]

Scheme 12



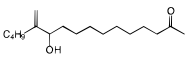
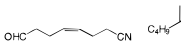
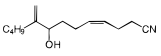
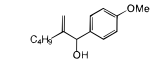
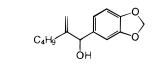
It has already been noticed in the model studies toward palytoxin[12] that alkenyl halides (triflates) bearing electron-withdrawing substituents in the β-position are particularly prone to oxidative insertion of Cr(II) into the C−X bond. This turned out to be general; hence, Barbier-type reactions of β-haloenones or -enoates with carbonyl compounds induced by $CrCl_2$ and $NiCl_2$ cat. generally provide the desired allyl alcohols in good to excellent yields (Table 16).[62] β-Iodoenones are most reactive, but β-bromoenones and even some β-chloro- or β-mesyloxyenones can also be used. A comparative study directed toward the synthesis of the taxane skeleton has confirmed the considerable activation effect exerted by an adjacent carbonyl group.[60] As can be seen from the example shown in Scheme 13, this electronic bias is

Scheme 13



crucial in reactions of tetrasubstituted alkenyl halides or similarly unreactive substrates.

Table 15. Cr(II)/Ni(II)-Mediated Additions of Alkenyl Triflates to Aldehydes

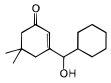
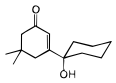
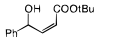
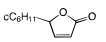
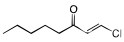
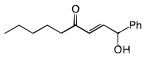
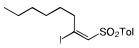
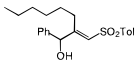
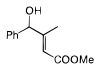
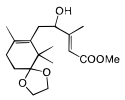
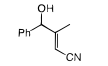
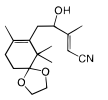
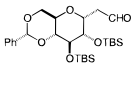
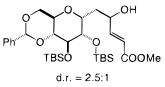
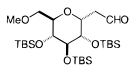
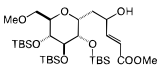
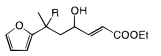
Alkenyl Triflate	Aldehyde	Product	Yield (%)	Ref.
	PhCHO		83	13
	RCHO		61 (R =C_7H_{15}) [a] 67 (R = Ph) [a]	35
	RCHO		72 (R = Ph) 81 (R = C_7H_{15}) 64 (R = PrCH=CH)	13
	MeC(O)$(CH_2)_8$CHO		87	13
			78	13
	p-$MeOC_6H_4CHO$		76 [a]	35
			80 [a]	35
	RCHO		74 (R = Ph) 83 (R = C_7H_{15}) 41 (R = PrCH=CH)	13
	$C_7H_{15}CHO$		76	13
	$C_7H_{15}CHO$		0 [b]	13
	PhCHO		92	13
	PhCHO		46	13
	PhCHO		85	13
	PhCHO		72	13

[a] With $CrCl_2$ (15 mol %), Mn(0), TMSCl. [b] Triflate recovered unchanged.

The use of 1-bromo-3-trimethylsilylpropene as the substrate in NHK reactions also deserves mentioning (Table 17).[63,64] The resulting hydroxysilanes can undergo vinylogeous Peterson elimination on treatment with acid, thereby leading to the formation of (*E*)-1,3-diene derivatives from aldehydes via a three-carbon homologation under mild conditions. Both steps, the Cr(II)/Ni(II)-mediated addition and subsequent elimination, can also be conveniently performed in a "one pot" procedure.[63]

Table 18 summarizes the results of intermolecular Cr(II)/Ni(II)-mediated addition reactions of alkenyl halides (triflates) to carbonyl compounds. Many entries constitute key steps in the synthesis of natural products and analogues thereof. They illustrate beyond doubt the pronounced chemoselectivity favoring additions to aldehydes over those to other carbonyl groups (ketones, enones, esters, amides, urethanes, etc.) as well as the excellent compatibility of the method with an array of other electrophilic groups. The major isomer formed in an addition reaction to chiral aldehydes can generally be deduced from the Felkin−Ahn model, although the diastereoselection is sometimes rather poor. Moreover, many examples in Table 18 show that chiral centers α to

Table 16. Chromium-Mediated Barbier-Type Reactions of Alkenyl Halides Bearing Electron-Withdrawing Groups at the β-Position

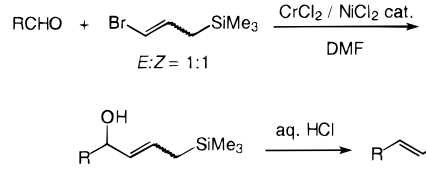
Halide	Carbonyl Compound	Product	Yield (%)	Ref.
	PhCHO		91 (X = I) 71 (X = OMs)	62
	n-C_5H_{11}CHO		72 (X = I)	62
	C_6H_{11}CHO		97	62
	cyclohexanone		43	62
	PhCHO		39	62
	*c*-C_6H_{11}CHO		50	62
	PhCHO		56	62
	PhCHO		44	62
	PhCHO		40	62
	PhCHO		64	182
			89	182
	PhCHO		59	182
			95	182
	 d.r. = 2.5:1		80	183
	 d.r. = 1:1		90	183
			52 (R=H) 60 (R=Me)	184
	PhCHO		57	62

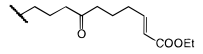
the reacting aldehyde are not racemized under the reaction conditions, indicating a rather low basicity of the intermediate alkenylchromium(III) species as compared with that of many other organometallic reagents. This notion is corroborated by the fact that even free −OH groups were found compatible in some cases.

This most attractive overall profile of NHK reactions shows only few limitations. Specifically, complications may arise in addition reactions involving (*Z*)-configured α,β-unsaturated enals as the substrates (Table 19). Alkenylchromium(III) reagents add selectively in a 1,2-manner, but the configuration of the starting enal may not be retained.[65] This unfavorable situation, however, is easily rectified by avoiding unduly long contact of the aldehyde with $CrCl_2$. If the halide is added to the chromium salt prior to a slow addition of the electrophile (i.e., preformation of the alkenylchromium species), it was possible to suppress this undesirable isomerization process.

A more significant limitation is the lack of a general method for performing enantioselective additions of alkenyl chromium reagents to aldehydes. Some exploratory studies toward this goal are discussed in section VI C6.

Table 17. Cr(II)-Induced Formation of Hydroxysilanes and Dienes



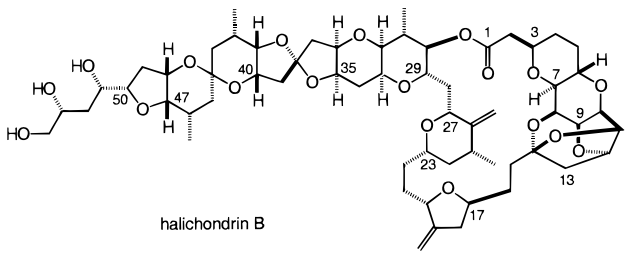
R	Hydroxysilane Yield %, (*E*:*Z*)	Diene Yield %, (*E*:*Z*)	Ref.
Ph	74 (3:1)	quant. (>10:1)	63
PhCH=CH	Complex mixture		63
4-NCC_6H_4	[a]		63
n-C_8H_{17}	69 (>10:1)	quant. (>10:1)	63
c-C_6H_{11}	79 (4:1)	quant. (>10:1)	63
t-Bu	57 (10:1)	quant. (>10:1)	63
$EtOOCCH=CH(CH_2)_4$	74 (10:1)	quant. (>10:1)	63
$EtOOCCH=CH(CH_2)_3C(O)(CH_2)_3$	72 (9:1)	quant. (9:1)	63
	72 (1:0)	---	64

[a] The pinacol is the major product (93%).

D. Applications to Halichondrin

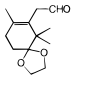
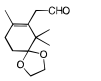
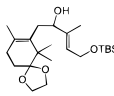
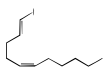
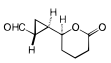
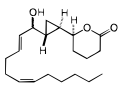
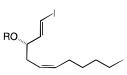
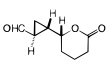
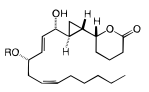
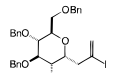
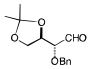
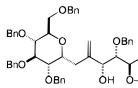
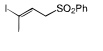
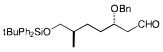
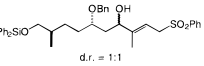
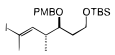
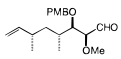
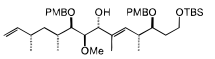
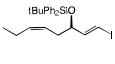
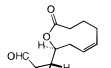
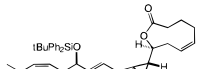
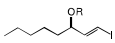
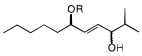
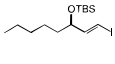
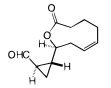
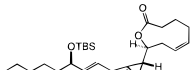
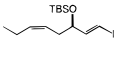
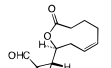
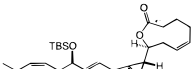
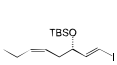
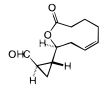
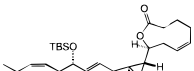
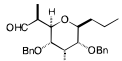
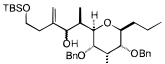
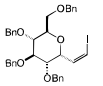
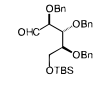
Among the many natural product syntheses involving the addition of alkenylchromium(III) reagents to aldehydes, the studies directed toward the halichondrin family of polyether macrolides deserve particular mentioning (Scheme 14). These very com-

Scheme 14



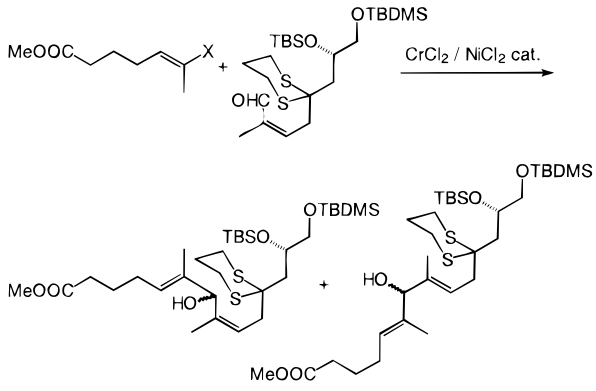
plex targets exhibit an extraordinary antitumor activity in vitro and in vivo and have been chosen by the National Cancer Institute for further development as anticancer drugs. They are hardly available from natural sources and therefore constitute particularly attractive targets for total synthesis which

Table 18. Cr(II)/Ni(II)-Induced Additions of Functionalized Alkenyl Halides or Triflates to Functionalized Aldehydes

Halide	Aldehyde	Product (major isomer depicted)	Yield (%)	Ref.
2-bromopropene			76	182
			73	182
			61	185
		 d.r. = 2:1 (R = TBDPS) d.r. = 1.4:1 (R = H)	70 (R=TBDPS) 70 (R = H)	185
		 d.r. = 10:1	n.r.	186
		 d.r. = 1:1	66	187
		 d.r. = 2:1 (4:1)	83 (87)	188
			62	189
		 d.r. = 1:1 (R = PMB) d.r. = 2,1:1 (R = TBS)	100	190
			73	190
			61	190
			70	190
			33 [a]	183
			n.r.	191
			98	192
			69%	193
			78	193
			86	194
R = TIPS		d.r. = 2.5:1	40	195
		d.r. = 3:1	60	196
		d.r. = 7:3	80	197
			80 [b]	198
		d.r. = 1:1	52	199
			23+27 [c]	200
			49 (33)	200
			41	201
			70	60
			n.r.	202
R = Alloc		R = Alloc	55	203
	R = Alloc	R = Alloc	88 [d]	203
			65 [a]	204

[a] Yield refers to coupling and subsequent Swern oxidation of the alcohol. [b] One isomer of the product formed spontaneously undergoes an intramolecular Diels–Alder cycloaddition. [c] In DMSO as the solvent; the reaction fails in DMF. [d] In the presence of bipyridinyl ligand.

Table 19. Additions to a (*Z*)-Configured Enal Substrate[65]

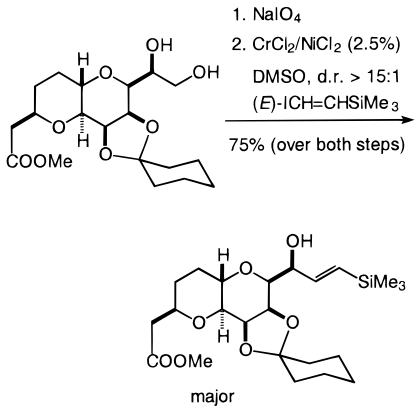


X	Halide (eq.)	Cr(II)/Ni(II) (eq.)	Solvent	[a]	*Z* : *E*	Yield (%)
Br	2	4	DMF	**A**	0:100	32
I	2	4	DMF	**A**	---	0
I	2	4	DMSO	**A**	0:100	92
I	1.5	3	DMSO	**B**	100:0	42
I	2	4	DMSO	**B**	94:6	68
I	3	6	DMSO	**B**	87:13	94
I	3	6	DMSO	**C**	100:0	94

[a] Method A: $CrCl_2/NiCl_2$ was added to a solution of halide and aldehyde. Method B: Mixture of halide and $CrCl_2/NiCl_2$ was stirred for 10 min prior to the addition of the aldehyde. Method C: Mixture of halide and $CrCl_2/NiCl_2$ was stirred for 60 min prior to the addition of the aldehyde.

has been accomplished by Kishi's group on the basis of repeated applications of the Cr(II)/Ni(II) methodology.[57b,66] Specifically, a practical synthesis of the C.1−C.13 segment of halichondrin B involves the addition of (*E*)-ICH=CHSiMe$_3$ to a sugar-derived aldehyde (Scheme 15).[67] It was noticed that the

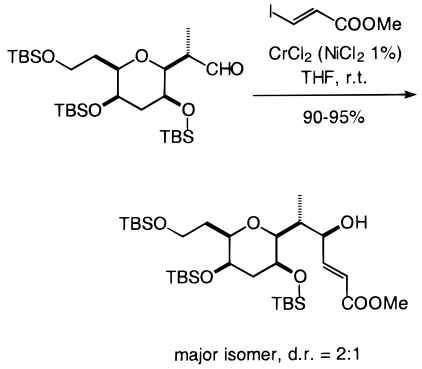
Scheme 15



workup significantly affects the yield obtained: while a standard extractive procedure with NH_4Cl gave only 45% of the desired compound, the results can be improved to 75% by sequestering the metal salts during workup upon addition of ethylenediamine, followed by treatment with aq HCl.[42,67] An alternative strategy to this segment involves the Cr(II)-mediated addition of an iodoacetylene derivative to a closely related aldehyde precursor as discussed in section V.

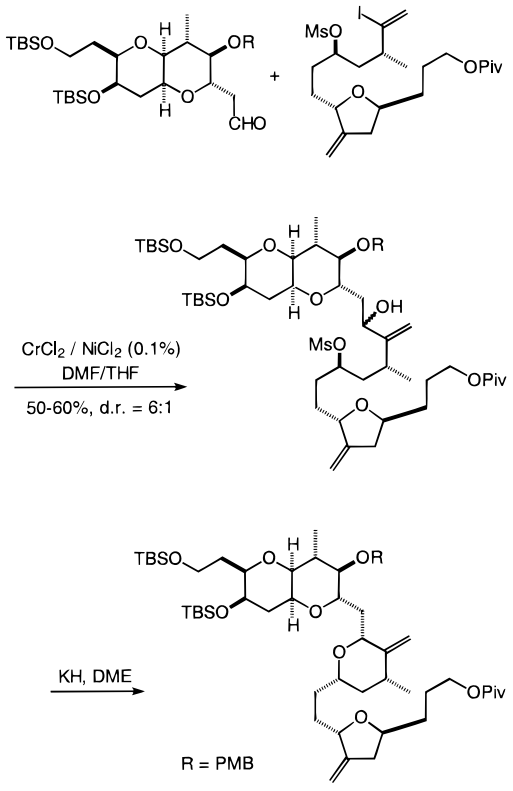
A second application concerns the synthesis of the C.27−C.38 fragment which makes use of the excellent reactivity of β-iodoenoates as substrates in Cr(II)-mediated processes (Scheme 16).[68] The yields obtained are very satisfactory, but this specific application features the notion that the diastereoselectivity of NHK reactions is often rather poor, requiring subsequent rectification by appropriate means.

Scheme 16



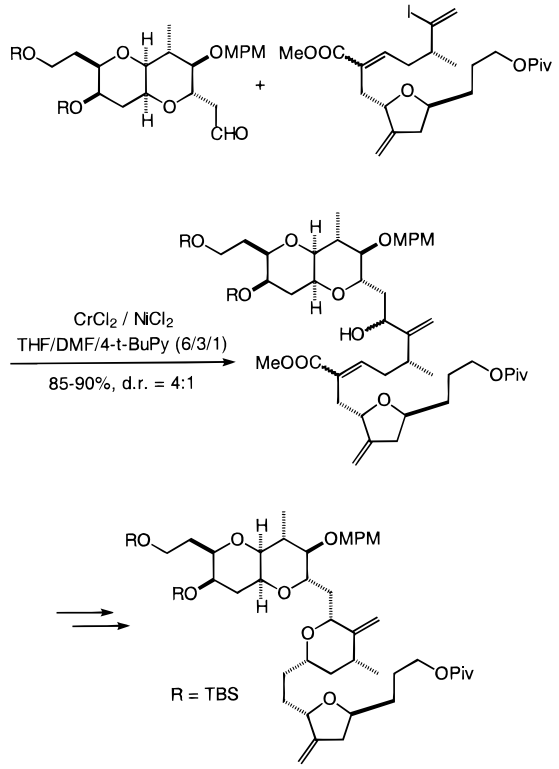
Furthermore, the formation of the C.26−C.27 bond of halichondrin was effected by a Cr(II)/Ni(II)-induced reaction. As shown in Scheme 17, this approach

Scheme 17



allows to combine two elaborate units to the fully protected C.14−C.38 portion of the target in a convergent manner.[57b,66] However, a difficulty associated with this step resides in the rather narrow window of the reaction time where the yield and diastereoselectivity of the coupling reaction is satisfactory. To overcome this shortcoming, Kishi et al. have subsequently developed an alternative route, in which the pyran entity is not formed via substitution of a mesylate (Scheme 17) but via a Michael addition reaction (Scheme 18).[43] Moreover, this "second

Scheme 18

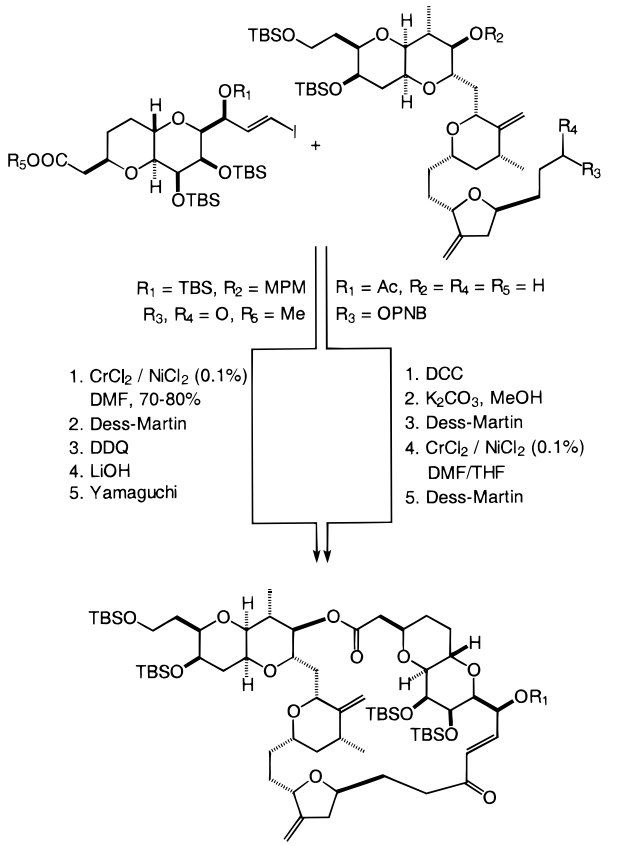


generation" approach also benefits from the finding that Cr(II)/Ni(II)-induced reactions of alkenyl halides are upgraded in practical terms (i) by adding 4-*tert*-butylpyridine to the reaction mixture (which assists in dissolving the metal salts and thus ensures fully homogeneous reaction conditions) and (ii) by using sodium or potassium serinate as a metal sequestering agent during the aqueous workup, thereby improving the mass recovery. The key step under optimized conditions is shown in Scheme 18.[43]

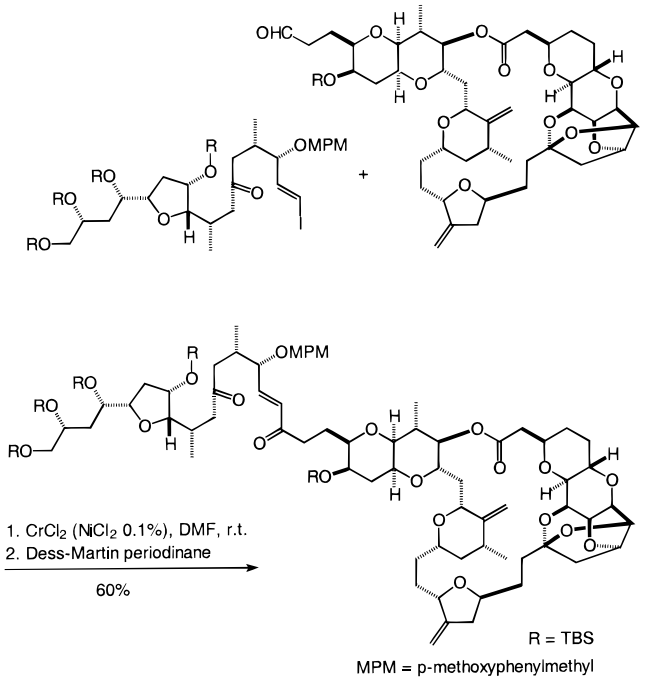
A sublime use of the NHK reaction allowed to assemble the entire macrocyclic C.1−C.38 segment of the halichondrins (Scheme 19).[57b] For this very purpose, Kishi et al. developed two different solutions: in an intermolecular variant, the required building blocks were combined under standard conditions via a Cr(II)/Ni(II)-mediated coupling reaction; the resulting product, after some adjustment of the proper oxidation states and protecting groups, was then cyclized to the target via a Yamaguchi lactonization. Alternatively, these authors demonstrated that by following essentially the same steps, just in a different order, one can also reach the same goal via an amazingly effective intramolecular Cr(II)/Ni(II)-mediated process.

Finally, an NHK reaction was employed for the assembly of the full carbon skeleton of halichondrin B by coupling of the entire macrocyclic right half to the left-hand segment as outlined in Scheme 20.[66] Like the palytoxin work summarized in section III B, the monumental endeavor of the halichondrin synthesis witnesses the exceptional performance, tolerance, and reliability of the NHK methodology.

Scheme 19



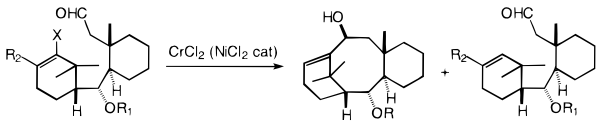
Scheme 20



E. Intramolecular Alkenylchromium Additions

In addition to the striking intramolecular case mentioned above (Scheme 19), macrocyclizations via NHK reactions are frequently encountered as key steps in the total synthesis of natural products and analogues thereof. The high stability of the emerging O−Cr(III) bond constitutes a formidable driving force

Table 20. Studies toward the Taxane Skeleton[60]



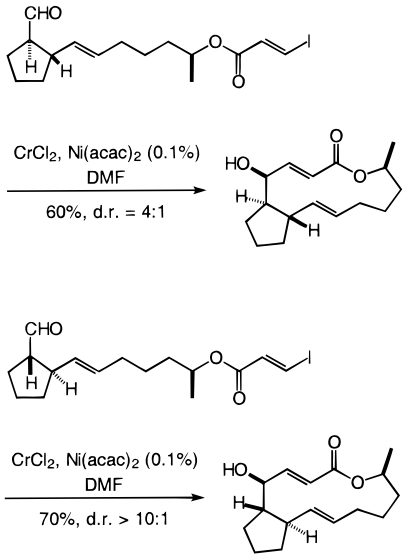
A B C

Entry	R_1	R_2	X	Solvent	Time (d)	Product Distribution
1	CH_2OBn	H	OTf	DMF	28	**B** (30%)
2				DMSO	20	**B** (50%)
3	Me	H	I	DMSO	1	**B** (60%), **C** (30%)
4	Me	Me	I	DMSO	4	**A** (40%), **B** (35%), **C** (20%)

for the formation of rather strained ring systems which are difficult to obtain otherwise. This includes many successful applications to the formation of medium-sized rings that are a priori handicapped by severe transannular interactions.

