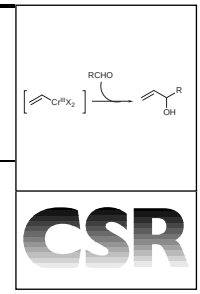
Synthetic variations based on low-valent chromium: new developments



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This article presents an overview of the synthetic chemistry of low-valent chromium, presumably Cr(II) species, and highlights most of the recent developments. These organometallic reactions represent a convenient strategy for the construction of carbon–carbon bonds displaying unique elements of stereocontrol, chemoselectivity, and functional-group compatibility. The introduction of milder protocols, catalytic versions, and the discovery of ligand tuning effects as a means of controlling carbanion selectivity, are the most salient improvements in this expansive field.

1 Introduction and background

The interest in organochromium species as reagents only arose in the late 1970s when Nozaki and Hiyama *et al.*[1] as well as Heathcock and Buse[2] recognized that these species could mediate Barbier–Grignard carbonyl additions, thereby taking part in carbon–carbon bond-forming reactions in organic solvents. Shortly afterwards, other research groups independently described this coupling with a variety of halides and tosylates unveiling a series of important and unique features:[3,4] (a) an exquisite chemoselectivity revealed by the ability of these reagents to add selectively to aldehydes in the presence of ketones; (b) an unprecedented compatibility with numerous functional groups such as esters or nitriles, which would otherwise be affected by other organometallics; (c) allylchromium reagents react with excellent 1,2-stereochemical control to afford, in general, *anti* adducts regardless of halide geometry, either (*E*)- or (*Z*)-configured; (d) such a preference may be reversed for very bulky aldehydes, and notably, it depends on the solvent system; (e) disubstituted alkenyl derivatives react with complete retention of their double bond configuration. An illustrative example is provided by the separate addition of (*E*)-bromostyrene and (*Z*)-bromostyrene to benzaldehyde yielding stereospecifically (*E*)- and (*Z*)-configurated products, respectively. However, trisubstituted (*E*)- and (*Z*)-alkenyl halides react with aldehydes in a stereoconvergent manner to produce the (*E*)-isomers in both cases; (f) alkyl and alkenyl halides remain unaffected under the conditions utilized in the preparation of allylchromium reagents.

There are, however, a series of practical limitations: Cr(II) is a good one-electron transfer donor and at least two moles of this reagent per mole of halide or donor are required, although in practice a large excess is usually employed. Water should be avoided because the formation of aquaorganochromium(III) species leads to reduction of organic halides. The mechanism proceeds by single-electron reduction of the C–X bond followed by reduction of the resulting radical by a second equivalent of Cr(II), and finally protonolysis of the organochromium(III)

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intermediate.[3] Moreover, both Cr(II) and Cr(III) species are strongly oxophilic and oxygen-free solvents are recommended.

Generally referred to as Nozaki–Hiyama reactions[4] after two of the discoverers, these carbon–carbon couplings have acquired great importance in preparative organic chemistry. Other authors have also significantly contributed to the development and further understanding of this methodology and their names are often associated with those of Nozaki and Hiyama. In particular, Kishi[5] and Nozaki[6] made the independent and almost simultaneous discovery that Ni(II), employed as a catalyst, has a pronounced effect on the formation of the C–Cr bond. Furthermore, Kishi studied the scope and stereochemistry with chiral derivatives *en route* to the synthesis of palytoxin.[4,5] Important advances have also been reported by Takai and his group who have extended the process to organochromium reagents other than allyl derivatives; they have found a useful protocol for the olefination of aldehydes, and have rationalized the use of other catalysts as well.[3,4,7]

Low-valent chromium reagents, although utilized for various unrelated types of couplings, tend to react under very mild conditions affording synthetically useful yields. The reagents themselves, formally at least, are hard nucleophiles. Although Cr(II) species represent a borderline case between hard and soft acids (while Cr(III) is in fact a hard acid), the carbon of a carbonyl is a hard acceptor and the oxygen is a hard donor. Since organochromium species undergo 1,2-additions exclusively, they are prototype examples of hard nucleophiles. Nevertheless in many cases without the presence of counterions capable of enhancing Lewis acid character, most couplings do not occur. Such properties impart high chemoselectivity patterns not witnessed with other reactive organometallic species (organoalkali, Grignard or organozinc reagents). The remarkable tendency for organochromium reagents to add to carbonyl groups in a 1,2-fashion, together with their relative inertness towards conjugate additions in the case of α,β-unsaturated carbonyl systems, combine to enhance their worth as selective agents. Morever, their low basicity encourages displacement over competing elimination pathways.

An important feature of low-valent chromium, which has not yet been sufficiently appreciated, is its ability to effect macrocyclization reactions, and intramolecular couplings are largely independent of the size of the ring formed. It is well established that additions of organochromium reagents to chiral aldehydes are not chelation controlled, so that an explanation based on a strong template effect, as invoked in the case of other transition metals, should be questioned. Presumably, the cyclization is driven by the gain in enthalpy owing to the formation of the very stable Cr(III)–O bond.