In most cases, the standard procedure using $CrCl_2$ doped with nickel salts has been applied. In one case, however, an interesting influence of the additive was noticed. Thus, Schreiber et al. encountered during their studies directed toward brefeldin C that $CrCl_2$ doped with catalytic amounts of $Ni(acac)_2$ (0.1% w/w) effected a clean cyclization (Scheme 21), whereas the

Scheme 21

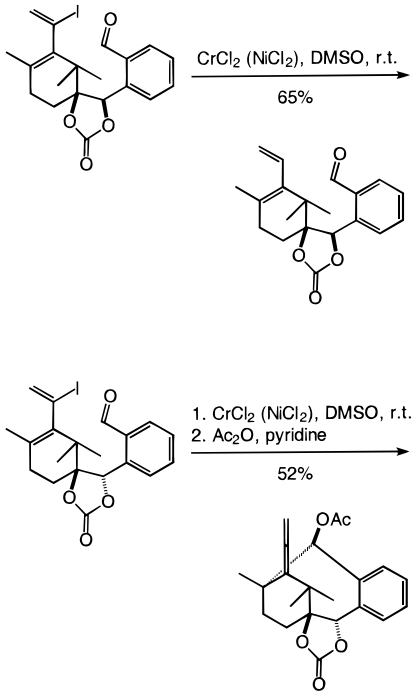


use of $Pd(OAc)_2$ as the cocatalyst led to substantial amounts of 1,3-dienes by subsequent dehydration.[69]

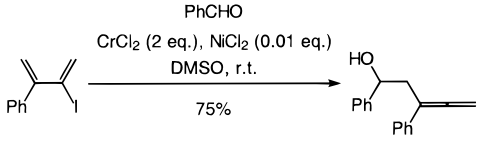
A systematic study of the synthesis of the taxane skeleton highlights not only the potential of NHK reactions for the formation of strained ring systems but also provides some important insights into the reactivity pattern on alkenyl halides and triflates (Table 20).[60] Specifically, the cyclization of the vinyl triflate derivative turned out to be unacceptably slow (entries 1, 2), whereas the analogous vinyl iodide reacted much faster (entry 3). Furthermore, by switching from the trisubstituted alkenyl iodide to its tetrasubstituted congener, substantial amounts of the starting material remained unchanged even after prolonged heating (entry 4). These data show (i) that alkenyl iodides insert Cr(II) more readily than the corresponding triflates and (ii) that the rate determining step in the trisubstituted cases is the C−C bond formation, whereas for the tetrasubstituted alkenyl halides, it is likely the oxidative insertion of Cr(II) into the C−X bond. During the course of this investigation it has also been demonstrated that β-iodoenones are considerably more reactive in inter- as well as intramolecular NHK reactions than alkenyl iodides lacking the vicinal electron-withdrawing group.[60]

In other model studies directed toward the taxane skeleton, a rather special NHK reaction of an alkenyl halide was observed (Scheme 22).[70] While the substrate with the cis-fused carbonate entity did not cyclize at all and led only to the reduction of its C−I bond, the analogous compound bearing a trans-fused carbonate group provided an allene as the only product in fair yield. This outcome is deemed to reflect the (partial) delocalization of the negative charge in the intermediate organochromium reagent as well as the spatial proximity of the reacting sites enforced by the rigid skeleton of the substrate. Although there is very little precedence concerning the behavior of 2-halo-1,3-dienes in NHK reactions, a recent disclosure of an intermolecular case suggests that these substrates may open up an interesting new approach to allene derivatives (Scheme 23).[71]

Scheme 22

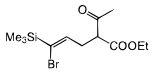
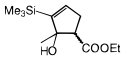
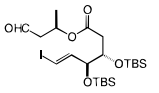
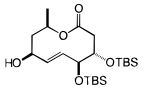
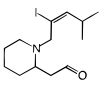
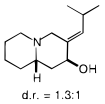
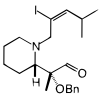
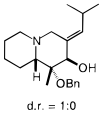
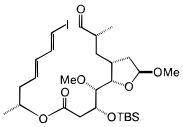
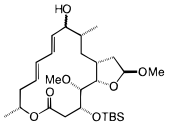
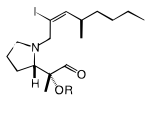
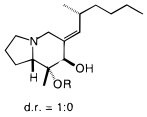
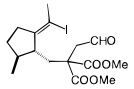
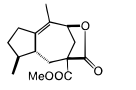
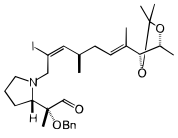
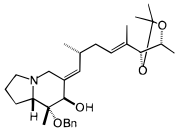
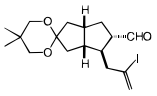
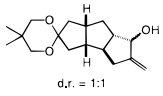
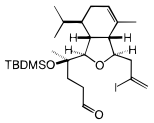
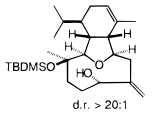
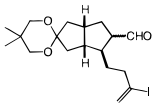
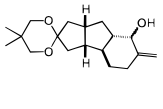
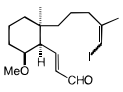
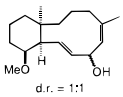
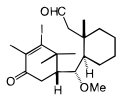
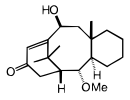
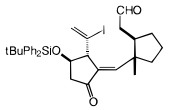
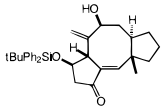
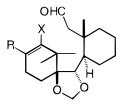
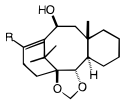
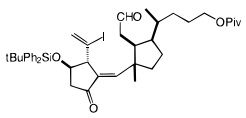
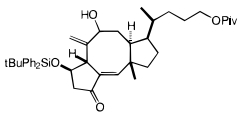
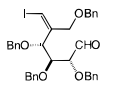
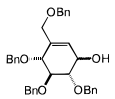


Scheme 23



Other intramolecular NHK reactions involved in highly imaginative syntheses of complex and polyfunctional target molecules are compiled in Table 21.

Table 21. Intramolecular Additions of Alkenyl Halides or Triflates to Carbonyl Groups Mediated by Cr(II)/Ni(II)

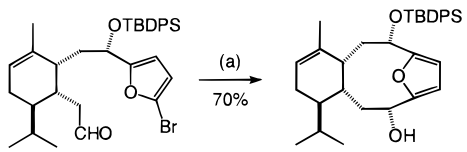
Substrate	Product (Major Isomer Depicted)	Yield (%)	Ref.	Substrate	Product (Major Isomer Depicted)	Yield (%)	Ref.
		54	205			30 [a]	210
	 d.r. = 1.3:1	81	206				
	 d.r. = 1:0	53	206			76	31
	 d.r. = 1:0	R = H (complex mixture) 53 (R = Bn)	206			74	211
	 d.r. = 1:0	79	206		 d.r. = 1:1	92	212
	 d.r. > 20:1	65	207			57 + 23	212
	 d.r. = 1:1	30	30			55-65	60, 213
		56	208			60 (R=Me, X=I) 0 (R=Me, X=OTf) 80 (R=H, X=I)	60
		73	209			61	214

[a] Overall yield for more than one step (including the cyclization reaction).

IV. Arylchromium(III) Reagents

It has been shown early on that aryl halides can be used as substrates in NHK reactions,[10] but this class of compounds has received comparatively little attention. One may speculate that this is because they insert Cr(II)/Ni(II) more reluctantly than other halides and thus require somewhat more forcing reaction conditions. Only aryl iodides afford good yields of the desired addition products, whereas bromides seem to denote one of the limitations. No successful use of an aryltriflate has been reported so far. The selectivity pattern, however, is essentially the same as in other chromium-mediated or chromium-catalyzed processes (Table 22). The reaction also proceeds well using the chromium-catalyzed procedures developed by Fürstner[35] and Grigg.[53] The most advanced application of arylchromium(III) reagents in synthesis refers to a remarkably efficient and stereoselective formation of the strained furano-[6]phane skeleton of the antitumor agent eleutheside (Scheme 24).[72]

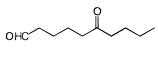
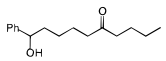
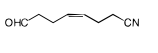
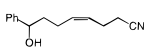
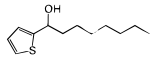
Scheme 24



(a) $CrCl_2$ ($NiCl_2$), DMF

In addition to aryl halides, diaryliodonium tetrafluoroborates can be used as substrates for Cr(II)-induced addition reactions to aldehydes (Table 23).[73] Importantly, these salts do not seem to require the assistance of catalytic amounts of Ni(II) in the oxidative insertion step. However, in the presence of

Table 22. Chromium-Induced Additions of Aryl Halides to Aldehydes

Aryl halide	Aldehyde	[a]	Product	Yield (%)	Ref.
PhI	PhCHO	A	PhCH(OH)Ph	85	10
	PhCHO	B	PhCH(OH)Ph	62-88	35
	PhCHO	C	PhCH(OH)Ph	66	53
	2-NaphthylCHO	C	2-NaphthylCH(OH)Ph	54	53
	n-C_8H_{17}CHO	A	C_8H_{17}CH(OH)Ph	83	10
	n-C_7H_{15}CHO	B	C_7H_{15}CH(OH)Ph	67-72	35
	c-C_6H_{11}CHO	B	c-C_6H_{11}CH(OH)Ph	71	35
	$Cl(CH_2)_5CHO$	B	$Cl(CH_2)_5CH(OH)Ph$	57	35
PhBr	PhCHO	A	PhCH(OH)Ph	31	10
	PhCHO	C	PhCH(OH)Ph	57	53
	2-NaphthylCHO	C	2-NaphthylCH(OH)Ph	51	53
	n-C_8H_{17}CHO	A	C_8H_{17}CH(OH)Ph	13	10
PhI		A		81	10
PhI		A		87	10
p-EtOOC-C_6H_4I	PhCHO	B	p-$EtOOCC_6H_4$CH(OH)Ph	57	35
2-thienyliodide	PhCHO	B		57	35

[a] Method A: $CrCl_2$ (4 equiv), DMF, rt. Method B: doped $CrCl_2$ (15 mol %), Mn powder, chlorosilane, DMF/DME (20/3), 50 °C. Method C: $CrCl_2$ (10 mol %), $Pd(OAc)_2$ (0.1 mol %), PPh_3 (0.4 mol %), constant current conditions, $LiClO_4$ as supporting electrolyte in DMF.

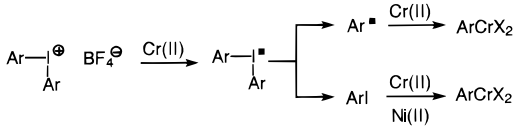
Table 23. Chromium-Mediated Arylation of Aldehydes with Diaryliodonium Salts Ar_2I^+ BF_4^- [73]

Ar in Ar_2I^+ BF_4^- (equiv.)	Aldehyde	$CrCl_2$ (equiv.)	$NiCl_2$ (equiv.)	Yield (%) [a]
Ph (1.5)	PhCHO	6	0.03	92
Ph (1)	p-ClC_6H_4CHO	4	0.02	82
Ph (1)	p-MeC_6H_4CHO	4	0.02	78
Ph (1)	p-$MeOC_6H_4CHO$	4	0.02	72
Ph (1)	o-MeC_6H_4CHO	4	0.02	79
Ph (1.5)	n-$C_{10}H_{21}$CHO	6	0.03	82
Ph (1)	i-PrCHO	4	0.02	74
Ph (1)	t-BuCHO	4	0.02	0
Ph (1.5)	E-MeCH=CHCHO	6	0.03	71
Ph (2)	E-PhCH=CHCHO	4	0	56
p-ClC_6H_4 (1.5)	PhCHO	6	0.03	79
p-MeC_6H_4 (1)	PhCHO	4	0.02	72

[a] Variable amounts of ArI and ArH are formed as byproducts.

$NiCl_2$ cat., the reaction is more "atom economical" since it then allows to transfer *both* aryl units of the iodonium salt to the aldehyde. This observation can be rationalized as shown in Scheme 25. This mechanism is supported, inter alia, by the outcome of the reaction of (*o*-allyloxyphenyl)mesityl iodonium tetrafluoroborate (Scheme 26). The fact that a dihydrobenzofuran derivative is the only detectable product of this reaction makes the initial formation and subsequent 5-*exo*-*trig* cyclization of an aryl radical Ar• intermediate very likely.[73]

Scheme 25



Scheme 26

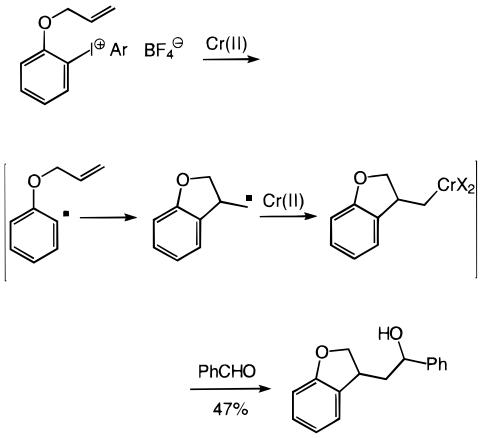
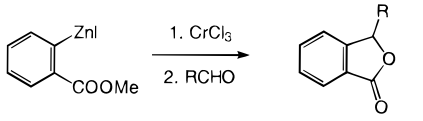


Table 24. Synthesis of 1(3*H*)-Isobenzofuranones Mediated by $CrCl_3$[74]

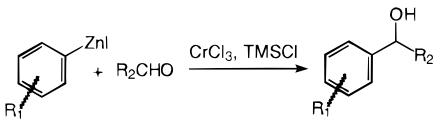


RCHO	Yield (%)
PhCHO	78
i-PrCHO	77
c-C_6H_{11}CHO	73
PhCH(Me)CHO	81
(E)-$CH_3CH_2CH_2CH$=CH-CHO	66
2,4,6-$(MeO)_3C_6H_2CHO$	83
4-$(AcO)C_6H_4CHO$	63
4-NCC_6H_4CHO	68
4-$(MeOOC)C_6H_4CHO$	78
4-bromo-2-thienyl-CHO	73

Arylchromium reagents can also be formed by transmetalation strategies rather than by oxidative insertion. However, the reader is reminded again of the very early studies of Hein et al. on the attempted transmetalation of phenylmagnesium halides with $CrCl_3$ leading to bis(benzene)chromium and of the investigations on the link between σ-bond and π-bond arenechromium reagents found in the mid 1950s.[1−3] Very recently, however, it has been shown that arylzinc halides are valuable precursors for arylchromium(III) reagents. Whereas arylzinc halides themselves add rather slowly to aldehydes, transmetalation with $CrCl_3$, particularly in the presence of TMSCl, speeds up this C−C bond formation (Tables 24 and 25).[74]

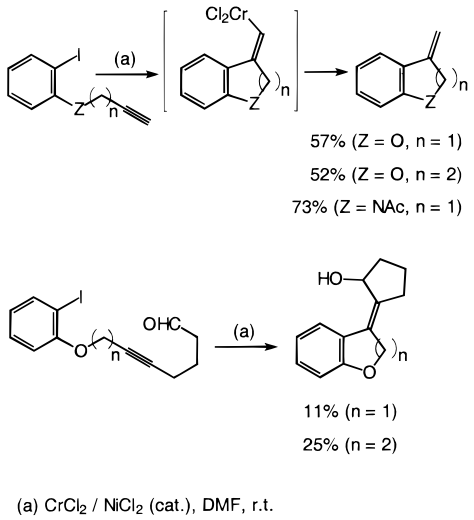
An imaginative incorporation of organochromium chemistry into a domino process has been described by Hodgson et al. (Scheme 27).[75] Thus, insertion of Cr(II)/Ni(II) into an aryl halide triggers a carbometalation process with a tethered alkyne to afford an alkenylchromium reagent that is finally protonated. Alternatively, the latter may be trapped by a suitably located aldehyde group in the tether, although the yield of the desired product was rather low in this particular case.

Table 25. Addition of Functionalized Arylzinc Iodides to Aldehydes Mediated by $CrCl_3$/TMSCl[74]



R_1	R_2	Yield (%)
2-F	4-NCC_6H_4	81
3-Cl	4-NCC_6H_4	81
3-COOMe	4-NCC_6H_4	82
4-COOMe	4-NCC_6H_4	81
4-Br	4-$O_2NC_6H_4$	81
3-Br	Et	68
3-Br	i-Pr	62
3-COOMe	i-Pr	72

Scheme 27

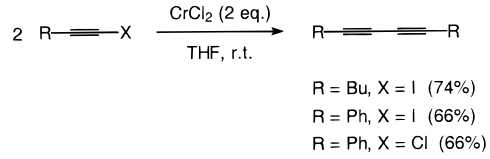


V. Alkynylchromium(III) Reagents

A. Intermolecular Additions

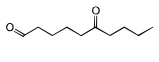
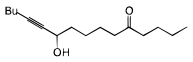
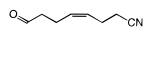
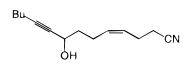
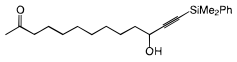
Treatment of alkynyl halides with $CrCl_2$ in the absence of electrophiles results in their reductive dimerization (Scheme 28).[76] However, in the presence

Scheme 28



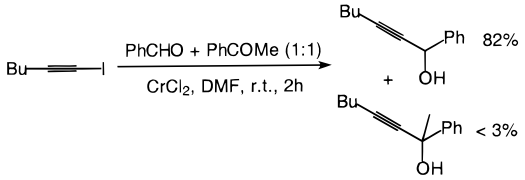
of an aldehyde, an efficient addition takes place which is once more distinguished by its high chemoselectivity. In close analogy to alkenyl-, aryl-, and allylchromium chemistry, a high preference for additions to aldehydes is observed, leaving unprotected ketone, ester, or cyano functions, etc., untouched (Table 26, Scheme 29). Enals provide exclusively 1,2-addition products.[76] While alkynyl iodides readily react at ambient temperature in DMF, the corresponding bromides need slightly higher

Table 26. Cr(II)-Mediated Reactions of Alkynyl Halides with Aldehydes

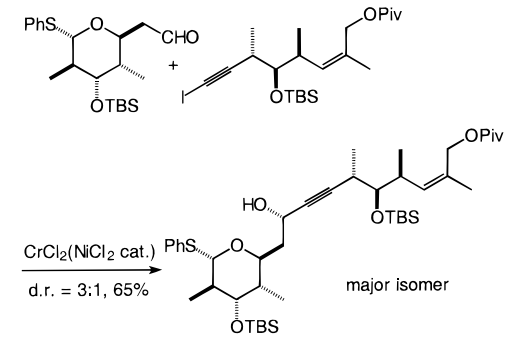
Halide	Aldehyde	Product	[a]	Yield (%)	Ref.
BuC≡CI	PhCHO	BuC≡CCH(OH)Ph	A	82	76
			B	74	76
			C	62	35
	$C_8H_{17}CHO$	BuC≡CCH(OH)C_8H_{17}	A	72	76
			B	65	76
	$C_5H_{11}CHO$	BuC≡CCH(OH)C_5H_{11}	C	79	35
	CH_3CH=CHCHO	BuC≡CCH(OH)CH=$CHCH_3$	A	62	76
			B	87	76
			A	76	76
			A	78	76
PhC≡CI	PhCHO	PhC≡CCH(OH)Ph	A	83	76
			B	89	76
	$C_8H_{17}CHO$	PhC≡CCH(OH)C_8H_{17}	A	71	76
			B	70	76
	CH_3CH=CHCHO	PhC≡CCH(OH)CH=$CHCH_3$	A	87	76
			B	73	76
$PhMe_2SiC$≡CBr	PhCHO	$PhMe_2SiC$≡CCH(OH)Ph	A	79	76
	$C_{11}H_{23}CHO$	$PhMe_2SiC$≡CCH(OH)$C_{11}H_{23}$	A	68	76
	$MeC(O)(CH_2)_8CHO$		A	73	76

[a] Method A: commercial $CrCl_2$, DMF. Method B: chromium reagent prepared from $CrCl_3$ + $LiAlH_4$ in THF. Method C: $CrCl_2$ (15 mol %), TMSCl, Mn powder, THF, rt.

Scheme 29



Scheme 30



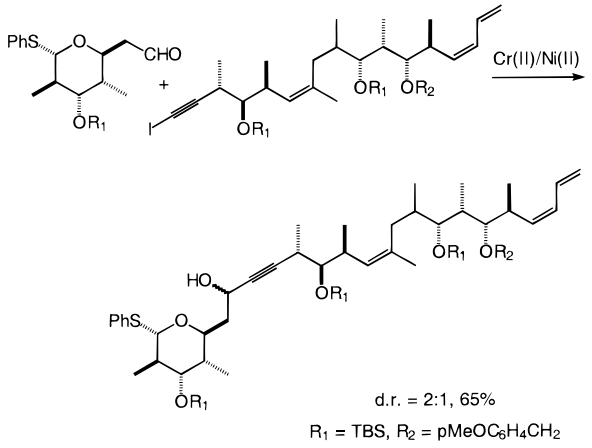
temperatures. It has been shown that the reaction can also be carried out with *catalytic* amounts of $CrCl_2$, Mn(0), and TMSCl as the oxophilic additive.[35]

The total synthesis of discodermolide reported by Schreiber et al. involves the addition of a polysubstituted alkynyl iodide to a functionalized aldehyde followed by Lindlar reduction of the resulting propargyl alcohol (d.r. = 3:1) as one of the key steps (Scheme 30).[77] Attempted additions of the appropriate (*Z*)-alkenyl iodide onto the same aldehyde, in order to avoid the Lindlar step, failed to afford the

desired product but led to the simple reduction of the C−I bond of the substrate. This suggests that the addition rather than the insertion step of the Cr(II) into the vinyl iodide is unfavorable in this particular case.

An alternative route to discodermolide was based upon the Cr(II)/Ni(II)-mediated addition of a more advanced alkynyl iodide to the same aldehyde substrate (Scheme 31). This reaction proceeded smoothly,

Scheme 31



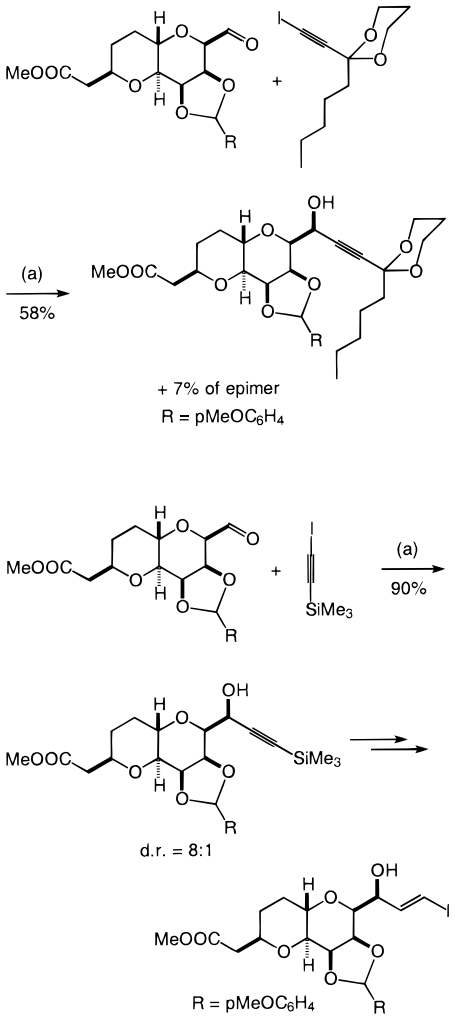
but it turned out to be a dead end for the total synthesis because the acetylene entity of the product could not be converted into the desired (*Z*)-alkene without concomitant reduction of the terminal diene.[77]

Another noteworthy application of alkynyl halides concerns model studies directed to the halichondrin family of natural products (see also section III D).[57b,78] Thus, the Cr(II)/Ni(II)-mediated addition of functionalized iodoalkynes to the rather labile aldehyde depicted in Scheme 32 proceeds smoothly without any complications due to enolization, epimerization, or subsequent dehydration.[78] It has also been noticed during these studies that the Ni(II) content in the $CrCl_2$ needs to be much lower in reactions of iodoalkynes than for iodoolefins.[57b,78]

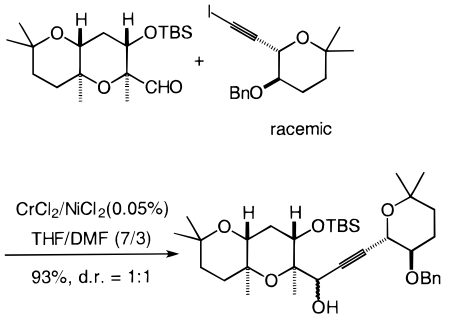
Another nice illustration of the utility of NHK reactions in multistep syntheses is also depicted in Scheme 32. Thus, trimethylsilyliodoacetylene is added in high yield to a polysubstituted aldehyde, and the adduct formed is subsequently converted into a new iodoalkene which itself becomes a substrate for the next NHK reaction. This sequence was used to assemble the entire right half of halichondrin and norhalichondrin (cf. section III D).[57b]

A study on the stereochemistry of maitotoxin, one of the most complex "low molecular weight" natural products isolated so far, involves a Cr(II)/Ni(II)-induced coupling of a racemic iodoacetylene with an optically active aldehyde. This transformation (Scheme 33) delivered only two out of four possible isomers in a 1:1 ratio, which were used as models for studying the stereochemistry of the C.92−C.107 segment of maitotoxin. Although the configuration of these

Scheme 32



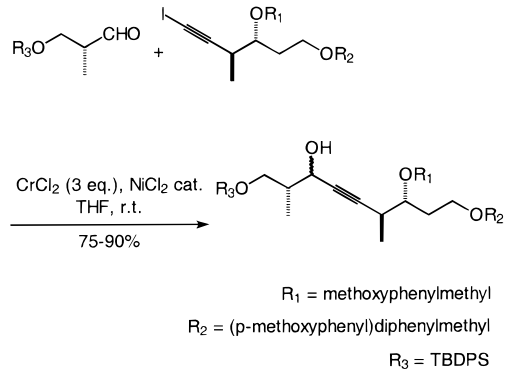
Scheme 33



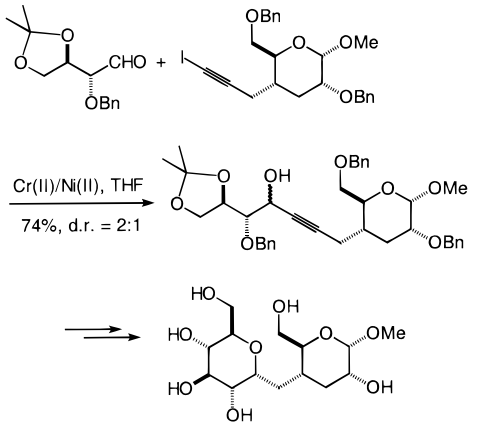
products at the propargylic alcohol site has not been rigorously assigned, this specific example shows that NHK reactions may sometimes take a stereoselective or even stereospecific course.[79]

Other applications of intermolecular Cr(II)-induced additions of polyfunctional alkynyl iodides to chiral aldehydes serve as key steps of a total synthesis of octalactins A and B (Scheme 34)[80] as well as of a convergent approach to C-disaccharides (Scheme 35).[81]

Scheme 34



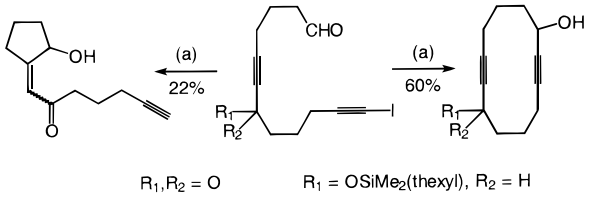
Scheme 35



B. Intramolecular Additions

Several intramolecular alkynylchromium addition reactions have been reported as excellent entries into highly strained cycloalkyne products. In this context, Keese et al. describe an efficient synthesis of cyclododec-2,8-diyne-1,7-dione based on a NHK reaction as the key step (Scheme 36).[82] These authors were

Scheme 36

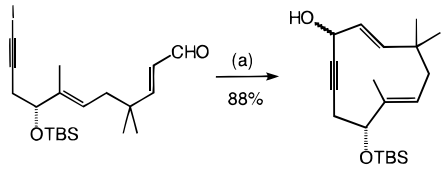


(a) $CrCl_2$, THF

able to obtain the desired 12-membered diol (R_1 = $OSiR_3$, R_2 = H) in 60% yield. Attempted cyclization of the corresponding keto aldehyde derivative (R_1, R_2 = O) failed to afford the desired macrocycle but afforded 22% of a five-membered hydroxy ketone, which is most likely formed by electron transfer to the aldehyde, 1,4-addition of the resulting ketyl radical to the ynone group, and (subsequent or simultaneous) reduction of the C−I bond.

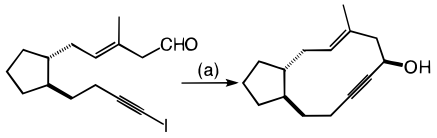
Elegant intramolecular alkynylations served as key steps in a recent total synthesis of epi-illudol (Scheme 37)[83] as well as for the construction of the dolabellane skeleton (Scheme 38).[84]

Scheme 37



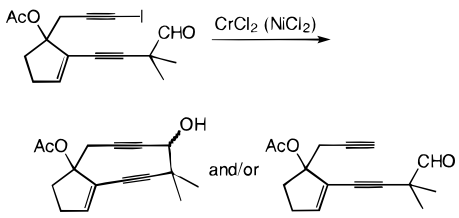
(a) $CrCl_2(THF)_2$, THF, slow addition

Scheme 38



(a) $CrCl_2$ (8 eq), $NiCl_2$ (0.06 eq), THF, slow addition

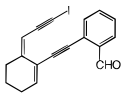
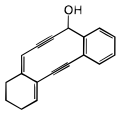
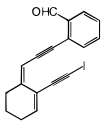
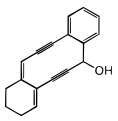
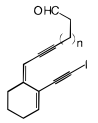
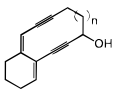
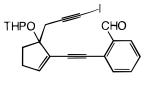
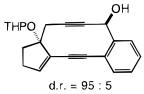
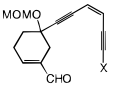
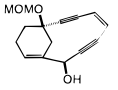
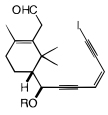
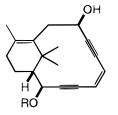
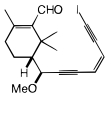
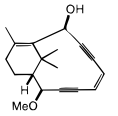
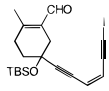
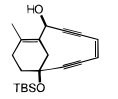
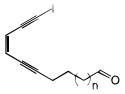
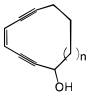
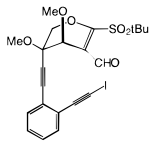
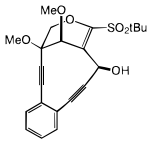
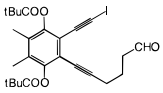
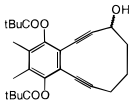
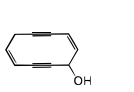
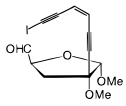
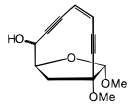
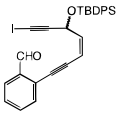
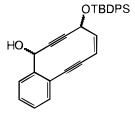
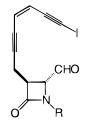
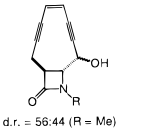
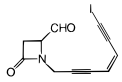
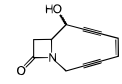
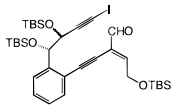
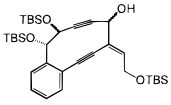
Table 27. $CrCl_2$-Mediated Formation of a Nine-Membered Ring: Effect of the Reaction Conditions[89]



$CrCl_2$ ($NiCl_2$)	Solvent	Molarity, M	Product
10 eq. (0.001 wt%)	THF, DMF, DMSO	0.01-0.05	reduction
10 eq. (0.1 wt%)	THF, DMF, DMSO	0.01-0.05	reduction
10 eq. (1 wt%)	THF, DMF, DMSO	0.01-0.05	reduction
10 eq. (0.1 eq.)	THF	0.01-0.05	reduction
10 eq. (0.3 eq.)	THF	0.01-0.05	reduction
10 eq. (0.5 eq.)	THF	0.01-0.05	reduction
10 eq. (1 eq.)	THF	0.01-0.05	reduction
10 eq. (0.6 eq.)	THF	0.002	cyclization (35%)
10 eq. (<1 wt%)	THF	0.001	cyclization (50%)
10 eq. (1 eq.)	THF	0.001	cyclization (50%)
20 eq. (1 eq.)	THF	0.001	cyclization (50%)

Not surprisingly, NHK reactions of alkynyl halides turned out to be a viable route to the highly cytotoxic endiyne antibiotics and various analogues thereof (Table 28). In some cases, 1 full equiv of $NiCl_2$ (!) in combination with ≥3 equiv of $CrCl_2$ were required. These conditions allow to run the reactions at low temperature (≤0 °C) in order to protect the thermally rather sensitive products from extensive decomposition by cycloaromatization.[85,86] Other authors, however, reported endiyne syntheses in which the Ni(II) content in the $CrCl_2$ could be kept in the usual, low range; even without any $NiCl_2$ added, some of the reactions afforded reasonable amounts of the desired endiynes.[87,88] One is tempted to interpret these contradictory data in the light of a publication of Buszek et al. who systematically studied the formation of a nine-membered diyne ring as a model reaction.[89] The results summarized in Table 27 indicate that the concentration of the substrate is the key parameter to success, whereas the yield is essentially insensitive to the Ni(II) content under high dilution conditions.

Table 28. Syntheses of Endiynes and Related Compounds

Substrate	Product	$CrCl_2$ (eq.)	$NiCl_2$ (eq.)	Yield (%)	Ref.
		3	1	26	85
		3	1	53	85, 215
		3	1	51 (n=1) 54 (n=2)	85
 d.r. = 95 : 5		9.7	1	41	86
		7	0.05	57 (X=I) 36 (X=Br)	87
		6	1.6	60 (R=MOM) 40 (R=Me)	88, 216 217
		8	0.06	37	217
		8		76	218
		5-8	0.07-0.1	34 (n=1) 76 (n=2)	219
		10	0.1	95	220
		9	0.64	75	221
		2.5	0.01	40	222
		4	0.016	26	223
		3	1	37	224
	 d.r. = 56:44 (R = Me) d.r. = 86:14 (R = $tBuMe_2Si$)	n.r.	n.r.	41 (R = Me) 68 (R = $SiMe_2tBu$)	225
		n.r.	n.r.	23 [a]	226
		3	1	58+11	227

[a] Refers to product isolated after in situ silylation of the crude alcohol.

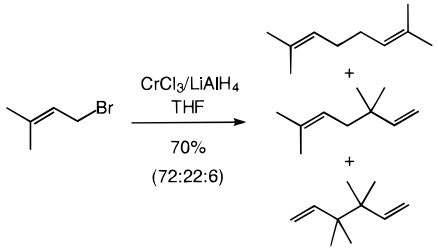
VI. Allylchromium(III) Reagents

A. Formation

The original 1977 publication of Hiyama and Nozaki et al. describes the $CrCl_2$-induced reaction of allylic halides and tosylates with carbonyl compounds.[7] It was noticed that the insertion of $CrCl_2$ into these substrates proceeds particularly well, and the resulting allylchromium species turned out to be highly valuable tools for advanced organic chemistry and natural product synthesis because of their pronounced chemo- and diastereoselectivity. The truely remarkable features of allylchromium(III) reagents formed as the likely nucleophiles in these reactions have been confirmed later on by many independent investigations. Consequently, a wealth of information has accumulated which is summarized below.[14] Most examples of Cr(II)-mediated reactions of allylic substrates follow the classical reaction conditions set forth by Nozaki's group[7] employing (over)stoichiometric amounts of Cr(II). However, it is appropriate to recall that such additions can also be conveniently carried out according to the recently discovered *catalytic* setup, with as little as 1 mol % of chromium salts being necessary in many cases (cf. section II B).[35]

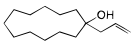
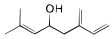
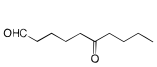
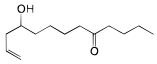
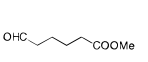
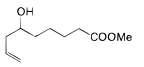
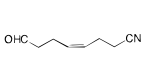
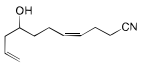
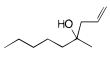
In the absence of other electrophiles, allylic halides undergo a smooth reductive dimerization when exposed to Cr(II) (Scheme 39).[7,8,90] Such Wurtz coupling

Scheme 39



reactions are significantly enhanced if the $CrCl_2$ is doped with Ni(II). Therefore, it is recommended to

Table 29. Cr(II)-Mediated Additions of Allyl Halides to Carbonyl Compounds[7,8]

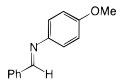
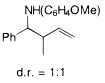
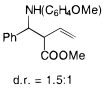
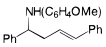
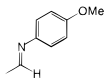
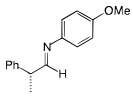
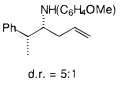
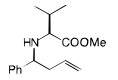
Carbonyl Compound	Halide	[a]	Product	Yield (%)
		A		90
PhCHO	prenyl bromide	B		89
Cyclohexanone	allyl bromide	A		78
	allyl iodide	B		74
	prenyl bromide	A		74
Cyclododecanone	allyl bromide	A		82
		B		83 (R=C_6H_{13})
RCHO	prenyl bromide	A		77 (R=i-Pr)
		A		82 (R=CH=$CHCH_3$)
PhCHO		A		81
PhCHO	allyl chloride	B		54
	prenyl bromide	A		88 (93)
		B		n.r.
	prenyl bromide	A		90
		B		98
	allyl bromide	B		66
	allyl bromide	B		75
	allyl bromide	B		66
2-heptanone	allyl bromide	B		78
4-heptanone	allyl bromide	B		33

[a] Method A: $CrCl_3 + {}^1/_2LiAlH_4$ as the reagent. Method B: commercial $CrCl_2$ as the reagent.

use *pure $CrCl_2$ without any doping agent in all cross-coupling experiments involving allylic substrates*, independent of whether the stoichiometric or catalytic protocol is adhered to! Note, however, that this is in contrast to aryl- and alkenyl halides (triflates) which are generally less reactive and usually require the assistance of Ni(II) or Pd(II) additives in order to guarantee well reproducible results (cf. section III).

In the presence of a carbonyl compound, a clean formation of the corresponding homoallyl alcohol is observed (Table 29).[7,14] The reactions are usually carried out in a "one-pot" Barbier-type manner by mixing the allyl halide, the aldehyde, and the Cr(II) salt in an appropriate solvent under an inert atmosphere. Stoichiometric amounts of allylic halides are sufficient, but it is common practice to use the halide in excess in order to improve the yields of the addition products, in particular if ketones rather than aldehydes are used as electrophiles.[8] The reactions proceed smoothly in THF or DMF, with the latter being beneficial if less reactive allyl chlorides are used. However, the strong stereochemical bias of such additions may be eroded by the more polar solvent (cf. section VI C).

Table 30. Reaction of Allylchromium Reagents with Imines in the Presence of $BF_3{\cdot}Et_2O$[98]

Imine	Allyl Halide	[a]	Product	Yield (%)
	allyl bromide	A		65 (R = C_6H_4OMe)
				67 (R = Bn)
	crotyl chloride	A	 d.r. = 1:1	52
		A	 d.r. = 1.5:1	75
	3-bromo-1-phenylpropene	A		57
	allyl bromide	B		45
	allyl bromide	B	 d.r. = 5:1	67
	allyl bromide	B	 de = 86%	75

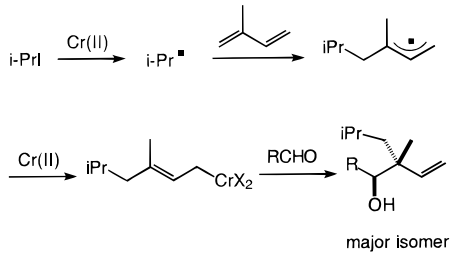
[a] Method A: using preformed imines. Method B: imine formed in situ prior to use from aldehyde and amine in the presence of MS 4 Å.

Allyl halides are by far the most widely used substrates, but other allylic compounds can also be converted into the corresponding allylchromium reagents without incident. Specifically, allyl tosylates and mesylates readily participate in NHK reactions,[7,8,91,92] particularly when carried out in aprotic dipolar solvents such as DMF or DMPU. Likewise, allyl phosphates are excellent starting materials.[92−94] Vinylepoxides also react with Cr(II) in the presence of LiI to afford functionalized allylic chromium reagents,[95] as do acrolein dialkyl acetals in the presence of Me_3SiI.[96] The reactivity of these functionalized species is discussed in section VI B. Attempted conversions of allyl sulfones into the corresponding organochromium reagents on exposure to Cr(II), however, met only with limited success.[97]

In addition to aldehydes and ketones, imines were found to be suitable substrates for reactions with allylchromium(III) species, provided that they are activated by means of $BF_3{\cdot}Et_2O$ (Table 30).[98] The observed diastereoselectivity, however, is generally rather low, because the N-substitutent precomplexed with BF_3 cannot interact with the Cr(III) cation and hence does not exert any stereodirecting effect.

In addition to the direct insertion of Cr(II) into allylic substrates, other methods for the preparation of allylchromium(III) species do exist. A rather unconventional approach is a three-component coupling reaction of a secondary or tertiary alkyl iodide, a 1,3-diene, and an aldehyde (Scheme 40).[49] It is assumed that the Cr(II) first reacts with the alkyl halide to afford the secondary or tertiary radical, which upon addition to the diene delivers an allyl radical; the latter is rapidly reduced by excess Cr(II) to the corresponding allylchromium intermediate which finally adds in the regular regio- and stereo-

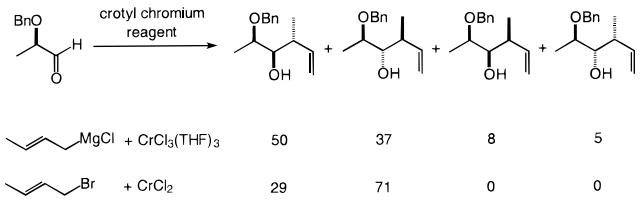
Scheme 40



selective manner to the aldehyde component.[49] This sequence of events is distinguished by two remarkable features: (i) It highlights that $CrCl_2$ can obviously distinguish between alkyl halides, alkyl radicals, and allyl radicals. (ii) Whereas the lifetime of the secondary or tertiary alkyl radical in the presence of $CrCl_2$ is long enough to add to the diene, the allyl radical thus formed is reduced to the anion before it initiates a radical polymerization of the diene substrate. This three-component coupling procedure can also be carried out catalytic in Cr(II) under Fürstner's conditions,[35] using $CrCl_2$ cat. in combination with Mn powder and TMSCl.

In contrast to the extensive use of the NHK approach to allylchromium reagents via oxidative addition to an allyl halide, there are only a few reports of C−C bond formations employing allylchromium species prepared by transmetalation of allylmagnesium halides with $CrCl_3(THF)_3$.[99] It is interesting to note, however, that the *genesis of the reagent seems to alter the stereoselectivity* in addition reactions to 2-benzyloxypropanal (Scheme 41). The

Scheme 41



reasons for this behavior have not been investigated in detail, but it is likely to assume that coexisting Lewis-acidic salts such as MgX_2 influence the course of the addition to a significant extent. Therefore, it is advisable to pay attention to the provenance of the $CrCl_2$ in any NHK reaction, because admixed salts formed during the reduction of $CrCl_3$ with one of the standard reducing agents may exert subtle influences on the outcome of the reaction (cf. section II A).

B. Functionalized Allylchromium Reagents

One of the most important advantages of NHK reactions in general terms stems from the tolerance of organochromium(III) species toward many different electrophilic sites on themselves. This possibility to prepare *functionalized nucleophiles* greatly improves the flexibility in retrosynthetic planning and accounts for many applications to advanced organic synthesis.

As can be gleaned from the examples outlined above, allylchromium reagents usually add in an S_N2' fashion to carbonyl compounds. In rare cases only,

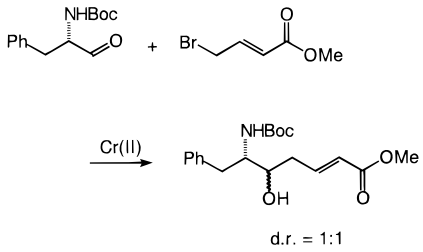
Table 31. Cr(II)-Mediated Additions of Methyl 4-Bromo-2-butenoate to Ketones R_1COR_2[104]

R_1	R_2	Solvent	Yield (%)	branched:linear
Me	Me	THF	53-71	100:0
		DMF	52	100:0
		[a]	51	100:0
Et	Me	[a]	94	95:5
		THF	44	95:5
		DMF	37	75:25
Ph	Me	MeCN	46	95:5
		THF	47	90:10
		DMF	24	85:15
		[a]	41	70:30
	-$(CH_2)_5$-	THF	83	82:18

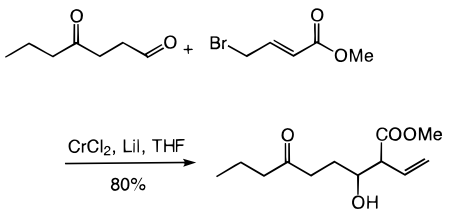
[a] The ketone was used as the solvent.

linear addition is observed.[100] However, the latter behavior becomes more pronounced if the double bond of the substrate is conjugated to an electron-withdrawing substituent.[101,102] Thus, 4-bromo-2-butenoates have been found to afford either branched (Scheme 43)[103] or linear adducts (Scheme 42),[102]

Scheme 42



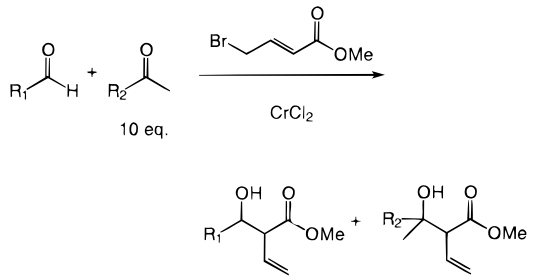
Scheme 43



although the data presently available do not allow to fully rationalize the course of the reaction. However, it is likely that the "linear" products are the thermodynamically more stable ones, whereas the "branched" products are formed under kinetically controlled conditions. Additions of 4-bromo-2-butenoates to ketones are also possible (Table 31),[104] although an excellent aldehyde selectivity was noticed in inter- as well as in intramolecular competition experiments (Table 32). As examplified in Scheme 44, even a distinction between methyl ketones and higher alkyl ketones can be reached.[103]

The insertion of Cr(II) into allylic halides is usually much faster than into vinylic ones, particularly in the absence of Ni(II) as the doping agent. This reactivity pattern can be exploited for the formation of halogen-substituted allylchromium reagents (Table 33).[7a,105] Thus, treatment of 3-bromo-1-chloro-(or bromo)-propene with $CrCl_2$ in THF or DMF leads to the selective formation of the respective halohydrins. Minor amounts of linear addition products and/or dienes,

Table 32. Cr(II)-Mediated Reactions of Methyl 4-Bromo-2-butenoate. Intermolecular Competition Experiments between Aldehydes and Methyl Ketones[103]



R_1	R_2	Conditions [a]	Yield (%)	Aldehyde Selectivity
Et	Me	DMF	83	50:1
		DMF/LiI	72	25:1
		THF/LiI	77	60:1
		MeCN/LiI	75	100:1
Ph	Ph	DMF	71	60:1
		THF/LiI	70	40:1
		MeCN/LiI	65	90:1

[a] Ratio 4-bromo-2-butenoate:aldehyde:methyl ketone = 1:4:40.

Scheme 44

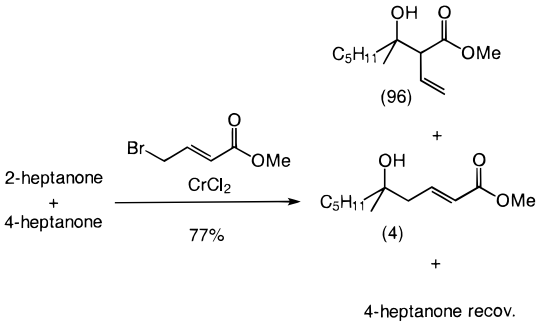
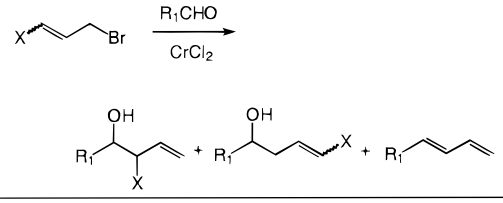


Table 33. Addition Reactions of Halogen-Substituted Allylchromium Reagents to Aldehydes[105]

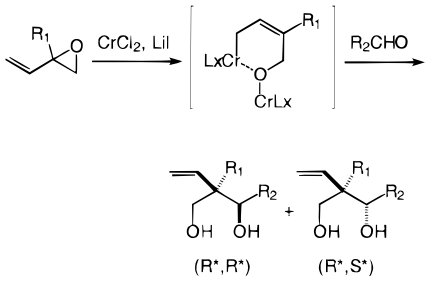


X	R_1CHO	Solvent	Ratio (crude)	Halohydrin (Yield, %)	Linear Adduct (Yield, %)
Cl	PhCHO	THF	85:13:2	62	12
Cl	$PhCH_2CHO$	THF	85:13:2	29	8
		DMF	72:23:5	64	21
Br	PhCHO	THF	46:34:20	25	20

obviously formed by over-reduction processes, may accompany the halohydrin products.

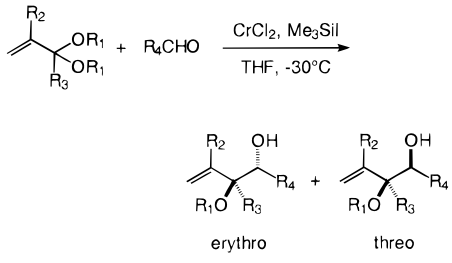
Functionalized allylchromium(III) reagents can also be formed by reaction of vinylepoxides with Cr(II) in the presence of LiI (Table 34).[95] The reaction is triggered by the attack of LiI to the oxirane; the substituted allylic iodide formed inserts the Cr(II) giving rise to a functionalized allylchromium entity. As shown in Table 34, an internal ligation of the

Table 34. $CrCl_2$-Mediated Reactions of 1,3-Diene Monoepoxides with Aldehydes in the Presence of LiI[95]



R_1	R_2	Yield (%)	(R*,R*):(R*,S*)
Me	Ph	95	98:2
Me	$PhCH_2CH_2$	97	96:4
Me	n-C_8H_{17}	96	96:4
Me	c-C_6H_{11}	98	97:3
Me	PhCH=CH	95	90:10
n-$C_{11}H_{23}$	Ph	99	94:6
n-$C_{11}H_{23}$	n-C_8H_{17}	93	92:8
H	Ph	54	95:5

Table 35. Cr(II)-Mediated Addition Reactions of Acrolein Dialkylacetals to Aldehydes[96,228]



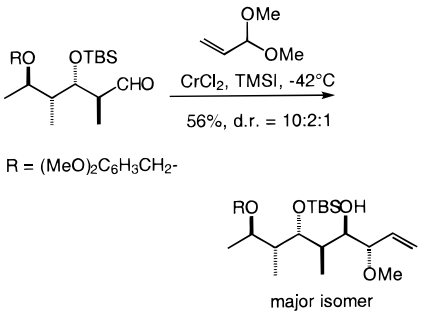
R_1	R_2	R_3	R_4	Yield (%)	*erythro:threo*
Me	H	H	Ph	99	88:12
Bn	H	H	Ph	98	88:12
			n-C_8H_{17}	95	87:13
			$PhCH_2CH_2$	99	88:12
			c-C_6H_{11}	93	88:12
			t-Bu	91	33:67
			PhCH=CH	97	76:24
Bn	Me	H	Ph	99	85:15
			n-C_8H_{17}	99	88:12
Bn	H	Me	Ph	88	92:8
			n-C_8H_{17}	83	93:7
Bn	H	H	$CH_3CO(CH_2)_8$	86	87:13
Me	H	H		62	10:1.1:1 [a]

[a] Stereochemistry of the byproducts not specified, cf. ref 228.

oxygen atom likely locks the configuration of the double bond of this species, which subsequently is translated into a high diastereoselectivity in reactions with aldehydes. When applied to isoprene monoepoxide (R_1 = Me), this method even allows to form quarternary centers in a highly diastereoselective manner.[95]

Acrolein acetals are activated by $CrCl_2$ in the presence of Me_3SiI (Table 35).[96] The resulting allylchromium reagents add regioselectively at the alkoxy-substituted site to aldehydes. A high preference for

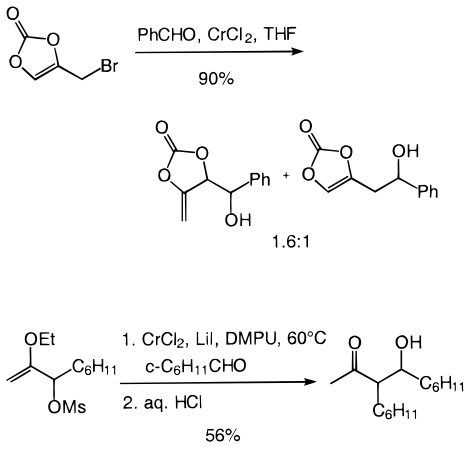
Scheme 45



the erythro-configured 1,2-diol derivatives is observed in most cases.[96] The reaction has been employed as a key step in a study directed toward the synthesis of the C.13−C.25 segment of bafilomycin A_1 (Scheme 45).[106] Crotonaldehyde acetals, however, could not be used as substrates. A very elegant modification of this procedure has been recently described by Boeckman et al., which employs only catalytic amounts of $CrCl_2$ in combination with Mn(0), TMSCl, and NaI cat.[48] Details of this improved setup are discussed in section II B.

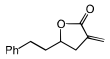
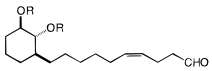
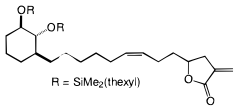
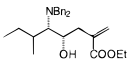
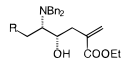
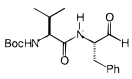
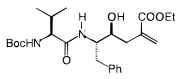
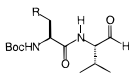
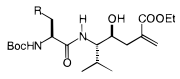
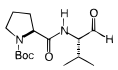
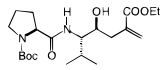
Particularly interesting are reactions involving functionalized allylchromium reagents bearing leaving groups at the C-atom *vicinal* to the C−metal bond. Organometallic species of this type are usually prone to reductive elimination and are therefore rarely found in the literature. However, organochromium chemistry seems to open access to reagents of this type as can be seen from the clean conversions of bromomethyl vinylene carbonate[105] as well as of a functionalized allyl mesylate[92] depicted in Scheme 46.

Scheme 46



In addition to the examples shown above, many other functionalities are tolerated at the central C-atom of the allylchromium reagents, including ester, sulfone, or silyl groups. Noteworthy are reactions starting from 2-(bromomethyl)acrylates because the hydroxyesters primarily formed can (spontaneously) cyclize to α-methylene-γ-butyrolactones (Table 36, Scheme 47).[24,93,102,107,108] 2-(Bromomethyl)acrylonitrile can also be used as starting material for similar purposes.[108] The reactions also proceed with catalytic amounts of $CrCl_x$ ($x = 2, 3$) according to Fürstner's procedure.[35] Oshima et al. noticed that the

Table 36. Chromium-Mediated Additions of 2-(Bromomethyl)acrylates

Aldehyde	Product (Major isomer depicted)	Yield (%)	Ref.
RCHO		94 (R = Ph) 82 (R = *n*-Bu) 46 (R = CH=CHCH$_3$) 80 (R = i-Bu) 85 (R = $C_{11}H_{23}$)	24 107
$PhCH_2CH_2CHO$		80 [a]	35
		,83	107
		n.r.	93
		75	93
		78	93
		53	93
		67	93
		71	93
		59	93

[a] Using Fürstner's catalytic setup with $CrCl_2$ (7 mol %), Mn, TMSCl, THF, rt, cf. ref 35.

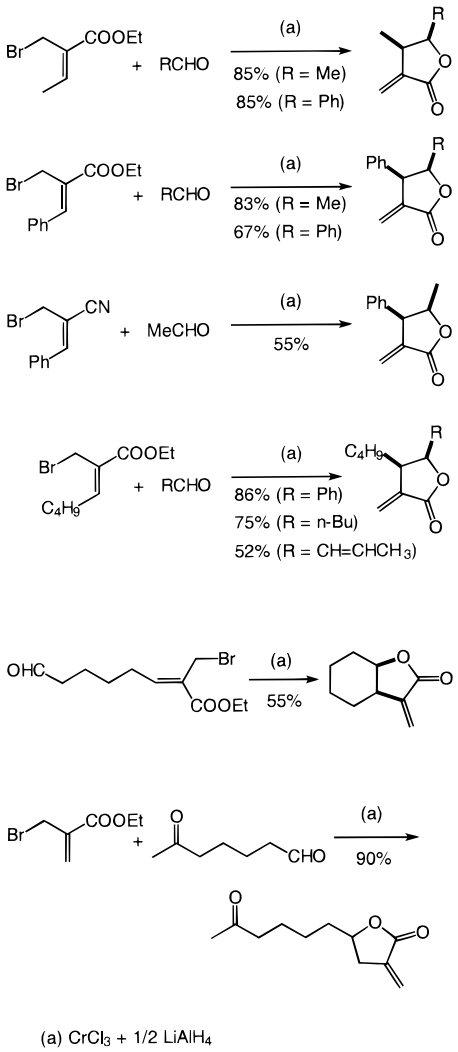
reaction stops at the hydroxyester stage if commercially available $CrCl_2$ is used as the reagent, whereas $CrCl_2$ formed in situ from $CrCl_3$ and $LiAlH_4$ leads directly to the corresponding α-methylene-γ-butyrolactones.[24] This different behavior is ascribed to the presence of Lewis acidic aluminum salts in the latter case. The reactions exhibit the usual chemoselectivity for aldehydes and lead exclusively to cis-disubstituted products in inter- and intramolecular reactions of appropriately substituted derivatives (Scheme 47). NHK reactions of 2-(bromomethyl)-acrylates also found many applications for the preparation of hydroxyethylene peptide isosteres (Scheme 48).[102]

C. Stereochemistry

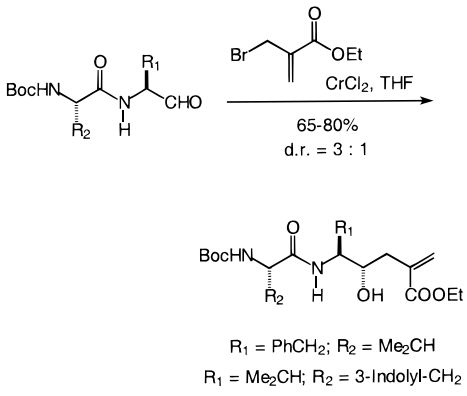
1. Syn/Anti Ratio

Reactions of aldehydes with γ-substituted allylchromium reagents usually afford homoallyl alcohols with an excellent degree of anti selectivity.[14,109] This stereochemical preference was first analyzed and interpreted by Heathcock et al. on the basis of the experiments summarized in Scheme 49.[110]

Scheme 47

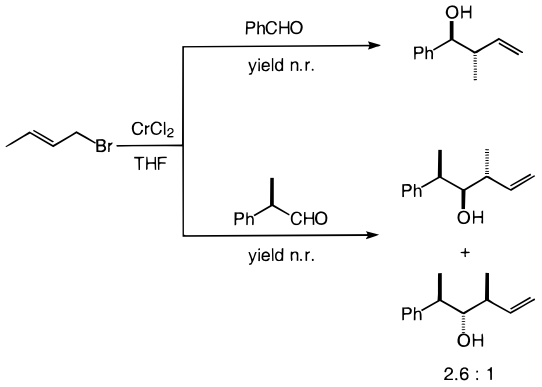


Scheme 48

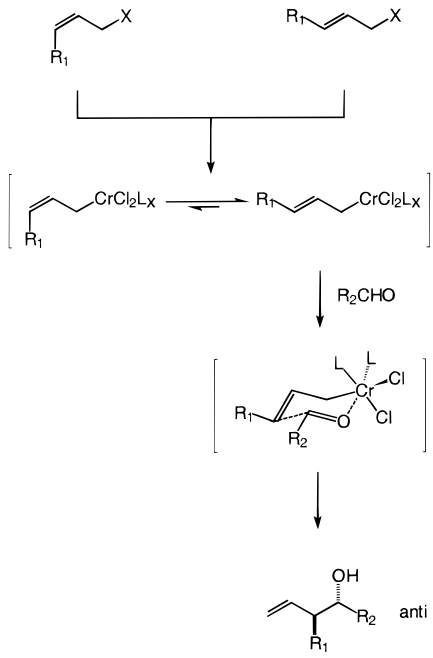


It turned out that this high anti-selectivity is independent of whether the starting halide is (*E*)- or (*Z*)-configured.[8,9,14,109] This *characteristic stereoconvergent path* may be interpreted in terms of a rapid equilibration of the intermediates, with the (*E*)-allylchromium species being highly favored (and/or eventually more reactive) (model A, Scheme 50). Its subsequent addition to the aldehyde via a Zimmerman−Traxler transition state involving an octahedrally coordinated Cr(III) ion leads to the observed

Scheme 49



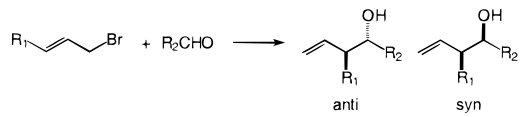
Scheme 50. Standard Model A for the Cr(II)-Mediated Addition of Allyl Halides to Aldehydes

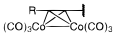
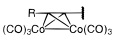


anti configured product.[9,110] In line with this rationale, aprotic-dipolar solvents or cosolvents such as DMF or pyridine usually decrease the diastereoselectivity as they compete with the aldehyde for the coordination sites on the organochromium intermediates and hence result in a less compact transition state.[8,9] Changing the reaction temperature or adding phosphines to the mixture has little effect on the stereoselectivity.[9] However, very bulky aldehydes such as tBuCHO may force the transition state to adopt a twist-boat rather than a chair conformation and hence favor the syn product.[8,9] This notion is corroborated by an investigation on the crotylation of propynal derivatives: while ynals usually afford a high anti:syn ratio, increasing the steric demand by complexation of the triple bond to the $Co_2(CO)_6$ fragment lowers the diastereoselectivity due to deviations from the Zimmerman−Traxler model (Table 37).[111]

However, it should be noted that an alternative explanation has also been launched in the literature (model B, Scheme 51).[14c] According to this rationale, the first electron is transferred from the Cr(II) to the

Table 37. Cr(II)-Mediated Addition of γ-Substituted Allyl Halides to Achiral Aldehydes



R_1	R_2	Solvent	*anti:syn*	Yield (%)	Ref.
Me	*c*-C_6H_{11}	THF	n.r.	n.r.	229
	Ph	THF	100:0	96 (87 [a])	11,9
	Ph	DMF	75:25	92	11, 9
	n-C_3H_7	THF	93:7	59	11, 9
	i-Pr	THF	95:5	55	11, 9
	i-Pr	DMF	66:34	78	11, 9
	n-C_5H_{11}	THF	97:3	70	11, 9
	n-C_5H_{11}	DMF	68:32	77	11, 9
	t-Bu	THF	35:65	64	9
	t-Bu	DMF	37:63	63	9
	$CH_3CH{=}CH$	THF	83:17	73	9
			96:4 (R = Ph)	75 (R = Ph)	
			97:3 (R = CH_2OBn)	70 (R = CH_2OBn)	
	RC≡C	THF	96:4 (R = *n*-C_5H_{11})	72 (R = *n*-C_5H_{11})	111
			95:5 (R = $SiMe_3$)	77 (R = $SiMe_3$)	
			94:6 (R = TIPS)	75 (R = TIPS)	
			87:13 (R = Ph)	75 (R = Ph)	
			87:13 (R = CH_2OBn)	61 (R = CH_2OBn)	
		THF	93:7 (R = *n*-C_5H_{11})	89 (R = *n*-C_5H_{11})	111
			95:5 (R = $SiMe_3$)	79 (R = $SiMe_3$)	
			54:46 (R = TIPS)	79 (R = TIPS)	
	RC≡C	DMF	71:29 (R = TIPS)	81 (R = TIPS)	111
		DMF	62:38 (R = TIPS)	68 (R = TIPS)	111
Ph	Ph	THF	83:17	n.r.	100
Me_3Si [b]	Ph	THF	100:0	69	230
	C_3H_7	THF	100:0	54	230
	c-C_6H_{11}	THF	100:0	65	230
$MeCH{=}CH$	Ph	THF	73:27	82	9

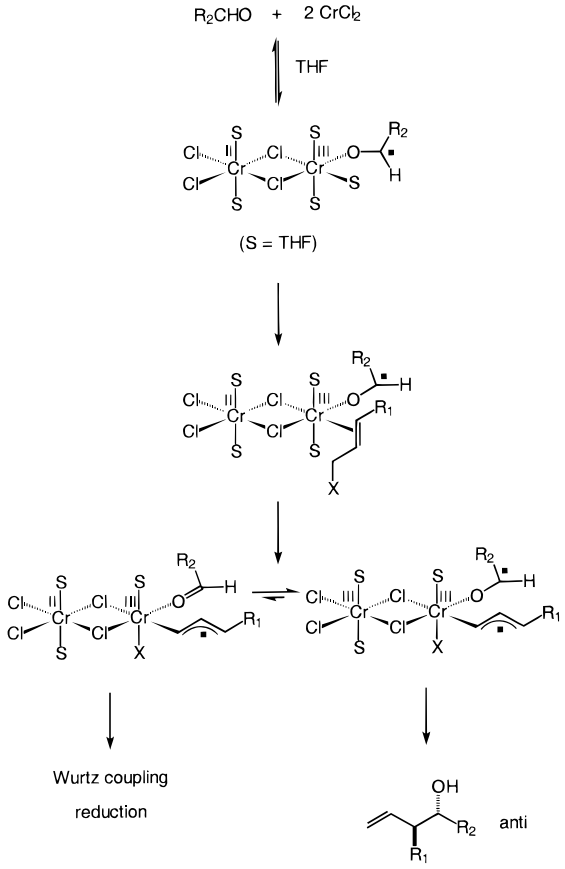
[a] Yield obtained with (*Z*)-1-bromo-2-butene. [b] The starting material, i.e. 1-bromo-3-trimethylsilyl-2-propene, contains some 1-bromo-1-trimethylsilyl-2-propene.

aldehyde rather than to the allyl halide. The resulting ketyl radical reversibly passes its unpaired electron onto the coordinated allylic substrate. Equilibration of the stereoisomers occurs at the stage of the allylradical intermedate thus formed. A second s.e.t. process followed by a coupling of the resulting diradical via a Zimmerman−Traxler-type transition state affords the final product. Wurtz-type dimerization of the allyl halide and/or reduction, which frequently compete with productive NHK reactions of allylic substrates, can be readily explained by this scenario.[14c]

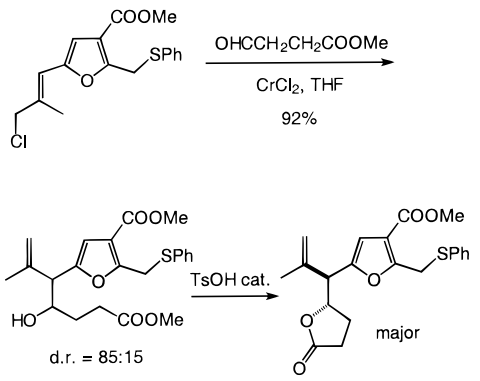
Presently, no detailed mechanistic investigations are available which allow to distinguish between these two alternative mechanisms. Most authors, however, argue on the basis of model A. Anyway, the data summarized in Table 37 reveal that the preference for the anti-configured isomer is a rather general feature of Cr(II)-mediated additions of γ-monosubstituted allylic substrates to aldehydes.[14,109]

An illustrative example for the stringent stereochemical preferences outlined above as well as for the excellent functional group tolerance of organochromium chemistry was reported during a study directed toward the synthesis of furanocembranolides (Scheme 52).[112]

Scheme 51. Model B for the Cr(II)-Mediated Addition of Allyl Halides to Aldehydes



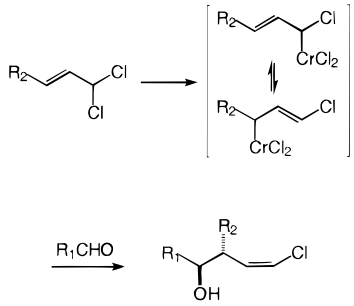
Scheme 52



Again, *functionalized* crotylchromium(III) reagents are widely used in stereoselective addition reactions. For example, α-chloro crotylchromium reagents are likely intermediates in reactions of 1,1-dichloro-2-propenes with $CrCl_2$.[113] These halogenated organometallic species exhibit no peculiarities, leading to anti-*Z*-configured products with good to excellent degrees of selectivity (Table 38). 1,3,3-Tribromopropene reacts similarly, affording predominantly the anti-*Z*-configured bromohydrins (Table 39). In these cases the stereoselectivity strongly depends on the reaction temperature.[114]

A few important exceptions to the overall preference for anti configured homoallyl alcohols must be mentioned: (1) In contrast to the stereoconvergent reactivity pattern of γ-monosubstituted allyl substrates outlined above, *γ,γ-disubstituted allylic ha-*

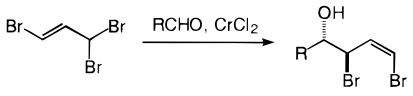
Table 38. Stereoselective Additions of α-Chloro Crotylchromium Reagents to Aldehydes[113]



anti-Z (major isomer)

R_1	R_2	Yield (%)	Z:E	*anti:syn*
Ph	Me	96	97:3	97:3
$PhCH_2CH_2$	Me	95	96:4	93:7
n-C_8H_{17}	Me	88	95:5	99:1
c-C_6H_{11}	Me	86	97:3	>99:1
PhCH=CH-	Me	58	88:12	95:5
$CH_3CO(CH_2)_8$	Me	85	98:2	>99:1
Ph	*n*-C_3H_7	92	99:1	100:0
$PhCH_2CH_2$	*n*-C_3H_7	87	99:1	100:0
n-C_8H_{17}	*n*-C_3H_7	90	97:3	100:0
c-C_6H_{11}	*n*-C_3H_7	83	>99:1	100:0
$CH_3CO(CH_2)_8$	*n*-C_3H_7	89	100:0	100:0

Table 39. Cr(II)-Induced Addition Reactions of 1,3,3-Tribromopropene[114]



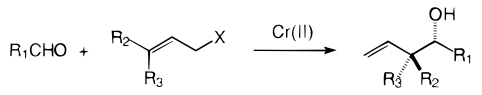
major isomer

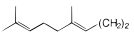
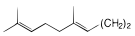
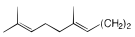
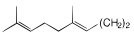
R	[a]	T (°C)	Yield (%)	*anti-E*	*anti-Z*	*syn-Z*	*syn-E*
Ph	**B**	-28	66	17	63		20
	A	-28	76	11	80		9
	A	-12	88	6	83	7	4
	A	0	67	3	83	13	1
	A	+20	51	4	59	36	1
n-C_7H_{15}	**A**	-25	79	22	66	1	11
$PhCH_2CH_2$	**A**	-12	40	10	79	7	4
i-Pr	**A**	-12	57		90		

[a] Method A: addition of tribromopropene to a suspension of the aldehyde and $CrCl_2$ (2:1:4) in THF. Method B: addition of a mixture of the aldehyde and tribromopropene to a suspension of $CrCl_2$ in THF (1:2:2).

lides or phosphates follow a stereodivergent course, translating the configuration of the starting material into the stereochemistry of the product, even if the substituents R_2 and R_3 are of similar size. This implies that the equilibration of the trisubstituted allylchromium(III) intermediates is slow relative to their addition to the aldehyde. The examples compiled in Table 40 clearly illustrate this point.[35,92,94] (2) In close analogy, slow interconversions are responsible for the fact that substrates bearing large substitutents X at the *central* C-atom of the allylic unit also show a stereodivergent reaction path (Scheme 53). A study employing stereomerically pure 2-silyl-3-alkyl-substituted allyl phosphates as

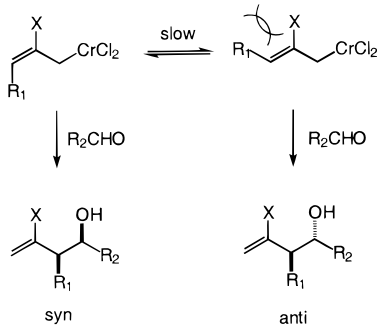
Table 40. Cr(II)-Mediated Reactions of γ,γ-Disubstituted Allylic Halides or Phosphates with Aldehydes



R_1	R_2	R_3	X	[a]	d.r.	Yield (%)	Ref.
Ph		Me	$OP(O)(OEt)_2$	**A**	97:3	94	92
	Me		$OP(O)(OEt)_2$	**A**	99:1	98	92
	Me		Cl	**A**	99:1	93	94
n-C_5H_{11}		Me	$OP(O)(OEt)_2$	**A**	94:6	93	92
	Me		$OP(O)(OEt)_2$	**A**	99:1	94	92
Pr-CH=CH		Me	$OP(O)(OEt)_2$	**A**	96:4	77	92
	Me		$OP(O)(OEt)_2$	**A**	97:3	84	92
	Me		Cl	**A**	96:4	68	94
BuC≡C		Me	$OP(O)(OEt)_2$	**A**	>99:1	86	92
	Me		$OP(O)(OEt)_2$	**A**	98:2	89	92
n-C_6H_{13}	Pr	Bu	$OP(O)(OEt)_2$	**A**	>99:1	90	92
	Bu	Pr	$OP(O)(OEt)_2$	**A**	98:2	64	92
Ph	Pr	Bu	$OP(O)(OEt)_2$	**A**	93:7	66	92
	Bu	Pr	$OP(O)(OEt)_2$	**A**	>99:1	75	92
	Me	Bu	$OP(O)(OEt)_2$	**A**	97:3	95	92
c-C_6H_{11}	Me	Bu	$OP(O)(OEt)_2$	**A**	90:10	89	92
Ph		Me	$OP(O)(OEt)_2$	**A**	95:5	84	92
					97:3	94	94
		Me	Br	**B**	94:6	79	35
n-C_6H_{13}		Me	$OP(O)(OEt)_2$	**A**	93:7	80	92
c-C_6H_{11}		Me	$OP(O)(OEt)_2$	**A**	94:6	86	92

[a] Method A: excess $CrCl_2$, LiI cat., DMPU. Method B: $CrCl_2$ (7 mol %), Mn, Me_3SiCl, THF.

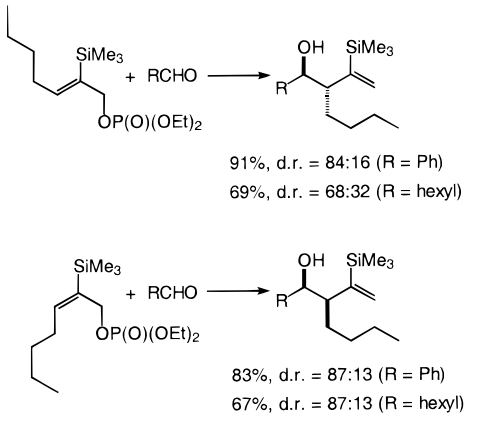
Scheme 53



starting materials suggests that the $E \rightleftharpoons Z$ isomerization of the intermediate allylchromium(III) species is slow relative to the addition of these species to aldehydes (Scheme 54). Therefore, the configuration of the double bond is translated into the stereochemistry of the resulting homoallyl alcohol.[94]

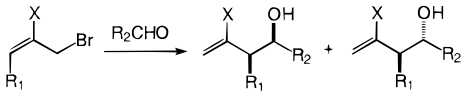
This pattern is confirmed by many additional examples in the literature in which allylic compounds bearing the γ-substituents and the $-CH_2CrX_2$ group in a (*Z*) arrangement preferably deliver the syn rather than the anti homoallyl alcohol (Table 41).[101,109,115]

Scheme 54



(a) $CrCl_2$, LiI cat., DMPU

Table 41. Chromium-Mediated Reactions of Allylic Substrates Bearing Substituents X on the Central C-Atom of the Allylic Unit



R_1	R_2	X	Yield (%)	*syn : anti*	Ref.
Me	t-Bu	SO_2Ph	92	81:0 [a]	101
					115
Me	i-Bu	SO_2Ph	93	99:1	101
					115
Me	MeCH=CH	SO_2Ph	83	90:10	101
					115
Me	$CH_3(CH_2)_4$	SO_2Ph	89	98:2	101
Me	2-thienyl	SO_2Ph	96	100:0	101
Pr	$CH_3(CH_2)_4$	SO_2Ph	93	94:6	101
					115
Pr	i-Bu	SO_2Ph	95	96:4	101
					115
i-Bu	$CH_3(CH_2)_4$	SO_2Ph	89	90:10	101
					115
Bu	$CH_3(CH_2)_8$	SO_2Ph	91	93:7	101
Me	$CH_3(CH_2)_4$	SO_2Ph	75 [b]	100:0	101
Pr	$CH_3(CH_2)_4$	SO_2Ph	70 [b]	99:1	101
Me	Ph	$SiMe_3$	91	67:33	230
Me	Et	$SiMe_3$	61	63:37	230
Me	i-Pr	$SiMe_3$	57	68:32	230
H	Ph	Cl	94	---	8

[a] Together with 19% of the linear adduct. [b] Using CrI_2 instead of $CrCl_2$.

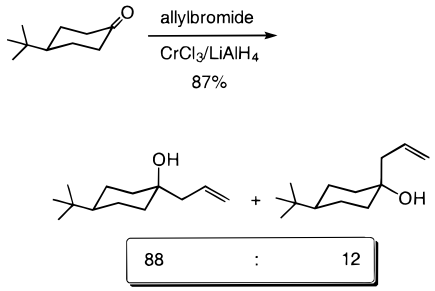
2. Axial/Equatorial Attack

Equatorial attack prevails in the addition of allylbromide to *tert*-butylcyclohexanone induced by $CrCl_3$/$LiAlH_4$ or by commercial $CrCl_2$ (Scheme 55).[7,8]

3. Substrate-Controlled Stereoselectivity

Controlled additions of crotylmetal reagents to α-substituted aldehydes give access to defined stereotriads and have therefore been extensively studied. In this context, various systematic investigations have shown that allyl (crotyl) chromium species (i) mainly deliver the Cram product (1,2-anti/2,3-syn)

Scheme 55



Scheme 56

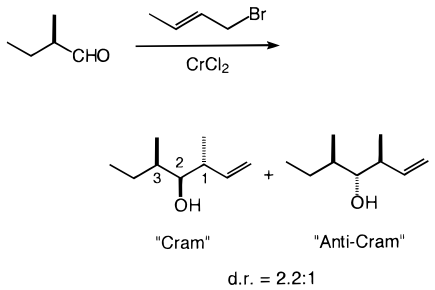
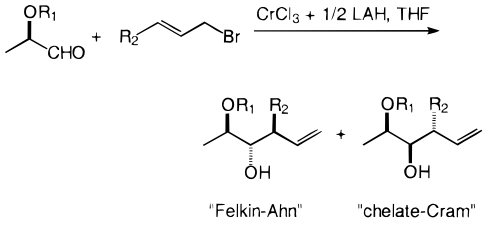


Table 42. Stereoselectivity of Cr(II)-Mediated Additions of Allyl Bromides to Differently Substituted Lactaldehyde Derivatives[117]

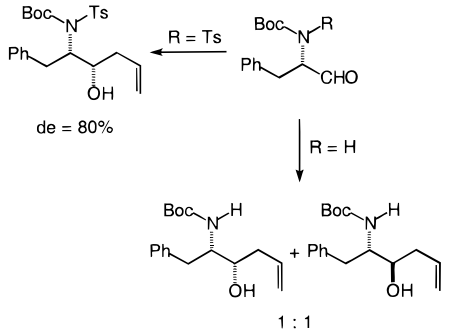


R_1	R_2	Felkin-Ahn:Chelate-Cram	Yield (%)
THP	Me	89:11	80
THP	Ph	91:9	71
THP	*n*-C_4H_9	>99:1	75
$SiMe_2tBu$	*n*-C_4H_9	>99:1	90

in additions to α-chiral aldehydes, although the Cram:anti-Cram selectivity is often quite modest; a prototype example is shown in Scheme 56[116] and (ii) generally afford the Felkin−Ahn rather than the chelate−Cram product with moderate to good selectivity in additions to aldehydes bearing heteroatoms in the α- or *β*-position.[14b,116,117] A systematic investigation by Mulzer et al. nicely illustrates this stereochemical bias for a series of differently O-protected lactaldehyde derivatives,[117] whereby a raising preference for the Felkin−Ahn product was observed with increasing size of the O-substituent (Table 42).

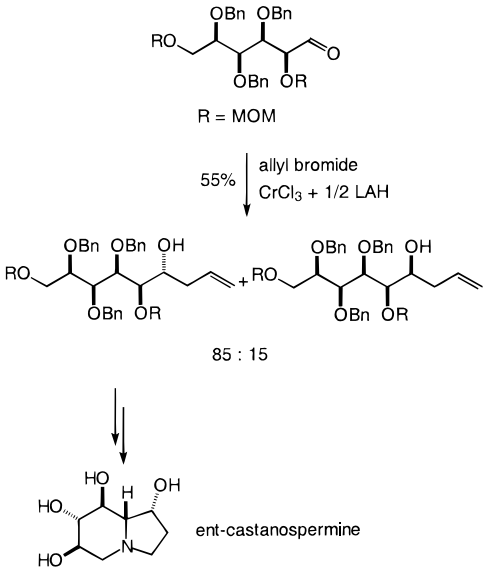
This overall profile shows that the *course of the additions is mainly governed by steric interactions and that organochromium reagents are no good candidates for chelation-controlled reactions.*[14,93,99,116−122] Even intramolecular heteroatom-assisted additions induced by Cr(II) do not afford any higher level of selectivity than those employing Mg or Sm(II).[123] In addition to the examples compiled above, the reactions of allylchromium reagents to differently protected aminoaldehydes (Scheme 57) show that steric

Scheme 57



effects override chelation. While −NHBoc-protected substrates provide essentially a 1:1 mixture of the diastereoisomeric products, an N(Boc)(Ts)-protected congener leads to an appreciable diastereoselectivity.[102] This reliable Felkin−Ahn selectivity of NHK reactions sets the basis for Mulzer's concise approach to all possible isomers of the antimycin A_3 degradation product blastmycinone[117] as well as for a total synthesis of the unnatural enantiomer of castanospermine (Scheme 58).[118]

Scheme 58



The examples compiled in Tables 43−45 further confirm the notion that additions of allylic NHK reagents to chiral aldehydes are distinguished from many other allylmetal reagents by their pronounced *tendency for a nonchelated mechanism*. In view of this very consistent picture, an earlier report[124] claiming the highly selective formation of the chelate−Cram product in very similar cases has to be met with caution and is therefore not duplicated here.

4. Reagent-Controlled Stereoselectivity

Cr(II)-mediated reactions of chiral allylic bromides with achiral aldehydes also proceed with (high) Felkin−Ahn selectivity.[125] As can be deduced from the examples compiled in Table 46, the configuration is determined by the stereocenter δ to the halide. Further remote chiral centers may increase the degree of induction but do not alter its sense. Particularly high selectivities are observed if the steric interactions in the chairlike transition states are maximized by appropriate branching of the substrates.[125] This strategy has been used to prepare a key intermediate for the total synthesis of nephromopsinic acid.[125]

Using differently protected allyl bromides bearing an ethereal stereogenic substitutent at C-2, Mulzer et al. also noticed significant levels of 1,4-syn-asymmetric induction if the reactions are carried out in DMF at −20 °C (Table 47).[126] Although some bromide for chloride exchange due to Finkelstein reactions with $CrCl_2$ could not be suppressed, reactions in DMF turned out to be higher yielding than those in THF, which are complicated by competing Oppenauer-type oxidation of the resulting alcohols

Table 43. Chromium-Mediated Addition of Allyl Bromide to Chiral Carbonyl Compounds

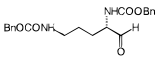
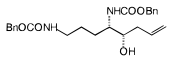
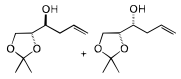
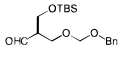
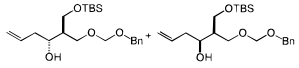
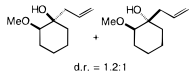
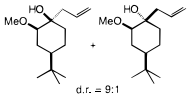
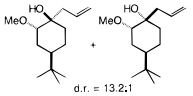
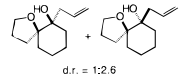
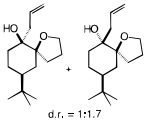
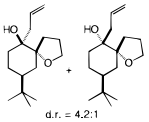
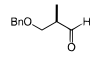
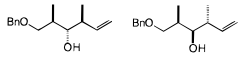
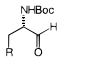
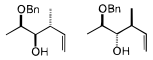
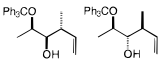
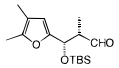
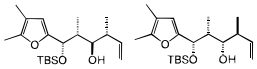
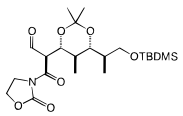
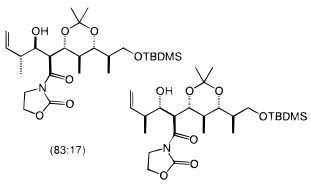
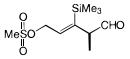
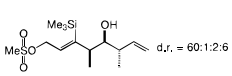
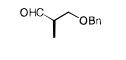
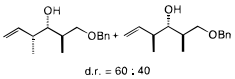
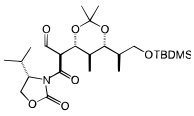
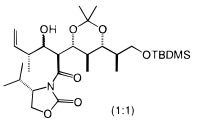
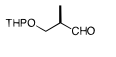
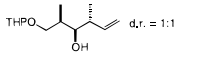
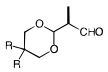
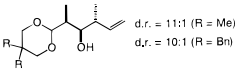
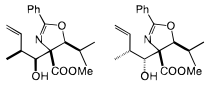
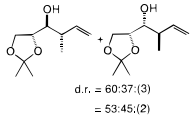
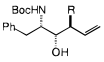
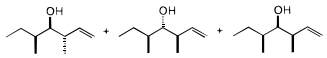
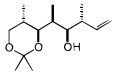
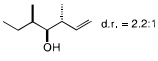
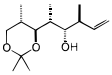
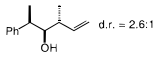
Carbonyl Compound	Product Major Isomer, d.r.	Yield (%)	Ref.
	 d.r. = 60:40	72	93
	 d.r. = 65:35	65	93
	 d.r. = 60:40	61 (R = 3-indolyl) 77 (R = Ph)	93
	 d.r. = 60:40	48	93
	 d.r. = 10:1	n.r.	93
	 d.r. = 70 : 30	56	231
	 d.r. = 45:55	53	232
	 d.r. = 1.2:1	78	233
	 d.r. = 9:1	72	233
	 d.r. = 13.2:1	55	233
	 d.r. = 1:2.6	90	233
	 d.r. = 1:1.7	95	233
	 d.r. = 4.2:1	72	233

Table 44. Cr(II)-Mediated Addition of Crotyl Bromide to Chiral Aldehydes

Aldehyde	Product (d.r.)	Yield (%)	Ref.	Aldehyde	Product (d.r.)	Yield (%)	Ref.
	 (40:60)	70	122, 116	 R = 3-indolyl	 d.r. = 8:1	71	93
	 (29:71)	80	99		 d.r. = 15:1	63	93
	 (25:75)	94	99		 1 : 1.5	70-75	236
	 (83:17)	75-84	121		 d.r. = 60:1:2:6	72	23, 237
	 d.r. = 60 : 40	70	238				
	 (1:1)	n.r.	121b		 d.r. = 1:1	n.r.	116
	 d.r. = 11:1 (R = Me) d.r. = 10:1 (R = Bn)	n.r.	116				
	 (2 : 1)	n.r.	120		 d.r. = 60:37:(3) = 53:45:(2)	75 71	117 239
	 R = Me, Ph (de > 90%)	n.r.	102				
	 (62 : 31 : 7)	90	234, 235, 9		 d.r. = 4:1	n.r.	116
	 d.r. = 2.2:1	n.r.	116		 d.r. = 20:1	n.r.	116
	 d.r. = 2.6:1	n.r.	116		d.r. = 4:1	n.r.	116
	(>20 : 1 : 0.5 : 0.5)	[a-c]	235		d.r. = 11:1	n.r.	116
	(>20:1)	[a, c]	235		d.r. = 2:1	n.r.	116
	d.r. = 9:1	73	93		d.r. = 20:1	n.r.	116

[a] Using crotyliodide as the starting material. [b] The stereochemistry was found to be independent of whether (*E*) or (*Z*) crotyliodide is used. [c] Only the stereochemistry of the major isomer was rigorously assigned.

to the corresponding ketones. Because no significant influence of the protecting group on the ethereal substituents has been noticed, chelation of the chromium atom to these neighboring groups obviously does not play a significant role in the stereodetermining step. The observed long-range stereochemical communication is best rationalized by assuming an antiperiplanar approach of the aldehyde to the oxygenated function on the allylmetal species; a conformation which minimizes the 1,3-allylic strain with the hydrocarbon residue, and the steric interaction with the incoming aldehyde explains the observed preference for the 1,4-syn isomer.[126]

A further example for efficient 1,4-stereochemical communication in chromium-mediated reactions of chiral allyl halides with achiral aldehydes delivers a key intermediate for the preparation of 1α,25-dihydroxyvitamin D_3 (Scheme 59).[127]

Scheme 59

Table 45. Cr(II)-Mediated Addition of Various Allylic Substrates to Chiral Aldehydes

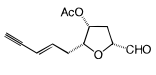
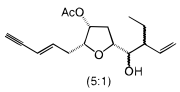
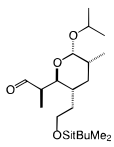
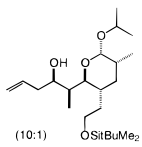
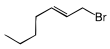
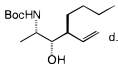
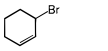
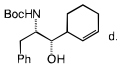
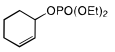
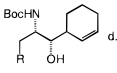
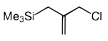
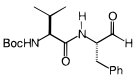
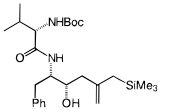
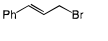
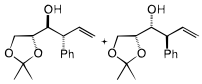
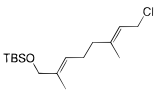
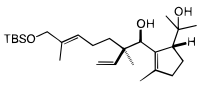
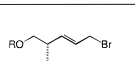
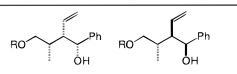
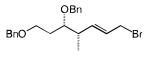
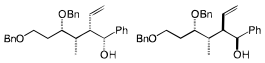
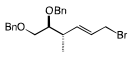
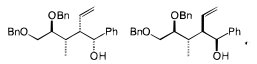
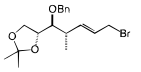
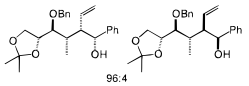
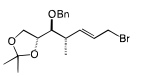
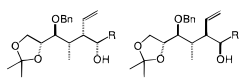
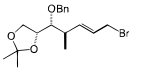
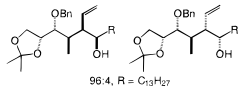
Halide	Aldehyde	Product (d.r.)	Yield (%)	Ref.
		 (5:1)	quant.	119
allyl iodide		 (10:1)	78	240
		 d.r. = 8:1	73	93
		 d.r. = 8:1	71	93
	 R = 3-indolyl	 d.r. = 8:1	64	93
			55	93
		 d.r. = 53:45	71	117
		 d.r. = 53 : 9 : 3 : 2	67	241

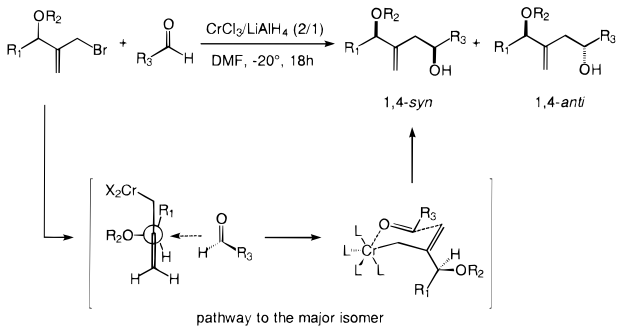
Table 46. Reactions of Achiral Aldehydes with Chiral Allylic Bromides[125]

Aldehyde	Halide	Product (Ratio)	Yield (%)
PhCHO		 83:17 (R = $tBuPh_2Si$) 82:18 (R = Bn)	68 (R = $tBuPh_2Si$) 80 (R = Bn)
PhCHO		 93:7	68
PhCHO		 91:9	84
PhCHO		 96:4	75
$C_{13}H_{27}CHO$		 96:4, R = $C_{13}H_{27}$	60
$C_{13}H_{27}CHO$		 96:4, R = $C_{13}H_{27}$	60

5. Double Stereodifferentiation

As outlined above, Cr(II)-induced additions of chiral allylic halides to achiral aldehydes can be described according to the Felkin−Ahn model. Therefore, all reactions with chiral aldehydes favoring Felkin−Ahn control can be regarded as "matched" cases, resulting in high degrees of induction.[125] For "mismatched" pairs, however, it has been shown that the allylic halide rather than the chiral aldehyde is usually the stereodominating component.[109,125,128] This bias is illustrated by the examples compiled in Table 48, in which the effect of the halide overrides the stereodirecting influence of the chiral aldehyde in many, though not in all, cases. Such double diastereodifferentiation has been used in a key step of a total synthesis of natural as well as unnatural dihydrocanadensolide.[128]

Table 47. 1,4-Asymmetric Induction in Chromium-Mediated Additions of Allyl Bromides Bearing Ethereal Stereogenic Centers[126a]



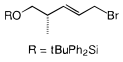
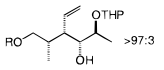
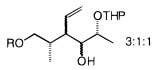
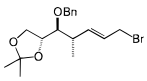
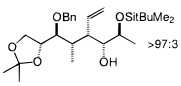
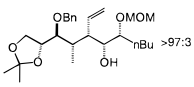
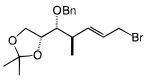
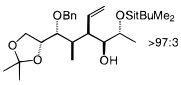
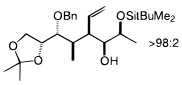
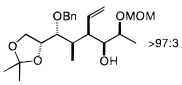
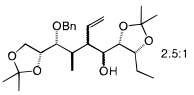
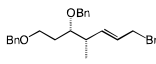
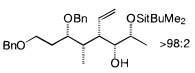
R_1	R_2	R_3	Yield (%)	1,4-*syn*:1,4-*anti*
Me	Bn	Ph	64	87:13
		Me	75	83:17
		Et	68	85:15
		i-Pr	71	81:19
		t-Bu	69	81:19
		CH_2=CH	26 [a]	85:15
		COOEt	[b]	
Ph	Bn	Ph	71	91:9
		Et	70	85:15
		i-Pr	68	87:13
i-Pr	Bn	Ph	60	95:5
		Et	66	91:9
		i-Pr	51 [c]	91:9
Me	TBDMS	Ph	34	83:17
Ph	TBDMS	Ph	75	89:11
i-Pr	TBDMS	Ph	64	90:10
Me	MOM	Ph	61	81:19
Ph	MOM	Ph	75	83:17
i-Pr	MOM	Ph	72	88:12

[a] 47% of allyl chloride formed. [b] Complex mixture. [c] 34% of allyl chloride formed.

6. Enantioselective Additions

Obviously, any device allowing to control the absolute stereochemical outcome of NHK reactions would endow additional versatility to this important transformation. Unfortunately, however, a general solution for this problem has yet to be found. Enantioselective additions of organochromium(III) reagents to aldehydes are inherently difficult to achieve for several reasons: (i) Cr(II) does not show any particular affinity for any standard type of chiral ligands such as phosphines, phosphites, diolates, amino alcohols, etc. (ii) Chiral amines or diamines may be reasonably good candidates for asymmetric

Table 48. Double Stereodifferentiation: Systematic Study of Matched and Mismatched Pairs[125]

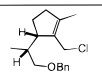
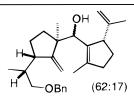
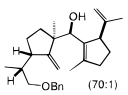
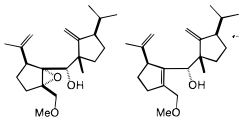
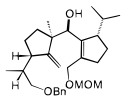
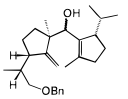
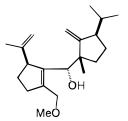
Halide	Aldehyde	Product (Major Isomer), d.r.	Yield (%)
		 >97:3	62
		 3:1:1	80
		 >97:3	72
		 >97:3	63
		 >97:3	55
		 >98:2	66
		 >97:3	65
		 2.5:1	40
		 >98:2	90

NHK reactions, although a rather narrow window between efficient chiral modification of the Cr(II) centers and loss of activity due to coordinative saturation has to be dealt with. (iii) Depending on the mode of preparation, admixed Lewis-acidic salts may compete efficiently with the Cr(II) for the complexation of the chiral ligand. (iv) In all reactions in which $CrCl_2$ doped with catalytic amount of $NiCl_2$ has to be used, one must ensure that the chiral ligand does not quench the catalytic effect of Ni(II). (v) Cr(II) sources other than simple CrX_2 salts, which may be amenable to chiral modification, have yet received little attention as reagents in NHK reactions (for exceptions, see section II A,B).

As a consequence, very few reports on enantioselective NHK reactions have been published. Early reports on the use of the lithium salt of ephedrine or *N*-methyl ephedrine as a chiral ligand to chromium met with very limited success, with the best ee being 29% in the allylation of pentanal; moreover, the yields were rather poor in these conversions (Table 50).[129] Upon using the lithio carboxylate of phenyl alanine or lithio menthylate, the results were even worse.

A slightly better level of asymmetric induction has been achieved by Kishi et al. in chromium-mediated allylation and alkenylation reactions using specially designed bipyridyl ligands.[130] Bipyridyl itself inhibits the cross-coupling. It is, however, possible to tune the complexation capacity by introducing substituents at the 6-position, with the best ligand being **1d** (Tables

Table 49. Addition of Chiral Allylchromium Reagents to Chiral Aldehydes

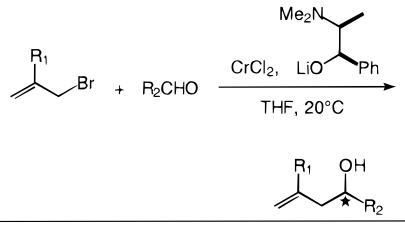
Halide	Aldehyde	Product (d.r.)	Yield (%)	Ref.
		 (62:17)	79	242
		 (70:1)	71 [a] 88	41 39
			56 + 23	243
			83	244
		 (ß-OH : α-OH = 64 : 18)	82	245
			68	246
			90 [a]	40
		d.r. = 9:1	67	93
		d.r. = 3:2	80	247

[a] In the presence of i-PrOH as cosolvent.

51 and 52). Moreover, no homocoupling of the starting halide was observed in the presence of this ligand; therefore, even a 1:2 mixture of $NiCl_2$:$CrCl_2$ could be used leading to a dramatic increase in rate, thus allowing smooth reactions even at −20 °C. However, the bipyridine derivative must be used in (over)-stoichiometric amounts, thus limiting the practicality of the method.[130]

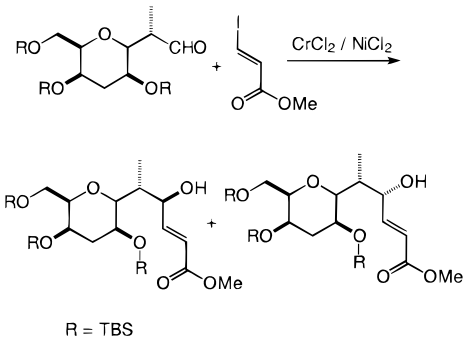
The most advanced asymmetric NHK protocol reported to date makes use of allylic chromium alkoxide reagents, which are prepared by ligand exchange of $CrCl_2$ with R*OLi.[131] The $Cr(OR^*)_2$ formed in situ effects the addition of allyl bromide to aromatic aldehydes. Various mono- and bidentate alkoxides have been screened, with the *N*-benzoyl-L-prolinol derivative **A** being the most effective in terms of yield and enantiomeric excess. It was speculated that a dialkoxyallylchromium(III) species

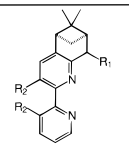
Table 50. Use of Lithio *N*-Methyl Ephedrinate as Chiral Ligand to Cr(II)[129]



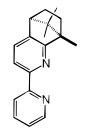
R_1	R_2	ee	Yield (%)
H	Pr	16 (S)	49
H	i-Bu	16 (S)	58
H	n-C_7H_{15}		48
H	Ph	11.5 (R)	60
Me	n-C_3H_7	17 (S)	52
Me	Ph	6 (R)	53

Table 51. Product Distribution in $CrCl_2(NiCl_2)$-Induced Reactions in the Presence of Pyridyl-Based Ligands[130]

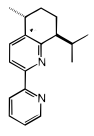




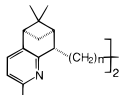
1a 1.5:1 (R_1=R_2=H)
1b 2.2:1 (R_1=Me, R_2=H)
1c 2.5:1 (R_1=Et, R_2=H)
1d 4.2:1 (R_1=Pr, R_2=H)
1e 3.5:1 (R_1=Bu, R_2=H)
1f 3.8:1 (R_1=Pent, R_2=H)
1g 2.9:1 (R_1=Bn, R_2=H)
1h 2.4:1 (R_1=iPr, R_2=H)
1i 2.3:1 (R_1=iBu, R_2=H)
1j 3.1:1 (R_1=iPent, R_2=H)
1k 1.4:1 (R_1=H, R_2=Me)



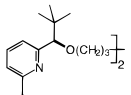
2 1.2:1



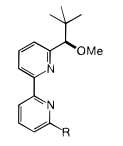
3 3.1:1



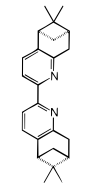
4a 3.0:1 (n=3)
4b 3.4:1 (n=4)
4c 3.0:1 (n=5)



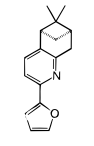
5 1:1



6a 1.2:1 (R=H)
6b 1:1 (R=CH(OMe)tBu)



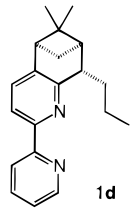
7 1:1



8 1:1.2

such as **B** is responsible for the observed results (Table 53).[131]

Table 52. Asymmetric Nozaki Reactions of Benzaldehyde with Various Halides[130]

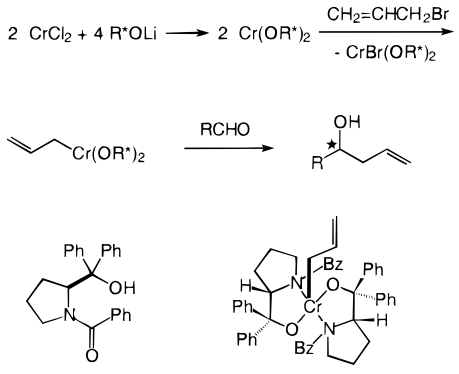


1d

Halide	Ligand	T (°C)	t (h)	e.r. [a]
(*E*)-1-iodo-1-hexene	**1d**	30	1	1.8:1
	1d	-20	48	2.5:1
Methyl (*E*)-3-iodoacrylate	**1d**	30	1	2.2:1
	1d	-20	48	3.1:1
Allyl bromide	**1d**	30	1	4.9:1
	1d	-20	48	6.7:1
	Chiraphos	30	11	1:1
	(S)-(-)-BINAP	0	11	1:1

[a] The absolute configuration of the products is not established.

Table 53. Asymmetric Allylation Using Chiral Ligand A[a] [131]



R	Yield (%)	ee (%)	Configuration
Ph	62	82	*R*
4-$MeOC_6H_4$	84	49	*R*
4-ClC_6H_4	72	88	*R*
4-ClC_6H_4 [b]	47	98	*R*
1-Naphthyl	43	80	*R*
$PhCH_2CH_2$	60	61	*S*

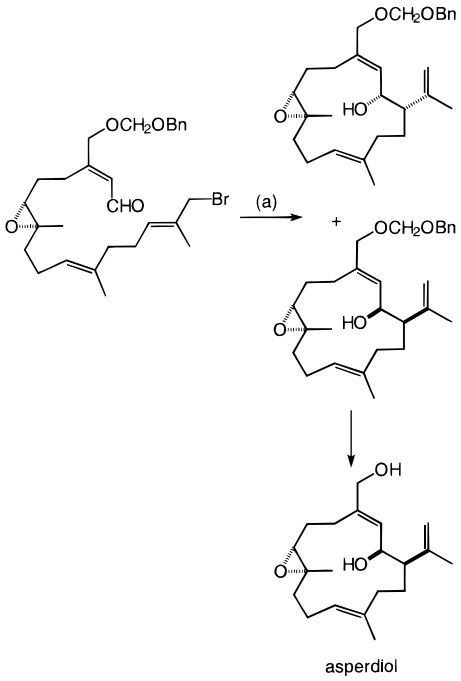
[a] Reactions carried out at −30 °C unless stated otherwise. [b] At ambient temperature.

Finally it must be mentioned that asymmetric NHK reactions using catalytic amounts of Cr(II) and chiral ligands are still elusive.

D. Intramolecular Additions

The efficiency of Cr(II)-mediated intramolecular addition reactions involving allylic substrates is remarkable. This favorable profile has been exploited for the formation of strained medium-sized and macrocyclic rings. The high stability of the O−Cr(III) bond obviously serves as the thermodynamic sink which overrides the strain build-up during cyclization. Many applications to the total synthesis of complex natural products and analogues thereof illustrate this preparatively highly useful feature.

Scheme 60



(a) $CrCl_2$ (5 eq.), THF, r.t., 64%, d.r. = 1:4

An early, seminal contribution in this context is the asperdiol synthesis of Still et al. (Scheme 60).[132] These authors ingeniously used an NHK reaction to create the fairly complex macrocyclic ring of this cembranoid antitumor agent with concomitant threo-selective generation of two stereogenic centers. In stark contrast to the smooth $CrCl_2$-mediated intramolecular addition, attempted cyclizations via related allylsilanes and allylstannanes failed to afford the desired product.

Other applications of chromium-mediated additions of allylic halides to tethered carbonyl groups following a similar rationale are compiled in Table 54.

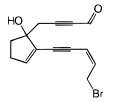
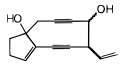
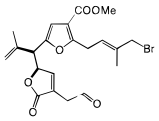
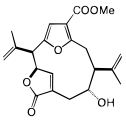
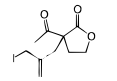
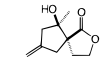
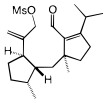
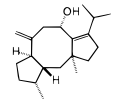
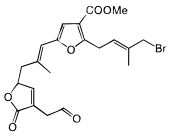
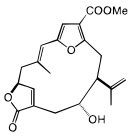
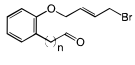
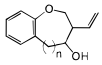
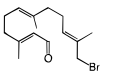
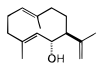
VII. Benzylchromium(III) Reagents

In the absence of electrophiles, benzylic halides are smoothly reduced by $CrCl_2$ to dimeric products, i.e., benzyl bromide to 1,2-diphenylethane, (dichloromethyl)benzene to stilbene, (trichloromethyl)benzene to diphenylacetylene, or bromodiphenylmethane to 1,1,2,2-tetraphenylethane.[7,8,90] Selective cross-coupling can be achieved if an organic halide is added to preformed benzylchromium reagents (Table 55).[90]

Relatively few reports on the reaction of (heterocyclic) benzylchromium reagents with carbonyl compounds have been reported in the literature so far. A notable exception concerns the total synthesis of the potent antibiotic pristinamycin II_B and model studies related to it (Scheme 61).[133] The yield in the Cr(II)-induced macrocyclization step is rather low, which may, however, be due to an unfavorable conformation enforced by the peptidic backbone of the substrate.

Despite the usual lack of reactivity between a C−Cr bond and an ester moiety, entropically favored

Table 54. Intramolecular Addition Reactions Involving Allylchromium(III) Intermediates

Substrate	Product	Yield (%)	d.r.	Ref.
		77-88	1:1	248
		25	1:0 [a]	249, 250
		84	6.8:1	123
		64	1:0	91
		78		91b
		20	1:0	251, 22
		11 (n=0) 68 (n=1) 60 (n=2)	1:1 (n=0) 1:15 (n=1) 1:3.2 (n=2)	105
		42		252

[a] The two references cited depict different stereochemistries for this cyclization; the one shown here was confirmed by X-ray as described in ref 249.

Table 55. Chromium-Mediated Cross-Coupling Reactions of Benzylic Halides[90]

R_1X	R_2X	Product	Yield (%)
$PhCH_2I$	allyl iodide	$PhCH_2CH_2CH{=}CH_2$	85
$PhCH_2Br$	$(CH_3)_3CBr$	$PhCH_2C(CH_3)_3$	55
$PhCH_2I$	Ph_3CCl	$PhCH_2C(Ph)_3$	90
Ph_2CHBr	allyl iodide	$Ph_2CHCH_2CH{=}CH_2$	41
Ph_2CHBr	Ph_3CCl	$Ph_2CHC(Ph)_3$	89

intramolecular reactions between these entities are possible in the benzylic series (Table 56). However, it is necessary to work under high dilution conditions and to avoid aprotic dipolar cosolvents such as HMPA in order to suppress competing Wurtz coupling of the substrates. The reaction in THF primarily leads to the corresponding hydroxy ketones which can be isolated in fair to excellent yields; however, if the reactions are carried out in the presence of $BF_3{\cdot}Et_2O$ (1.25 equiv), the hydroxy ketones cyclize spontaneously to afford furan derivatives.[134] However, Wurtz coupling remains a serious threat (i) with substrates bearing sterically hindered R groups, (ii) with secondary benzyl bromides, and (iii) with all benzyl iodides as starting materials. Benzyl chlorides react only under rather forcing conditions. Reactions in THF or DME give similar results, whereas DMF and pyridine were found to be unsuitable solvents for this application. Interestingly, $CrBr_2$ could not be used instead of $CrCl_2$ as it showed a significantly lower propensity to insert into the C−Br bond of the substrates.[134b] This entry into aromatic heterocycles

Scheme 61

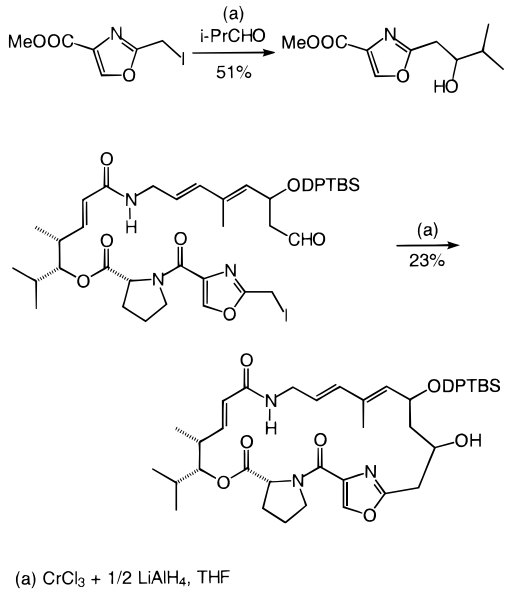
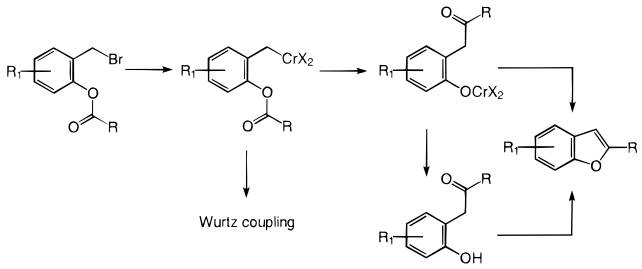


Table 56. Intramolecular Reactions of Benzylchromium(III) Reagents with Esters[134]



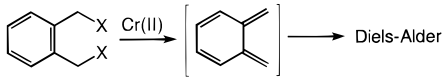
R	R_1	Hydroxyketone [a]	Benzofuran [b]
Me	H	65	93
Et	H	85	96
Ph	H	65	80
p-$MeOC_6H_4$	H	20	80
Ph	3-OCOPh	80	85
Me	4-Cl	82	92
n-Pr	H	78	83
i-Pr	H	25	42
t-Bu	H	0 [c]	15 [c]
n-Pent	H	80	90
Me	4-OAc	85	77
2-ClC_6H_4	H	0 [c]	0 [c]
4-ClC_6H_4	H	67	82
4-$NO_2C_6H_4$	H	n.r.	trace [d]
2-thienyl	H	62	81

[a] As obtained by slow addition of the substrate to $CrCl_2$ in refluxing THF. [b] As obtained by slow addition of the substrate to a refluxing mixture of $CrCl_2$ and $BF_3 \cdot Et_2O$. [c] Dimer formed by Wurtz coupling is the major product formed. [d] Complex mixture.

is somewhat reminiscent of a more general approach based on titanium-mediated cross-coupling reactions.[135]

Another investigation on the insertion of Cr(II) into benzylic halides should be briefly mentioned, although it does not directly involve a C–Cr(III) bond in the C–C bond forming step. Thus, α,α′-dibromo-*o*-xylenes are readily reduced by $CrCl_2$ in THF/HMPA to afford the corresponding *o*-quinodimethanes which

Scheme 62

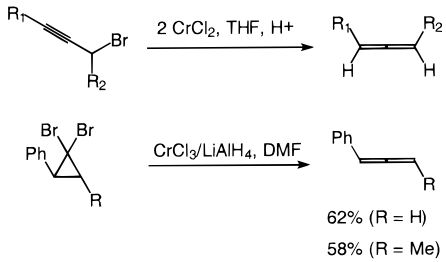


can be trapped with various dienophiles to afford the corresponding Diels–Alder products (Scheme 62).[136]

VIII. Propargylchromium(III) and Allenylchromium(III) Reagents

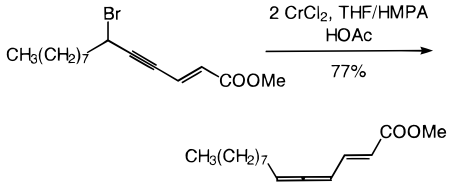
The reader is referred to the fact that racemic allenes are obtained by the reaction of 1,3-disubstituted propargylic halides with $CrCl_2$ in the presence of proton donors such as HOAc.[137,138] All attempts, however, to prepare optically active allenes by quenching the intermediate propargylchromium species with enantiomerically pure proton sources such as (−)-menthol, (−)-borneol, or camphanic acid met with very limited success.[137] This approach to allenes complements a route previously developed by Hiyama et al., converting dibromocyclopropenes via the corresponding chromium carbenoids into the respective allene products (Scheme 63).[7,55] This allene synthesis

Scheme 63



provided access to the sex pheromone of *Acanthoscelides obtectus* containing a vinyl allenyl substructure (Scheme 64).[139] Good yields have been

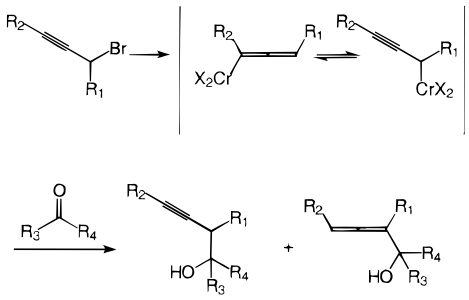
Scheme 64



obtained by running the reaction in THF/HMPA with anhydrous HOAc as the protonating agent, but attempted asymmetric induction has essentially failed.[139]

During these studies, some insights into the nature of the propargylchromium and/or allenylchromium intermediates have been obtained by careful analyses of the product distributions as well as by IR studies of the reaction mixture. Thus, it has been shown that the equilibrium between the propargyl- and allenylchromium(III) entities (i) strongly depends on the steric and electronic properties of the substrate and (ii) can be considerably shifted by aprotic dipolar cosolvents such as HMPA.[139,140] Moreover, the mechanism of protonation of the chromium intermediates

Table 57. Cr(II)-Induced Formation of Allenyl- and Homopropargyl Alcohols in THF[137,141,253]

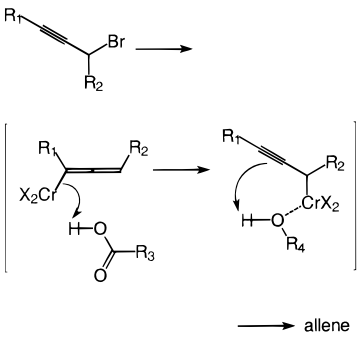


R_1	R_2	R_3	R_4	Yield (%)	Acetylenic : Allenic Alcohol
H	H	*n*-C_7H_{15}	H	72	85:15
		Me	Me	30	25:75
		$(CH_2)_5$		68	65:35
		$CH_3CH=CH$	H	22	80:20
H	C_5H_{11}	Pr	H	80	0:100
		$(CH_2)_5$		78	0:100
		$CH_3CH=CH$	H	12	0:100
H	Ph	Pr	H	60	0:100
		Me	Me	77	0:100
		$(CH_2)_5$		77	0:100
		$CH_3CH=CH$	H	45	0:100
n-C_7H_{15}	H	Pr	H	76	100:0
		Me	Me	66	0:100
		$(CH_2)_5$		75	60:40
Pr	Et	Pr	H	65	100:0
		Me	Me	60	75:25
		$(CH_2)_5$		50	80:20
H	$-CH=CH_2$	Me	Me	50	0:100
H	$-C(Me)=CH_2$	Me	Me	70	0:100
H	1-cyclohexenyl	$(CH_2)_5$		75	0:100
		Pr	H	69	0:100
		Me	Me	75	0:100
n-C_7H_{15}	$-C(Me)=CH_2$	Pr	H	89	38:62 [a]
Me	1-cyclohexenyl	Pr	H	72	18:82

[a] In the presence of HMPA.

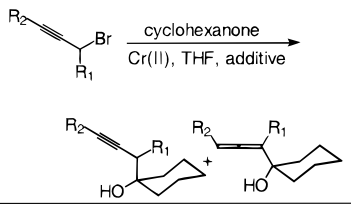
seems to depend on the pK_a and the donor strength of the acid used: while carboxylic acids immediately quench the allenylchromium reagent initially formed via an S_E2 mechanism, alcohols allow the equilibration to the propargylchromium reagent to proceed, which is then protonated in an S_Ei' fashion (Scheme 65).[140]

Scheme 65



Obviously, the intermediate organochromium species cannot only be trapped with protons but may also

Table 58. Cr(II)-Induced Formation of Allenyl- and Homopropargyl Alcohols: Influence of Added HMPA on Reactions of Propargyl Halides with Cyclohexanone[141]



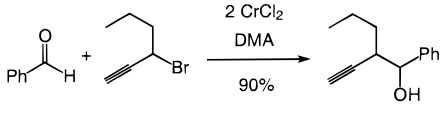
R_1	R_2	HMPA (eq.)	Yield (%)	Acetylenic : Allenic Alcohol
H	H	0	68	65:35
H	H	2	65	55:45
H	H	3	65	44:56
H	H	5	70	21:79
H	H	7	50	28:72
H	H	[a]	50	40:60
n-C_7H_{15}	H	0	75	41:59
n-C_7H_{15}	H	1	68	20:80

[a] In pure HMPA as the solvent.

be intercepted with carbonyl compounds, thus leading to allenyl and/or homopropargylic alcohols. As evident from Table 57, the product distribution strongly depends on the substitution pattern of the starting propargyl halide and, to some extent, on the particular carbonyl compound chosen. Moreover, addition of HMPA to the reaction mixture favors the formation of the allenic alcohol (Table 58). Enones and enal derivatives as the substrates tend to give lower yields because of the instability of the polyunsaturated products formed.[141] It has been speculated that the allenyl/propargyl interconversion occurs at the radical stage after the first s.e.t. from the Cr(II) to the halide.[141] The fact that homocoupling of the substrates competes with the formation of the product alcohols has been interpreted as indication of such relatively long-lived radical intermediates.[137,141]

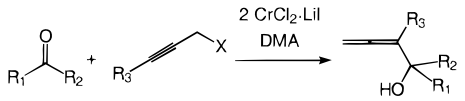
These studies have been extended by Knochel et al. who demonstrated that polyfunctional propargyl halides react with a wide range of aldehydes and ketones in the presence of $CrCl_2$·LiI to afford almost exclusively the corresponding allenic alcohols (Table 59).[142] The best yields and regioselectivities were obtained in dimethylacetamide (DMA) as the solvent. Surprisingly, however, these authors noticed a complete reversal of the regiochemical preference using an α-substituted propargyl halide, thus leading to the exclusive formation of the corresponding acetylenic rather than the allenic alcohol (Scheme 66).[142]

Scheme 66



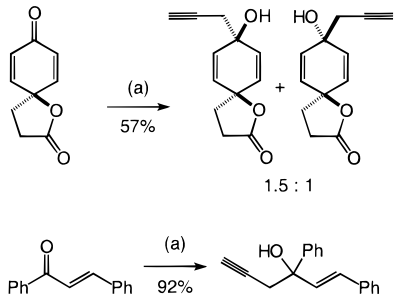
Wipf et al. reported two examples in which the use of Ph_2Cr·TMEDA instead of $CrCl_2$ cleanly delivers

Table 59. Formation of Allenic Alcohols from (Functionalized) Propargyl Halides[142]



R_1	R_1	R_3	X	Allenic:Acetylenic Alcohol	Yield (%)
Ph	H	Bu	Cl	97:3	92
			Br	98:2	79
c-C_6H_{11}	H	Bu	Cl	97:3	76
n-C_5H_{11}	H	Bu	Cl	98:2	81
Ph	Me	Bu	Cl	>99:1	69
Ph	H	$EtOOC(CH_2)_3$	Br	98:2	84
n-C_5H_{11}	H	$EtOOC(CH_2)_3$	Br	97:3	92
Ph	Me	$EtOOC(CH_2)_3$	Br	>99:1	79
-$(CH_2)_5$-		$EtOOC(CH_2)_3$	Br	98:2	84
c-C_6H_{11}	H	$EtOOC(CH_2)_3$	Br	97:3	82
i-Pr	H	$Cl(CH_2)_3$	Br	98:2	87
Ph	H	$Cl(CH_2)_3$	Br	97:3	93
-$(CH_2)_5$-		$Cl(CH_2)_3$	Br	97:3	72
Ph	H	$NC(CH_2)_3$	Br	96.5:3.5	82
c-C_6H_{11}	H	$NC(CH_2)_3$	Br	94:6	86

Scheme 67



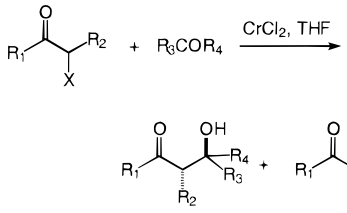
the corresponding homopropargyl rather than the allenic alcohols (Scheme 67).[44]

IX. Cr(II)-Mediated Reformatsky Reactions

Cr(II) in combination with an appropriate proton source can be used as a mild reagent for the reductive dehalogenation of α-halocarbonyl compounds.[7,8,143,144] Because this reductive cleavage likely proceeds via Cr(III) enolate intermediates, it was also worthwhile to probe the reactivity of these species against electrophiles other than H^+. Such transformations may be referred to as Reformatsky reactions,[145] as they involve an enolate formation by oxidative addition of a metal or a low-valent metal salt into a carbon−halogen bond activated by an adjacent carbonyl group. Cr(III)-enolates have also been prepared by transmetalation routes, although their reactivity has not been fully investigated.[146]

Attempts to trap the chromium enolate derived from 2-bromocyclododecanone with methyl iodide or trimethylchlorosilane met with failure.[7,8] However, Barbier-type reactions of α-bromo ketones with various aldehydes in the presence of $CrCl_2$ afford the corresponding aldol products in good to excellent

Table 60. Chromium-Mediated Reformatsky Reactions of α-Halo Ketones



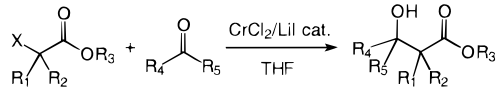
R_1	R_2	R_3	R_4	X	Yield (%)	*anti:syn*	Ref.
t-Bu	Me	Me	H	Br	50	0:100	147
		Et	H	Br	81	0:100	147
		i-Pr	H	Br	70	0:100	147
		Pr	H	Br	83	0:100	147
		Ph	H	Br	75	0:100	147
		t-Bu	H	Br	87	0:100	147
Ph	Me	Ph	H	Br	68	50:50	147
	$(CH_2)_4$	Ph	H	Br	75	100:0	147
Ph	H	Me	Me	Br	78		104
		Ph	Me	Br	44		104
Ph	Me	Me	Me	Br	88		104
		Et	Me	Br	84		104

yields.[147] This reaction turned out to be completely syn selective when bulky substituents on an acyclic enolate moiety are present (Table 60); however, if R_1 = Ph, a stereorandom conversion has been observed, whereas 2-bromocyclohexanone as the starting material leads exclusively to the anti-aldol product. This latter case is rationalized by assuming a Zimmerman−Traxler transition state of the (*E*)-configured chromium enolate that is formed upon insertion of the Cr(II) into the cyclic bromoketone.[147]

Cr(II) also promotes Reformatsky reactions of α-halo esters, -lactones, -nitriles, or -amides.[103,104,148,149] The following advantages were quoted in the literature: (i) The high chemoselectivity characteristic for chromium nucleophiles in general also holds true for chromium enolates; (ii) no retro-aldolization is observed; (iii) the reaction can be easily performed on a microscale; (iv) *anti*-aldols are preferably formed in contrast to most other Reformatsky protocols of α-halo esters (Table 61); (v) even α-chloro esters may be used which react reluctantly in conventional Reformatsky protocols, although they require somewhat higher temperatures and longer reaction times; and (vi) reasonable degrees of asymmetric induction can be achieved by attaching the α-halo acid to an Evans-type oxazolidinone auxiliary (Table 63).[148]

Chromium-Reformatsky reactions are facilitated upon addition of LiI to the reaction mixture.[149] Reactions with ketones as the electrophiles are also possible,[104] but intermolecular competition experiments show that chromium enolates are able to distinguish rigorously between aldehydes and ketones (Table 62).[103] The selectivity depends, to some extent, on the solvent (DMF < DMF < MeCN) and on additives, with the combination THF/LiI being the best compromise.[103] In similar competition experiments, no product formation was noticed with esters, nitriles, amides, imines, Eschenmoser's salt, Michael acceptors, or alkyl halides as electrophiles.

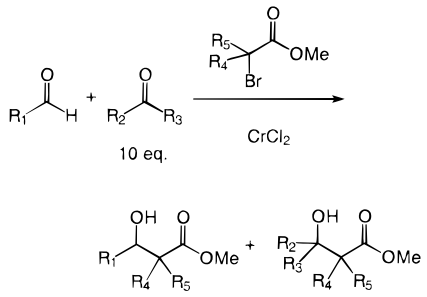
Table 61. $CrCl_2$/LiI cat. Promoted Reformatsky Reactions (X = Br Unless Stated Otherwise)



R_1	R_2	R_3	R_4	R_5	T (°C)	*anti:syn*	Yield (%)	Ref.
H	H	Me	Ph	H	55		89	149
		Et	Ph	H	55		72	149
		t-Bu	Ph	H	55		63	149
Me	Me	Me	Et	H	20		81 [a]	149
			i-Pr	H	55		93	149
			Ph	H	55		90	149
			$PhCH_2$	H	20		98	149
H	Me	Me	i-Pr	H	55	71:29	72 [b]	149
					20	77:23	84	149
H	Me	t-Bu	Ph	H	20	70:30	95	149
		Me	Ph	H	20	78:22	81	149
					55	60:40	88	149
H	Et	Me	Ph	H	55	74:26	82	149
H	i-Pr	Me	Ph	H	55	30:70	85	149
H	Ph	Me	Ph	H	55	79:21	84 [b]	149
H		$-CH_2CH_2-$	Ph	H	20	>95:5	81	149
Me	Ph	Me	i-Pr	H	20	68:32	86	149
Me	Me	Me	PhCH(Me)	H	20	76:24	84	149
			Me	Me			54	104
			Et	Me			52 [a]	104
			Ph	Me			67	104
			Ph	Me			64 [a]	104
Me	H	Me	Me	Me			34	104

[a] In DMF as the solvent. [b] X = Cl.

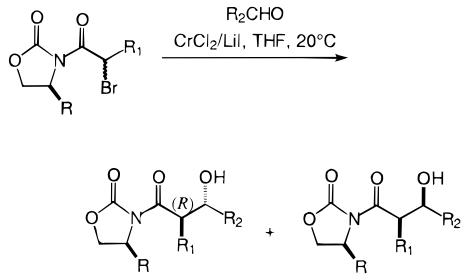
Table 62. $CrCl_2$-Mediated Reformatsky Reactions: Intermolecular Competition Experiments[103]



R_1	R_2	R_3	R_4	R_5	Cond.	Yield (%)	Aldehyde selectivity
Ph	Ph	Me	Me	H	DMF/LiI	31	30:1
					THF/LiI	46	50:1
					MeCN/LiI	5	-
Et	Me	Me	Me	Me	DMF/LiI	82	15:1
					THF/LiI	88	8:1
Ph	Ph	Me	Me	Me	THF/LiI	67	7:1

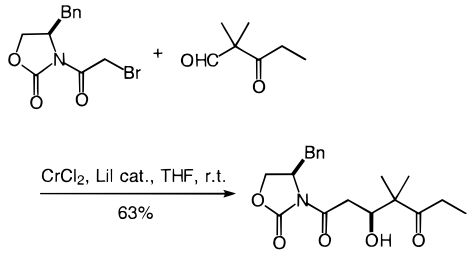
The Cr(II)-Reformatsky reaction has been employed en route to the enantioselective formation of the "aldol" fragment of the promising anticancer agent epothilone (Scheme 68).[150] "Vinylogous" Reformatsky reactions with 4-bromo-2-butenoates and similar donors have also been reported. These transformations, however, fall into the category of substituted allylic halides and are therefore reviewed in section VI B.

Table 63. Stereoselective Reformatsky Reactions Using Evans-Type Oxazolidinones as Chiral Auxiliaries[148]



R	R_1	R_2	Yield (%)	*syn:anti*	α-*R* : α-*S*
i-Pr	Me	i-Pr	96	11:89	>98:2
Bn	Me	i-Pr	88	< 5:95	>98:2
i-Pr	Me	Ph	86	23:77	>98:2
Bn	Me	Ph	81	16:84	97:3
Bn	H	i-Pr	91	< 4:96	
Bn	H	Ph	88	13:87	

Scheme 68

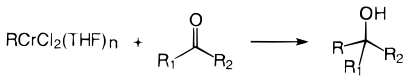


X. Alkylchromium(III) Reagents

Various types of alkylchromium(III) reagents can be prepared by transmetalation of organolithium, -magnesium, or -aluminum compounds with $CrCl_3$ or $CrCl_3(THF)_3$.[3,151] It has been noticed that monoalkylchromium(III) species constitute valuable alkylating agents that distinguish between aldehydes and ketones as well as between functionalized and unfunctionalized carbonyl compounds. Specifically, Kauffmann et al. have shown in a series of publications that $RCrCl_2(THF)_n$ reagents provide good yields of the desired secondary alcohols in reactions with aldehydes, whereas ketones remain essentially unaffected and can be recovered unchanged (Tables 64 and 65).[152−155] Only in the case of R = *sec*-butyl, some reduction of the aldehyde to the corresponding primary alcohol has been noticed. Surprisingly, carboxylic acid chlorides and anhydrides, which are usually considered to be among the most reactive organic electrophiles, were found inert (!) toward $MeCrCl_2(THF)_3$.[153]

It is interesting to note that the alkylating properties of $RCrCl_3(THF)_n$ are *enhanced* upon addition of small amounts of water or ethanol to the reaction mixture.[154] It is assumed that one or more of these solvent molecules are incorporated into the ligand sphere of the metal cation. One may therefore speculate to what extent the formation of a more stable solvation of the Cr(III) ion contributes to the driving force of carbonyl addition reactions.

Table 64. Addition of Alkylchromium(III) Reagents to Various Carbonyl Compounds[152]



R	R_1	R_2	Yield %
Me	Ph	H	90
	n-C_6H_{13}	H	85
	Me	Me	0
Et	Ph	H	65
	n-C_6H_{13}	H	38-70
n-Pr	n-C_6H_{13}	H	73
	Et	Et	40
sec-Bu	Ph	H	27-30 [a]
	n-C_6H_{13}	H	44
		$(CH_2)_5$	0
n-C_8H_{17}	n-C_6H_{13}	H	39
	Et	Et	0
$PhCH_2$	n-C_6H_{13}	H	65
	Et	Et	0
Me_3SiCH_2	n-C_6H_{13}	H	47 [b]
	n-C_8H_{17}	H	45 [b]
	Ph	Me	0

[a] Together with benzyl alcohol (25%). [b] Yield of olefin after acid-catalyzed Peterson elimination of the addition product formed.

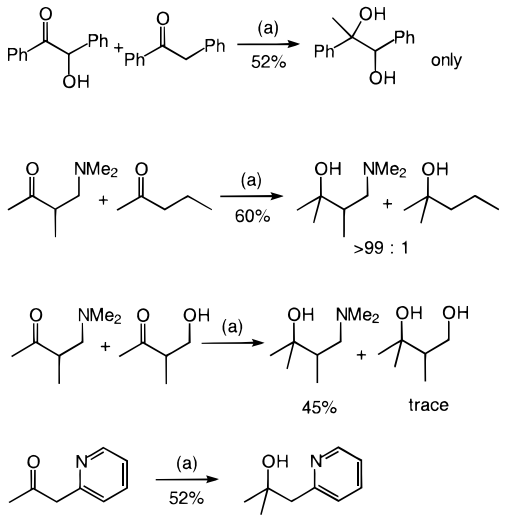
Table 65. Aldehyde Selective Additions of $RCrCl_2$ in Reactions with PhCHO + PhCOMe (1:1) (A) or Heptanal + 4-Heptanone (1:1) (B)[152a]

R	Substrates	Addition to Aldehyde	Addition to Ketone	Recovered Aldehyde	Recovered Ketone
Me	**A**	81	0	10	100
Et	**A**	45	0	43	90
n-Pr	**A**	51	0	34	100
sec-Bu	**A**	17	0	53	87
Me	**B**	94	0	n.r.	n.r.
Et	**B**	52	0	4	94
n-Pr	**B**	70	0	10	100
sec-Bu	**B**	33	0	27	100

In line with this solvent effect, it was noticed that substrates bearing donor groups such as OH, OMe, or NMe_2 substituents at the α- or β-position to the carbonyl group react particularly well (Scheme 69). Even ketones with this substitution pattern undergo alkylation reactions, whereas unfunctionalized ketones remain untouched.[155] The expression "chele-selectivity" was coined to describe this *preference of alkylchromium reagents for reactions with functionalized substrates*. In some cases it is advisable, however, to use purified $RCrCl_3(THF)_n$ reagents rather than those prepared in situ.[152a]

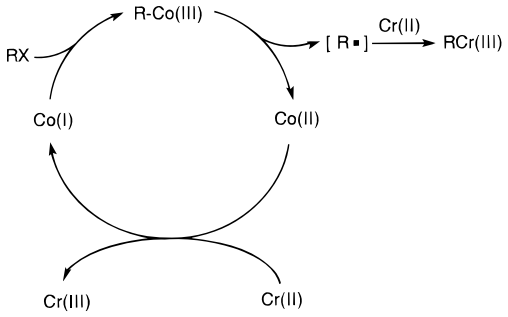
Despite some early studies on the reduction of benzyl and alkyl halides with Cr(II) in protic media proceeding via organochromium intermediates,[3b,5,156] the NHK-like oxidative insertion of low valent chromium salts into alkyl halides has long received little attention.[157] This may be because alkyl halides react more reluctantly than, e.g., allyl-, benzyl-, or even alkenyl halides. For example, treatment of a mixture of 1-iodododecane and benzaldehyde with $CrCl_2$ in DMF at 30 °C for 16 h affords only 7% of the desired addition product, whereas the major part of the

Scheme 69



(a) $MeCrCl_2(THF)_3$, THF, -70 °C to r.t.

Scheme 70

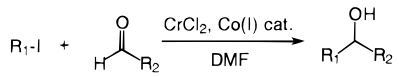


substrate is converted into 1-chlorododecane. This indicates that the S_N2 substitution reaction by Cl^- is faster than the oxidative insertion of Cr(II) into the primary alkyl iodide.[49] Obviously, however, an NHK-like direct preparation of alkylchromium reagents has some major advantages over the transmetalation methods outlined above, as it may be applicable to substrates bearing functional groups that do not survive the formation of an organomagnesium or -lithium reagent.

An elegant solution to this problem was devised by Takai and Utimoto et al.[158] On the basis of the fact that alkyl radicals are rapidly reduced by Cr(II) to afford the corresponding alkylchromium(III) species,[159] these authors proposed to use a combination of $CrCl_2$ and catalytic amounts of cobalt complexes such as vitamin B_{12} or Co-phthalocyanine.

According to the mechanism depicted in Scheme 70, these pairs of reagents allow to form functionalized alkylchromium reagents from alkyl halides or alkyl tosylates (RI > RBr > RCl ≈ ROTs) which exhibit the usual reactivity pattern vis-à-vis carbonyl compounds.[158] Thus, they show the pronounced preference for additions to aldehydes, whereas ketone or ester groups are tolerated (Table 66). Limitations for the method were found in reactions of iodocyclododecane which afford cyclododecene as the only product and in reactions of isobutyl iodide which lead to rather low yields of the addition products. The fact that 6-iodo-1-hexene delivers mainly cyclized mate-

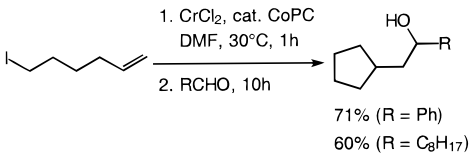
Table 66. Grignard-Type Addition of Iodoalkanes to Aldehydes Mediated by $CrCl_2$ in the Presence of Cobalt(I)-Phthalocyanine in DMF at 30 °C[158]



R_1	R_2	Time (h)	Yield (%)
n-$C_{12}H_{25}$	Ph	2.5	91
	n-C_8H_{17}	6	89
	c-C_6H_{11}	10	75
	PhCH=CH-	3.5	50
	$MeCO(CH_2)_8$-	10	86
$MeCO(CH_2)_5$	Ph	5	89
	n-C_8H_{17}	10	73
$EtOOC(CH_2)_5$	Ph	5	91 (85 [a])
	n-C_8H_{17}	11	80 (74 [a])
$Cl(CH_2)_{12}$	Ph	3.5	85
i-Bu	Ph	10	64
	n-C_8H_{17}	15	38
c-$C_{12}H_{23}$	Ph	20	2 [b]

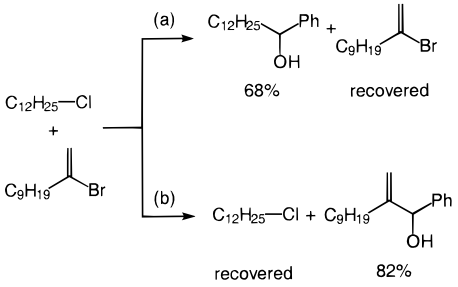
[a] Using the corresponding tosylate instead of the iodide. [b] Affords cyclododecene (54%) and cyclododecane (21%) as the major products.

Scheme 71



rial indicates the interference of a fast radical step during the reagent preparation (cf. Scheme 71). Particularly noteworthy is the fact that this cobalt-catalyzed procedure allows to form alkyl chromium reagents chemoselectively in the presence of alkenyl halides, whereas the latter react selectively when treated with $CrCl_2$ doped with $NiCl_2$ cat. as indicated by the experiments depicted in Scheme 72.[158]

Scheme 72



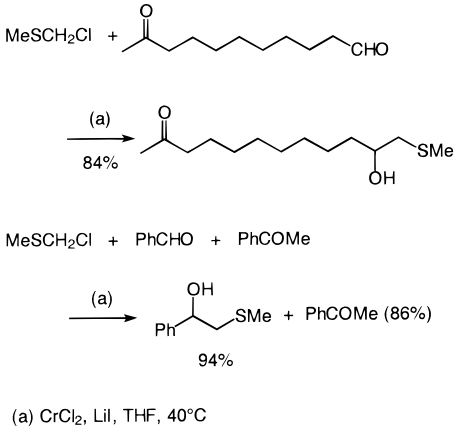
(a) PhCHO, $CrCl_2$, vitamine B_{12} cat., DMF, 30°C, 24h

(b) PhCHO, $CrCl_2$ / $NiCl_2$ cat., DMF, 25°C, 3 h

Perfluoroalkyl iodides (R_F-I) insert Cr(II) even without assistance of other metal salts, provided that the reactions are carried out in the presence of donor ligands that enhance the reducing ability of the chromium salt.[160] The best combination is $CrCl_2 \cdot (MeCN)_2$ in MeCN as the solvent. MeI, PrI, BuBr, and BnCl do not react under these conditions. The resulting $R_FCrCl_2(MeCN)_3$ complexes were found to be very robust and are only very slowly hydrolyzed even in 1 M HCl. In contrast, they are prone to ligand exchange if pyridine, bipyridyl, terpyridyl, phenanthrolin, deprotonated salen, or 1,3-dicarbonyl compounds (e.g., acac) are added. C−C bond formations, however, have not been reported.[160]

α-Halo sulfides are another class of substrates which smoothly insert Cr(II) even without the assistance of cobalt complexes.[161] The resulting (α-thioalkyl)chromium reagents add to aldehydes in the usual chemoselective manner as shown by the inter- and intramolecular competition experiments depicted in Scheme 73. Enals afford exclusively the 1,2-

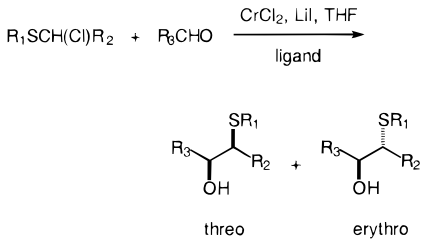
Scheme 73



(a) $CrCl_2$, LiI, THF, 40°C

addition products. Addition of LiI to the reaction mixture is essential for obtaining good yields; it converts the reasonably stable α-chloro sulfides in situ into the more reactive but very labile α-iodo

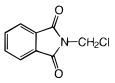
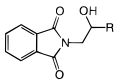
Table 67. Addition of α-Halo Sulfides to Aldehydes[161]



R_1	R_2	R_3	Ligand	Time (h)	Yield (%)	*threo:erythro*
Me	H	Ph		5	88	
		n-C_8H_{17}		9	72	
		PrCH=CH		13	64	
Ph	H	Ph		10	63	
		n-C_8H_{17}		10	48	
Ph	Me	Ph		16	58	80:20
			TMEDA	6	96	88:12
Ph	Pr	Ph	TMEDA	6	95	86:14
Ph	i-Pr	Ph	TMEDA	25	46	80:20
Ph	Me	n-C_8H_{17}		17	17 [a]	86:14
			TMEDA	1.5	25 [a]	90:10
			HMPA	20	33 [a]	97:3
			PPh_3	20	23 [a]	84:16
			dppe	20	56 [a]	90:10
Ph	Pr	n-C_8H_{17}	dppe	40	8 [a]	>98:<2
Ph	Me	c-C_6H_{11}	dppe	18	11 [a]	90:10
			TMEDA	18	65 [a]	81:19

[a] Traces of aldol byproducts detected (<3−23%).

Table 68. $CrCl_2$/LiI-Induced Additions of *N*-Halomethyl Imides to Aldehydes[162]

Substrate	Product	Yield (%)
		84 (R = Ph) 81 (R = *n*-C_5H_{11}) 68 (R = $(CH_2)_4COOMe$) [a]
		81 (R = Ph) 95 (R = *c*-C_6H_{11}) 88 (R = *n*-C_5H_{11}) 93 (R = *n*-C_5H_{11}) [b] 71 (R = p-NCC_6H_5) 76 (R = m-$AcOC_6H_5$) 36 (R = PhCH=CH-)

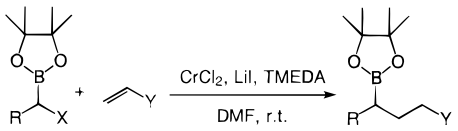
[a] Using the iodomethyl imide as the substrate. [b] Using *N*-(bromomethyl)phthalimide as the substrate.

sulfides which are the actual substrates. Addition of potential ligands for Cr(II) to the reaction mixture such as TMEDA or dppe (1,2-bis(diphenylphosphino)-ethane) may enhance the rate of reaction, the yield, and the diastereoselectivity of the addition process (Table 67).[161]

Similar to α-halo sulfides, other α-heteroatom-substituted alkyl halides were also found to be excellent substrates for chromium mediated C−C bond forming reactions. Specifically, *N*-(halomethyl)-succinimides and -phthalimides cleanly insert Cr(II) in the presence of LiI to afford the corresponding alkylchromium(III) reagents at the α-position to nitrogen. They can be trapped with aldehydes, thus providing an unconventional but highly efficient route to protected amino alcohol derivatives (Table 68).[162]

In contrast to the above-mentioned types of α-heteroatom-substituted alkyl halides, α-haloalkylboronic acid esters do not convert into the corresponding α-boryl alkylchromium reagents on exposure to $CrCl_2$ (activated by addition of TMEDA) but result in the formation of the α-boryl radicals which can be intercepted with acrylate, acrylonitrile, or α,*β*-unsaturated sulfones.[34] Similarly, additions of alkyl halides to electrophilic alkenes such as methyl acrylate or acrylonitrile mediated by $CrCl_2$ have also been reported which are believed to proceed via alkyl radicals as the actual intermediates (Table 69).[32b]

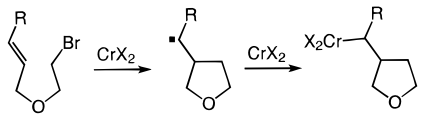
Table 69. 1,4-Addition of α-Boryl Radicals to Electron-Deficient Alkenes Mediated by $CrCl_2$[34]



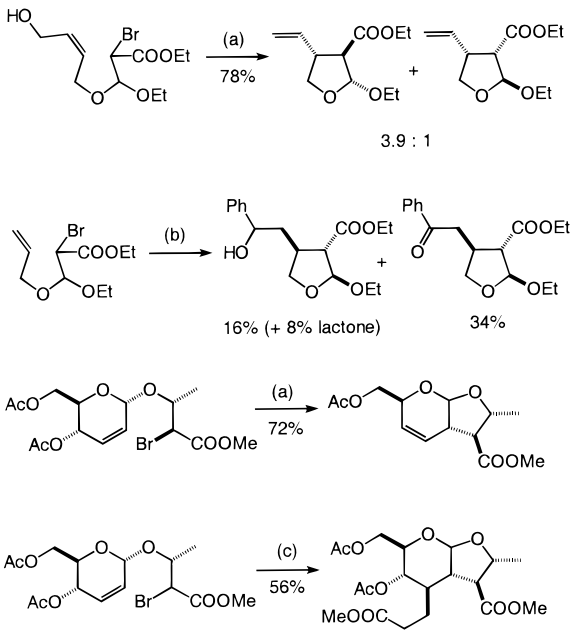
R	X	Y	Yield (%)
Bu	Cl	$COO(CH_2)_3Ph$	92
		CN	79
		SO_2Ph	85
H	I	$COO(CH_2)_3Ph$	< 2
c-C_6H_{11}	Cl	$COO(CH_2)_3Ph$	90
$Cl(CH_2)_4$	Br	COOEt	84
$EtOOC(CH_2)_4$	Cl	$COO(CH_2)_3Ph$	87

An interesting application of the radical/organochromium manifold involved in reactions of alkyl halides with Cr(II) has been reported by Schäfer et al.[163] Thus, activated bromides, on treatment with Cr(II), primarily lead to radicals that undergo rapid 5-*exo-trig* cyclizations with tethered olefins. The resulting radicals are then reduced to the corresponding alkyl chromium reagents, which may either be tapped with appropriate electrophiles or may enter subsequent dealkoxyhalogenation reactions (Schemes 74 and 75 and Table 70).[56,163] As to the reagent,

Scheme 74



Scheme 75



(a) $Cr(OAc)_2$ (3 eq.), r.t., THF/H_2O

(b) $CrCl_3$ + 1/2 $LiAlH_4$, THF, PhCHO (2 eq.)

(c) $Cr(OAc)_2$ (3 eq.), THF, H_2C=CHCOOMe

various modifications have been reported, with pure $Cr(OAc)_2$ or $Cr(OAc)_2$ in combination with donor ligands such as ethylenediamine or 2,2′-bipyridylamine being most frequently employed (Table 71). It is also possible to run the reactions with catalytic amounts of Cr(II) which is recycled either by chemical ($LiAlH_4$) or by electrochemical means.[56] If α-iodoesters are used as the substrates, it is possible to achieve inter- as well as intramolecular iodine transfer cyclization reactions leading to the formation of five-membered ring compounds (Scheme 76).[163c]

Related radical cyclization reactions of *ω*-alkynyl halides have been studied in some detail by Crandall et al. (Table 72).[20] These authors use solutions of $Cr(ClO_4)_2$ in aqueous DMF as the reagent, the reducing ability of which is further pushed by adding ethylenediamine. Depending on the length of the tether between the halide and the triple bond, the

Scheme 76

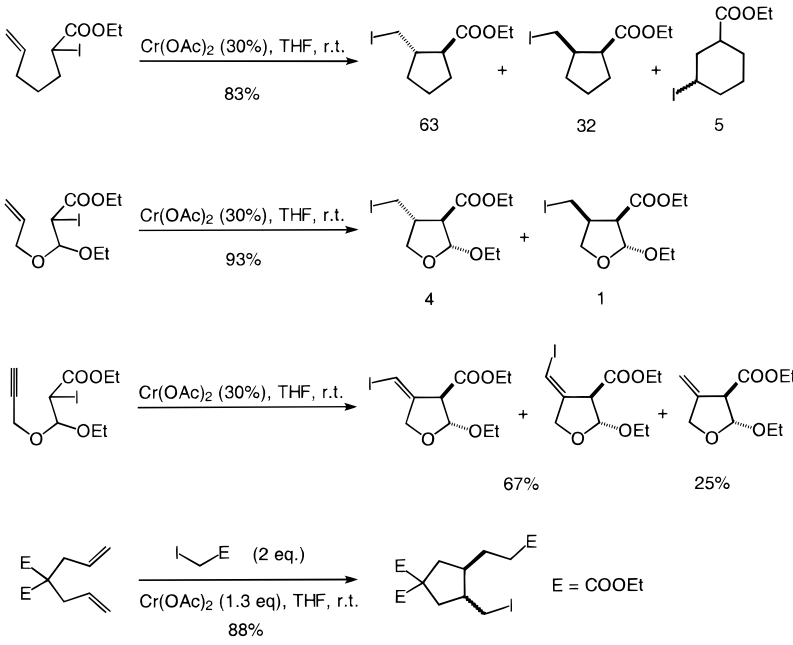
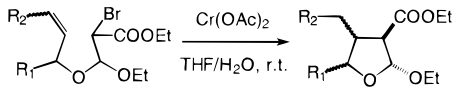
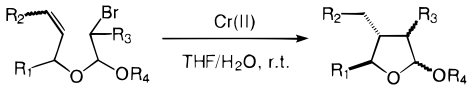


Table 70. Reductive Cyclization of Ethyl 3-Allyloxy-2-propionates by $Cr(OAc)_2$[163b]



R_1	R_2	Yield (%)	Isomer Ratio
H	H	79	1:3.9
Me	H	83	1:0.89
H	Me	83	1:1.68
	$-(CH_2)_3-$	78	1:1.04
n-C_5H_{11}	H	73	1:1.01
i-Pr	H	57	1:1.09
H	Ph	76	1:0.57
Ph	H	99	1:0.94
Me	Me	85	1:0.31

Table 71. Synthesis of Substituted Tetrahydrofurans by Cr(II)-Mediated Ring-Closure under Various Conditions[56]



R_1	R_2	R_3	R_4	Method [a], Yield %			
				A	B	C	D
H	H	H	C_4H_9	75	81		
Me	H	H	Et	66	67	71	77
C_4H_9	H	H	Et	84	88	93	70
C_5H_{11}	H	H	Et	89	86	75	84
H	H	Me	Et	54	75		
H	H	C_4H_9	Et	76	90	83	67
	$-(CH_2)_5-$	H	Et	75	70	83	75
H	H		$-(CH_2)_2-$	87	75	85	70
H	H		$-(CH_2)_3-$	80	71	89	80

[a] Method A: $Cr_2(OAc)_4(H_2O)_2$ (1.5 equiv), ethylenediamine (12 equiv), THF/H_2O (2/1). Method B: $Cr_2(OAc)_4(H_2O)_2$ (1.5 equiv), 2,2′-bipyridylamine (12 equiv), THF/H_2O (2/1). Method C: $Cr_2(OAc)_4(H_2O)_2$ (0.3 equiv), ethylenediamine (2.6 equiv), $LiAlH_4$ (8 equiv), THF. Method D: $Cr_2(OAc)_4(H_2O)_2$ (0.15 equiv), ethylenediamine (33 equiv), DMF, $LiClO_4$ (0.2 M), glassy carbon cathode, −1.15 V versus Marple electrode.

substituent R on the acetylene group, and the mode of addition, good to excellent yields of the corresponding exo-methylene cycloalkanes have been obtained. The best results are usually obtained by adding the solution of the Cr(II) reagent to the halide (inverse addition), with iodides reacting more efficiently than the corresponding bromides. While all substrates investigated adhere to the exo-cyclization mode, particularly good results have been obtained in the five-membered ring series.[20]

XI. gem-Dihaloalkanes

Nozaki et al. have addressed early on the reactivity of *gem*-dihalides with Cr(II). Specifically, they have found that 2,2-diiodopropane can be used as an isopropenyl donor (Scheme 77).[10]

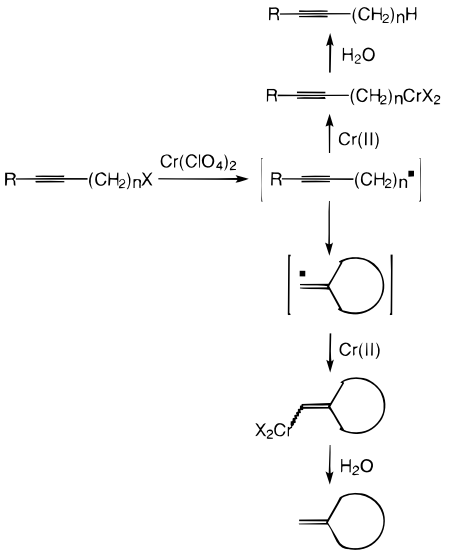
Depending on the reaction conditions, 1,1-dibromocyclopropane derivatives suffer either simple reduction of the C−Br bonds or can undergo dehalogenation followed by ring opening to afford allene products (for other allene syntheses, see section VIII).[7,55] However, attempts to intercept the reactive intermediates with electrophiles other than H^+ have not been reported.

As mentioned in section II B, a chromium-catalyzed procedure for the 1,4-addition of dibromodifluoromethane to electron-deficient alkenes using catalytic quantities of $CrCl_3 \cdot 6H_2O$ in combination with commercial Fe powder as the stoichiometric reducing agent has been developed (Scheme 78).[52]

The intermediates formed on treatment of 1,1-dichloro-2-propenes with Cr(II) behave like α-chloro allyl chromium reagents;[113] therefore, their chemistry is covered in section VI B.

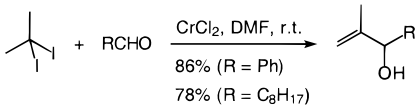
By far the most important chromium-mediated reaction of *gem*-dihaloalkanes is the *olefination of carbonyl compounds* developed by Takai and Utimoto

Table 72. Radical Cyclizations of ω-Alkynyl Halides Induced by $Cr(ClO_4)_2$/ethylenediamine in Aqueous DMF under Optimized Conditions (Inverse Addition, 0.1−0.05 M RX, 1 h)[20]

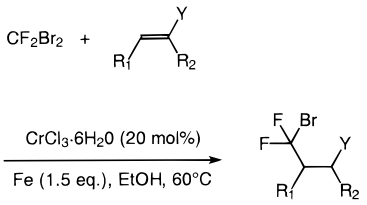


R	n	X	Cyclization Product, Yield (%)
n-C_4H_9	3	Br	0
		I	0
n-C_4H_9	4	Br	53
		I	85
Ph	4	Br	95
		I	96.5
n-C_4H_9	5	I	12
Ph	5	Br	79
		I	85
p-FC_6H_4	4	Br	93
p-$CH_3C_6H_4$	4	Br	93
p-$CH_3OC_6H_4$	4	Br	93

Scheme 77



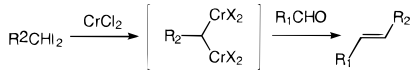
Scheme 78

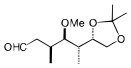
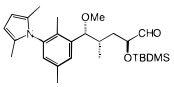
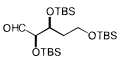
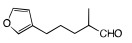
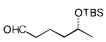
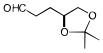


et al.[33] This transformation, which proceeds under notably mild conditions in THF or THF/DMF, combines a wide scope with the exceptional tolerance of organochromium reagents toward functional groups and is therefore very useful in cases where other olefination reactions fail to afford the desired products. Moreover, a high selectivity for the *E*-olefin is obtained in many cases, particularly with aliphatic substrates. The *E*:*Z* ratios increase with increasing steric bulk of the substitutent on the aldehyde. Diiodomethane and *gem*-diiodoethane are the most reactive substrates, whereas higher diiodoalkanes tend to give lower yields (Table 73). *gem*-Dibromo- and *gem*-dichloroalkanes by themselves are inappropriate. This is likely due to the slow reduction of these compounds by Cr(II). It is believed that the reaction proceeds via *gem*-dichromium compounds which nucleophilically attack the carbonyl compound, although the precise nature of these intermediates remains to be elucidated.[33]

Because of the low basicity of the chromium intermediates, this olefination protocol is also applicable to readily enolizable substrates.[33] Only very scattered reports are found in the literature, in which

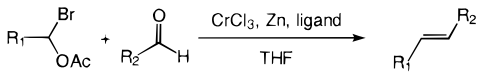
Table 73. Alkylidenation of Carbonyl Compounds with *gem*-Diiodoalkanes Mediated by Cr(II)



R_1CHO	R_2	[a]	t (h)	Yield (%)	*E* : *Z*	Ref.
$C_5H_{11}CHO$	Me	**A**	4.5	94	96:4	33
$C_{11}H_{23}CHO$	Me	**A**	5	81	95:5	33
$Ph(CH_2)_2CHO$	Me	**A**	10	85	97:3	33
Et_2CHCHO	Me	**A**	2	99	98:2	33
4-(iPr)C_6H_4CHO	Me	**A**	10	97	84:16	33
		C	5	84	78:22	33
	Me	**A**	7.5	93	89:11	33
	Me	**A**	3	74	11:1	254
$C_8H_{17}CHO$	Pr	**A**	24	38	95:5	33
		B	1.5	85	96:4	33
t-BuCHO	Pr	**B**	1	96	99:1	33
PhCHO	Pr	**B**	1	87	88:12	33
		C	0.5	60	51:49	33
$C_5H_{11}CHO$	i-Pr	**A**	24	12	72:28	33
		B	1	74	93:7	33
PhCHO	i-Pr	**B**	2	79	88:12	33
PrCHO	t-Bu	**B**	0.5	90	94:6	33
PhCHO	t-Bu	**B**	2	80	96:4	33
PhCHO	H	**A**	24	70		33
		B	3	92		33
$C_{11}H_{23}CHO$	H	**B**	3	73		33
$C_{14}H_{29}CH{=}CH(CH_2)_5CHO$	$(CH_2)_{12}C(OCH_2CH_2O)CH_3$			n.r.		255
	Et	[b]		75 [c]		164
	Me	**A**	2.5	91	>99:1	256
	H	**D**	n.r.	53	n.r.	210
	H	**D**	4	41	n.r.	257
	H	**D**		68 [d]	n.r.	258
	H	n.r.	n.r.	37 [d]	n.r.	259
	H	**D**		47	4:1	260

[a] Method A: aldehyde (1 mmol), diiodoalkane (2 mmol), $CrCl_2$ (8 mmol), THF. Method B: aldehyde (1 mmol), diiodoalkane (2 mmol), $CrCl_2$ (8 mmol), DMF (8 mmol), THF. Method C: using a reagent prepared in situ from $CrCl_3$ (8 mmol), Zn (6 mmol). Method D: in THF, no further details reported. [b] In CH_2Cl_2/DMF as the solvent mixture. [c] In addition to the 75% of the *E*,*E*-isomer, 25% of other isomers (*E*,*Z*-mixture) has been formed. [d] The yield refers to a sequence involving the Takai olefination as one of the steps.

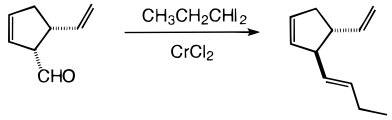
Table 74. Olefination of Aldehydes Using α-Acetoxy Bromides[165]



R_1	R_2	Ligand	T (°C)	Yield (%)	*E*:*Z*
Et	n-C_7H_{15}	DMF	25	56	91:9
		DMF	66	68	74:26
		TMEDA	66	33	54:46
		TEEDA	66	29	85:15
	$CH_3(CH_2)_4CH{=}CH(CH_2)_2$	DMF	25	49	90:10
		DMF	66	70	74:26
	$MeOOC(CH_2)_7$	DMF	66	61	73:27
	$CH_3(CH_2)_4CH{=}CH$	DMF	66	20	50:50
	Ph	DMF	66	20	50:50
	2-naphthyl	DMF	66	30	50:50
n-C_7H_{15}	n-C_7H_{15}	DMF	66	78	70:30
	Ph	DMF	66	29	50:50
Ph	n-C_7H_{15}	DMF	66	54	85:15
	Ph	DMF	66	97	70:30

a chiral center α to the aldehyde is affected under the reaction conditions. One example was reported by Boland et al., in which a very labile cis-disubstituted derivative isomerizes during the alkylidenation reaction, providing mainly the trans-product (Scheme 79).[164]

Scheme 79



A useful variant of this olefination procedure employs α-acetoxy bromides as starting materials instead of *gem*-diiodides because they are more readily available and somewhat more stable (Table 74).[165] In this case, it turned out to be essential to prepare the chromium reagent in situ from $CrCl_3$ and Zn in the presence of a donor ligand such as DMF or TMEDA. The reaction also shows a high selectivity in favor of the (*E*)-alkenes and turned out to be chemoselective for aldehydes, leaving, e.g., ester groups unchanged.[165]

The Takai−Utimoto olefination can also be accomplished with *catalytic* amounts of $CrCl_3$ in the presence of Sm and SmI_2 as the stoichiometric reducing agent (Table 75). In this modification, however, it is not clear if the intermediate *gem*-dimetallic species contain Cr(III) or Sm(III).[51] Anyway, they exhibit a pronounced nucleophilicity and are even applicable to ketones prone to enolization. Reactions with acylsilanes as the substrates have also been reported. Upon using dibromomethyltrimethylstannane or dibromomethyltrimethylsilane, it is possible to prepare alkenylstannanes and alkenylsilanes, respectively (vide infra).[51]

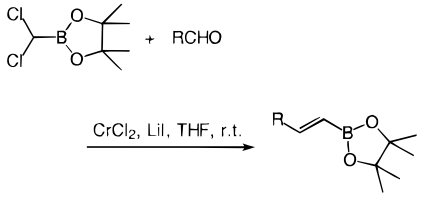
As in most other chromium-mediated syntheses, the *gem*-dihalide substrate may bear one or two additional functional groups. This allows to prepare *functionalized alkenes* such as alkenylsilanes, -stannanes, -halides, -sulfides, or -boronates.

Table 75. Chromium-Catalyzed Takai−Utimoto Olefinations[51]

Ketone	*gem*-Dihalide	SmI_2	Sm	$CrCl_3$	Yield (%) (*E*:*Z*)
		equiv.			
4-*tert*-butylcyclohexanone	CH_3CHBr_2	8	0	0	0 [a]
		2	2	0	22 [a]
		8	0	0.1	37
		2	2	0.1	71
	CH_3CHI_2	2	2	0.1	29
	$CH_3(CH_2)_4CHBr_2$	2	2	0.1	65
2-undecanone	CH_3CHBr_2	2	2	0.1	67 (50/50)
cyclopentanone	$CH_3(CH_2)_4CHBr_2$	2	2	0.1	51
ß-tetralone	$CH_3(CH_2)_4CHBr_2$	2	2	0.1	71 (56/44)
t-butylmethylketone	$CH_3(CH_2)_4CHBr_2$	2	2	0.1	71 (64/36)
diisopropylketone	$CH_3(CH_2)_4CHBr_2$	2	2	0.1	61
4-*tert*-butylcyclohexanone	$(CH_3)_2CBr_2$	2	2	0.1	53
	$EtOCOCHBr_2$	2	2	0.1	38
	$Me_3SiCHBr_2$	2	2	0.1	54
	$Me_3SnCHBr_2$	2	2	0.1	40 [b]
$CH_3(CH_2)_6C(O)SiMe_3$	CH_3CHBr_2	2	2	0.1	54 (66/34)
	$Me_3SiCHBr_2$	2	2	0.1	56 (80/20)

[a] 4-*tert*-Butyl-1-iodoethylcyclohexanol detected as byproduct. [b] 4-*tert*-Butyl methylenecyclohexane (19%) as a byproduct.

Table 76. Synthesis of Alkenylboronates via Takai−Utimoto Olefination[167]

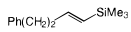
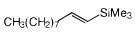
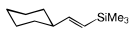
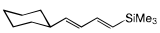
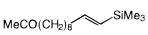
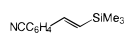
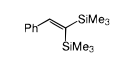
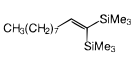
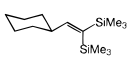
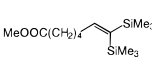
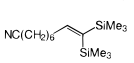
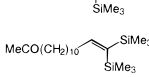
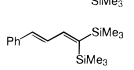
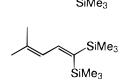
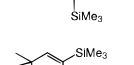
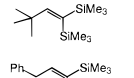


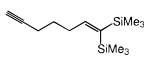
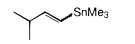
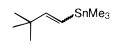
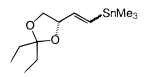
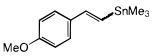
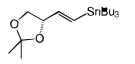
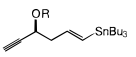
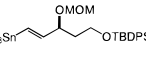
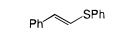
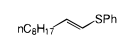
R	Yield (%)	*E* : *Z*
n-$C_{11}H_{23}$	84	97 : 3
$PhCH_2CH_2$	91	98 : 2
c-C_6H_{11}	86	99 : 1
t-Bu	69	>99 : <1
Ph	90	95 : 5
PhCH=CH	86	87 : 13
MeCH(OBn)	78	98 : 2
$MeC(O)(CH_2)_8$	85	98 : 2
p-NCC_6H_4	52	93 : 7

In all cases, the (*E*)-isomer is formed with reasonable to excellent selectivity. It is also interesting to note that the presence of the heteroatom may *facilitate* the reduction of the *gem*-dihalide by Cr(II) and improve the stereoselectivity of the olefination process.[166]

Specifically, reaction of various aldehydes with dichloromethylboronic esters in the presence of $CrCl_2$ and LiI in THF at ambient temperature cleanly delivers the corresponding (*E*)-configured 1-alkenylboronic esters by a one-carbon homologation (Table 76).[167] Addition of LiI is essential, as it converts the substrates in situ into the more reactive diiodo compounds. The latter insert Cr(II) to afford *gem*-dichromium reagents which react with the carbonyl group in very much the same way as outlined above. This approach to alkenylboronates is aldehyde selective, leaving, e.g., ketone or cyano groups in the

Table 77. Preparation of Alkenylsilanes, -stannanes, and -sulfides via Takai–Utimoto Olefination of Carbonyl Compounds

Halide	Product	Yield (%)	*E:Z*	Ref.
$Me_3SiCHBr_2$		82	100:0	166
		86	100:0	166
		82	100:0	166
		81	100:0	166
		79	100:0	166
		77	100:0	166
		76	100:0	166
		72	100:0	166
$(Me_3Si)_2CBr_2$		84 [a]		261
		78 [a]		261
		79 [a]		261
		64 [a]		261
		70 [a]		261
		58 [a]		261
		84 [a]		261
		73 [a]		261
		28 [a]		261b
		39 [a]		261b

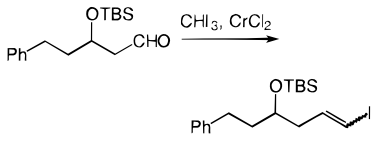
Halide	Product	Yield (%)	*E:Z*	Ref.
		38 [a]		261b
$Me_3SnCHBr_2$		77 [b]	69:31	169
		82 [b]	73:27	169
		60 [b]	84:16	169
		80 [b]	88:12	169
		0 [c]		169
$Bu_3SnCHBr_2$	n-$C_8H_{17}CH{=}CHSnBu_3$	60 [d]	100:0	168, 37
	c-C_6H_{11}-$CH{=}CHSnBu_3$	62 [d]	100:0	168, 37
	$HC{\equiv}C(CH_2)_5CH{=}CHSnBu_3$	60 [d]	100:0	168, 37
	$MeOOC(CH_2)_4CH{=}CHSnBu_3$	61 [d,e]	100:0	170, 37
	$NC(CH_2)_6CH{=}CHSnBu_3$	58 [d,e]	100:0	170, 37
	$MeCO(CH_2)_{10}CH{=}CHSnBu_3$	53 [d,e]	100:0	170, 37
	$Me_2C{=}CH{-}CH{=}CHSnBu_3$	58 [d,e]	83:17	170, 37
		63	100:0	170, 37
		42 (R = TBS) 18 (R = TES)	100:0	260
		54	n.r.	262
Bu_3SnCHI_2	$C_8H_{17}CH{=}CHSnBu_3$	85-89 [a]	„E“	171
	c-C_6H_{11}-$CH{=}CHSnBu_3$	80 [a]	„E“	171
	$MeOOC(CH_2)_4CH{=}CHSnBu_3$	82 [a]	„E“	171
$PhSCHCl_2$		83 [b]	82:18	166
		68 [b]	71:29	166

[a] The reactions are carried out in DMF without LiI being added. [b] The reactions are carried out in THF in the presence of LiI. [c] *p*-Methoxystyrene is formed. [d] In DMF/THF in the presence of LiI. [e] Some $RCH{=}CH_2$, formed by protodestannylation, is obtained as byproduct (34–41%).

substrates intact.[167] The high (*E*)-selectivity is believed to arise from the addition of the *gem*-dichromium reagent to the aldehyde via a chairlike transition state, followed by a rapid syn elimination of $(L_nCr)_2O$.[167] Attempts to replace $CrCl_2$ by other reducing agents such as Zn, $MnCl_2/LiAlH_4$, Sn, $SnCl_2$, or SmI_2 gave little or none of the desired product, thus showing the peculiar properties of Cr(II) as a reducing agent.

When the Takai–Utimoto olefination method is applied to R_3SnCHX_2 as the substrates, the stereoselectivity of the resulting alkenylstannanes depends, to some extent, on the substituents R on the tin moiety (Table 77). While $Bu_3SnCHBr_2$ generally affords the (*E*)-isomer exclusively,[168] $Me_3SnCHBr_2$ usually leads to (*E*):(*Z*) mixtures (69:31–88:12); however, the yields obtained are higher with the latter reagent.[169] In some cases, protodestannylation of the alkenylstannanes formed cannot be completely suppressed.[168,170] THF containing 1 equiv of DMF relative to $CrCl_2$ was reported to be the best reaction medium in terms of stereoselectivity.[37] A very recent paper describes that the use of Bu_3SnCHI_2 in DMF gives particularly satisfactory results, both in terms of yield and stereoselectivity.[171]

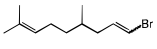
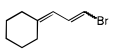
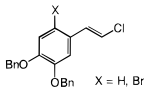
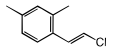
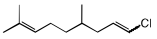
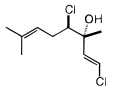
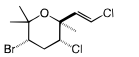
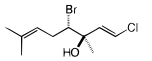
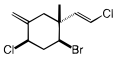
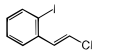
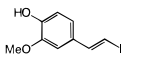
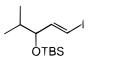
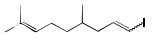
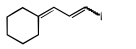
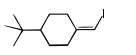
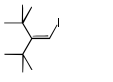
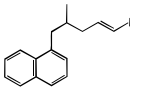
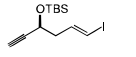
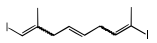
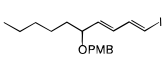
Table 78. Optimization of the Cr(II)-Mediated Vinyliodide Synthesis[38]



Solvent	t (h)	Yield (%)	*E:Z*
THF	4	73	4:1
1,4-dioxane	96	40	22:1
1,4-dioxane:THF (6:1)	8	69	13:1

One of the most important variants of the Takai–Utimoto olefination, and one of the most frequent applications of $CrCl_2$ in synthesis in general, concerns the direct preparation of alkenyl halides by one-carbon homologation of aldehydes with CHX_3 (Table 79).[27] The reaction is distinguished by its wide scope, an excellent compatibility with functional groups, the experimental ease, and by a high (*E*)-selectivity. Only in the case of α,β-unsaturated aldehydes as the substrates, the stereoselectivity is somewhat depressed. The stereoselectivity also depends, to some extent, on the haloform used, with the (*E*):(*Z*) ratios

Table 79. Preparation of Alkenyl Halides via Takai−Utimoto Olefination of Carbonyl Compounds with Haloforms

Halide	Product	*E*:*Z*	Yield (%)	Ref.
$CHBr_3$	PhCH=CHBr	95:5	70 [a]	27, 263
	$CH_3(CH_2)_6CH$=CHBr	87:13	61 [a]	27
	c-C_6H_{11}-CH=CHBr	94:6	66	27
		89:11	55 [a]	27
		81:19	73 [a]	27
$CHCl_3$	PhCH=CHCl	95:5	76	27
	 X = H, Br		n.r.	264
		85:15	n.r.	265
	$CH_3(CH_2)_6CH$=CHCl	94:6	76	27
		92:8	55	27
			n.r.	69	266
			76.6	267
			22 [d,f]	268
		94:6	58	269
		1.8:1	59	270
$^{13}CHI_3$	p-$MeOC_6H_4CH=^{13}CHI$	n.r.	75	271
CHI_3	PhCH=CHI	94:6	87	27, 272, 273
		95:5	97	
	p-$MeOC_6H_4$CH=CHI	n.r.	n.r.	274
		9:1	65-98	275
	n-C_6H_{13}CH=CHI	84:16	n.r.	276
	$CH_3(CH_2)_6CH$=CHI	83:17	82	27
	n-C_9H_{19}CH=CHI		36	277
	i-C_3H_7-CH=CHI	97:3	n.r.	276
	c-C_6H_{11}-CH=CHI	89:11	78	27, 273
		99:1	65	273
		82:18	84	27, 273
		variable	76	27
			75	27
			51 [b]	27
		>95:5	76	278
		4:1	47	260
		n.r.	75	279
		8:1	83	280

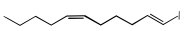
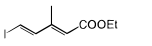
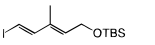
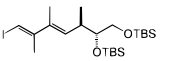
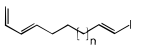
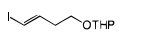
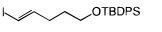
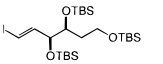
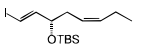
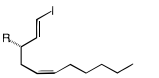
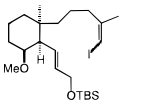
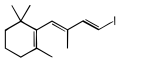
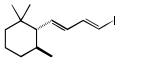
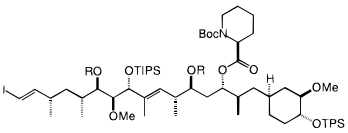
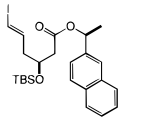
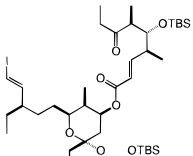
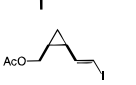
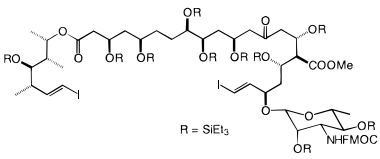
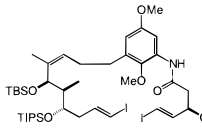
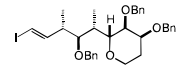
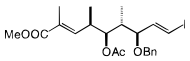
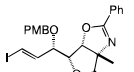
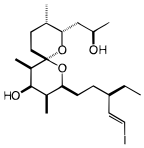
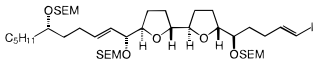
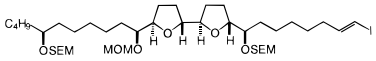
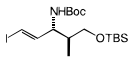
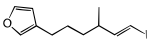
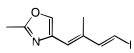
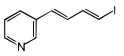
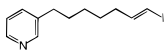
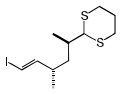
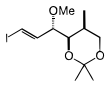
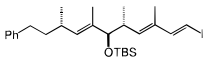
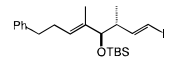
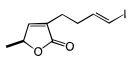
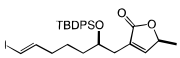
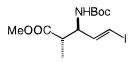
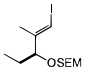
Halide	Product	*E*:*Z*	Yield (%)	Ref.
			n.r.	281
		14:1	50	282
		7:1	90	282
			37	283
		4:1	58 (n=1) 60 (n=2)	284
		5:1	65	285
		n.r.	n.r. [c]	197
			53 [d]	210
			45	286
		n.r.	54 (R=TBDPS) 95 (R=H)	185
		n.r.	42	30
			63	287
			89	288
	 R = PMB	4:1	94 [c]	188
		9:1 [c]	80 [c]	38
		100:0	76	174
		92:8	64	289
	 R = $SiEt_3$		62 [c]	290
			70	291

Table 79 (Continued)

Halide	Product	*E*:*Z*	Yield (%)	Ref.
			77 [d]	199
		98:2	80	292
			68 [d]	293
			79 [d]	294
			75	295
			72	296
			74 [d]	297
			41	257
			60	298
		4:1	72	299
			65	299
			80 [d]	300
			38 [e] 50 [e]	228
		20:1	70	173
			57 [d]	173
		8:1	85	301
		5:1	68 [c,d]	302
		1:0	75 53 [c,d]	303 304
		5:1	61	305
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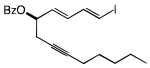
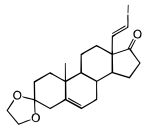
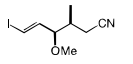
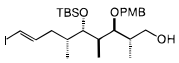
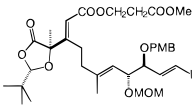
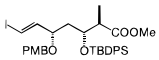
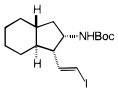
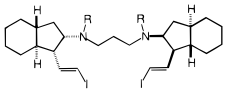
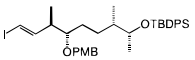
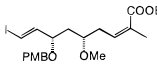
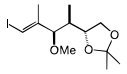
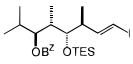
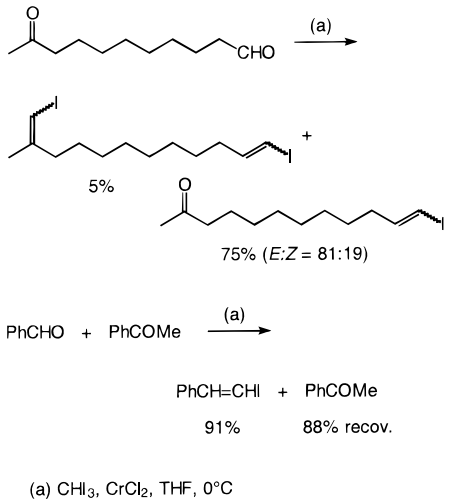
		4:1	70	307
			60	308
		>10:1	50	309
		14:1	79 [c,d]	310
			66	311
			62 [d]	312
			65	313a
			71 (R = Tf) [c] 65 (R = Ts)	313
		>9:1	48	204
			78 [c]	314
		2:1	45	315
		>95:5	73	316

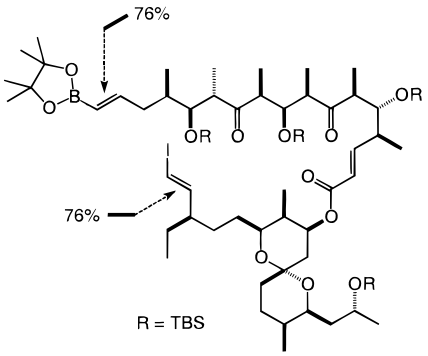
[a] Using $CrBr_3 + {}^1/_2LiAlH_4$ as the reagent. [b] 43% of the starting ketone recovered. [c] In 1,4-dioxane:THF as the solvent. [d] Overall yield for the formation of the aldehyde and the subsequent Takai olefination. [e] Refers to an overall yield over several steps, including the Takai olefination. [f] Together with ene reaction products.

usually increasing in the order I < Br < Cl. However, the rate of reaction of the haloforms is inverse (CHI_3 > $CHBr_3$ > $CHCl_3$), with iodoform reacting readily even at 0 °C, wheras the other haloforms require elevated temperatures. It has also been noticed that reactions of $CHBr_3$ may lead to mixtures of alkenyl bromides and alkenyl chlorides because of a preceding Finkelstein reaction with $CrCl_2$.[27,172] This problem can be overcome by using a Cr(II) reagent prepared by reduction of $CrBr_3$ with $LiAlH_4$.[27] Again, reducing agents other than Cr(II) such as Zn, $MnCl_2$/$LiAlH_4$, VCl_3/$LiAlH_4$, Sn, or $SnCl_2$ gave unsatisfactory results. Ketones can also be transformed into the corresponding alkenyl halides but tend to give lower yields. This different propensity is evident from the intermolecular competition experiment shown in Scheme 80 and can be used for chemoselective reactions of keto aldehyde derivatives.[27] Some authors noticed a decrease in yield upon scale-up of the olefination.[173]

Scheme 80



Scheme 81

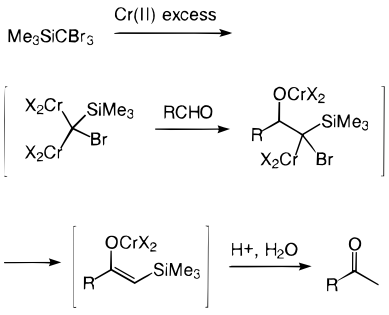


During the course of a total synthesis of lepicidin A, Evans et al. have found that the stereoselectivity of this chromium-mediated alkenyl iodide synthesis strongly depends on the solvent used.[38] A careful optimization allowed them to identify a mixture of 1,4-dioxane:THF = 6:1 as being the optimal reaction medium, ensuring both a high yield and an appreciable preference for the formation of the (*E*)-isomer (Table 78).

A recent total synthesis of rutamycin B constitutes a striking example for the performance and unique compatibility of the Takai−Utimoto olefination reactions.[174] White et al. have used this very useful transformation twice, both for the preparation of the vinyliodide and the vinylboronate groups in the highly functionalized seco-derivative depicted in Scheme 81. A subsequent intramolecular Suzuki cross-coupling reaction of these entities afforded the fully protected macrolide antibiotic.

Hodgson et al. reported a further useful modification of Takai−Utimoto reaction which corresponds to a one-step homologation of aldehydes into the respective methyl ketones using Me_3SiCBr_3 (Table 80).[28] Again, a Cr(II) reagent prepared from $CrBr_3$ and $LiAlH_4$ was employed in order to avoid undesirable halide scrambling. It is assumed that the primary adduct formed upon reaction of the *gem*-dichromium reagent with the aldehyde preferably reacts along an α-elimination pathway with (simultaneous?) insertion of the carbene formed into the adjacent C−H bond. The resulting chromium enolate loses its labile silyl group during aqueous workup to afford the final methyl ketone product.[28] This procedure is a convenient alternative to other carbonyl homologation methods, e.g., those employing diazomethane.

Table 80. One-Step Homologation of Aldehydes into Methyl Ketones Using Me_3SiCBr_3 and Cr(II)[28]



Aldehyde	Product	Yield (%)
PhCHO	PhCOMe	80
$CH_3(CH_2)_7CHO$	$CH_3(CH_2)_7COCH_3$	61
$MeOOC(CH_2)_4CHO$	$MeOOC(CH_2)_4COCH_3$	87
$4\text{-}NCC_6H_4CHO$	$4\text{-}NCC_6H_4COCH_3$	79
$CH_3CO(CH_2)_{10}CHO$	$CH_3CO(CH_2)_{10}COCH_3$	71

XII. Pinacol Coupling Reactions

The mechanism and kinetics of the reductive coupling of aldehydes by Cr(II) salts have been reported in some very early investigations.[175] Until very recently, however, this pinacolization method has received relatively little attention, maybe because large amounts of toxic chromium waste have to be dealt with. New impetus came from the possibility to perform such Cr(II)-mediated pinacol coupling reactions in a catalytic manner. Thus, Cr(II) cat. in combination with Mn(0) and TMSCl turned out to be an excellent reagent for effecting the reductive dimerization of variously functionalized aromatic aldehydes.[50] The reader is referred to section II B in which the present state of the art is summarized.

Another investigation makes use of a low-valent chromium reagent formed from $CrCl_3$ and 2 equiv of *n*-BuLi (formally a Cr(I) species depicted as "CrCl" by the authors) as an efficient pinacolization agent.[176]

XIII. Miscellaneous

As a result of the electron-transfer ability of Cr(II) to carbonyl compounds, Stevenson et al. have noticed, during a study aiming at the cyclization of substrate **9**, that cyclopropanol **10** was formed as the only reaction product, whereas the C−I bond was simply reduced (Scheme 82).[177] Obviously, s.e.t. from Cr(II) to the easily reducible α,β-unsaturated aldehyde

Scheme 82

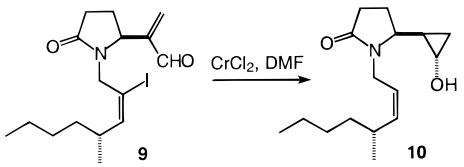
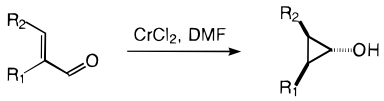


Table 81. Cr(II)-Induced Formation of Cyclopropanols from Enals[177]



R_1	R_2	t (h)	Yield (%)
Bu	H	3	32 [a]
c-C_6H_{11}	H	3	63
1,1-dimethylpropyl	H	3	69
H	Hexyl	3	51
H	Me	3	0 [b]
H	Ph	3	0 [b]
n-C_5H_{11}	Bu	16	0 [c]

[a] Pinacol formed as major product (45%). [b] Complex mixture formed. [c] Substrate recovered unchanged.

occurs much faster than the reduction of the alkenyl halide to the corresponding organochromium reagent. In line with the assumed triggering s.e.t. event, pinacolization of the substrate may compete with cyclopropanol formation. The scope of the method is limited (Table 81), but its stereoselective course may render it attractive in certain cases.[177]

A bimetallic catalyst consisting of polymer-bound $(PPh_3)_2NiCl_2$ in the presence of $CrCl_2$ has been described by Trost et al. which effects the cyclizations of functionalized enynes to dienes (Table 82).[178] The use of supported nickel salts ensures a separation of the catalytic sites and hence results in significantly higher yields of the cyclic monomers. $CrCl_2$ turned out to be much more effective than other reducing agents, such as sodium naphthalenide, DIBAL-H, SmI_2, and even $Cr(OAc)_2$; consequently, the authors speculated whether a mixed metal system like $(PPh_3)_3NiCrCl_4$ or $(PPh_3)_3NiCrCl_3$ accounts for the observed results. The same catalyst mixture also applies to the cyclization of ene-allenes (Table 82).[179] In this case, it is proposed that a metal hydride species formed in situ adds to the allene, giving rise to a π-allylmetal complex that cyclizes via a chairlike transition state to afford a 1,4-diene product. This mechanistic rationale is mainly based on the analysis of the stereochemistry of the products formed.

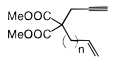
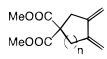
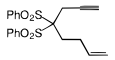
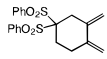
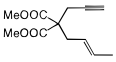
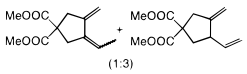
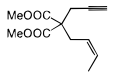
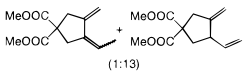
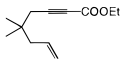
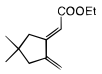
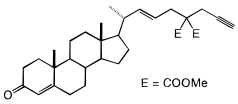
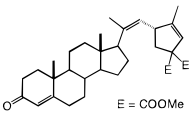
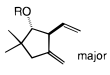
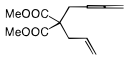
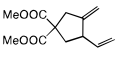
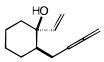
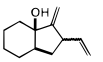
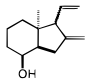
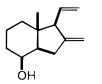
$Cp(\eta^3\text{-}C_3H_5)_2Cr$ readily effects the cyclotrimerization of alkynes with formation of $Cp(\eta^6\text{-arene})Cr$ compounds in high yields.[180] The catalytically active metal template is likely dinuclear in nature. The reaction is rather general and may also be used to prepare compounds containing substituted cyclopentadienyl groups.[19c,180]

Reference is given to a study on the formation and chemical reactivity of a formal Cr(I) salt (prepared by reduction of $CrCl_3$ with 2 equiv of *n*-BuLi in THF at −78 °C → rt), although it does not strictly fall into the scope of this review.[176] The reagent is a strong single electron donor and promotes pinacol as well as Wurtz coupling reactions very efficiently.

Similarly, the reader is referred to an exploratory study on the structure and reactivity of related bis-(η^3-allyl)chromium(**II**) complexes prepared by transmetalation of allyl-Grignard reagents with $CrCl_2$.[26]

Treatment of glycosyl halides with $CrCl_2$ in the presence of donor ligands affords pyranoid glycals in good yields. The reaction passes through glycosyl chromium(III) reagents which undergo subsequent reductive elimination to form the sugar-derived enol ethers. These intermediates are relatively long-lived and may therefore hold promise of being amenable to C−C bond formations at the anomeric center.[181]

Table 82. Cyclizations Catalyzed by Polymer-Supported $(PPh_3)_2NiCl_2$ (10 mol %) and $CrCl_2$ (30 mol %) in THF:EtOH (4:1)[178,179]

Substrate	Product	Yield (%)
		82 (n = 1) 60 (n = 2)
		80
	 (1:3)	75
	 (1:13)	74
		79
		53
		59
		47
		77
	 major	55 (R = H) 78 (R = TBS)
		80
		78
		72
		73
		86
		77

XIV. Acknowledgment

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Chemischen Industrie is acknowledged with gratitude.

XV. Abbreviations

Ac = acetyl
acac = acetylacetonate
Bn = benzyl
Boc = *tert*-butoxycarbonyl
Bz = benzoyl
DMA = dimethylacetamide
d.r. = diastereomeric ratio
Fmoc = 9-fluorenylmethoxycarbonyl
MOM = methoxymethyl
MPM = PMB = *p*-methoxybenzyl
Ms = methanesulfonyl
NHK = Nozaki−Hiyama−Kishi
n.r. = not reported
Piv = pivaloyl
PMB = MBM = *p*-methoxybenzyl
SEM = 2-(trimethylsilyl)ethoxymethyl
s.e.t. = single electron transfer
TBDPS = *tert*-butyldiphenylsilyl
TBS = TBDMS = *tert*-butyldimethylsilyl
TES = triethylsilyl
Tf = trifluoromethansulfonyl
THP = tetrahydropyranyl
TEEDA = *N*,*N*,*N*′,*N*′-tetraethylethylenediamine
TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TPS = triphenylsilyl
Tr = triphenylmethyl

XVI. References

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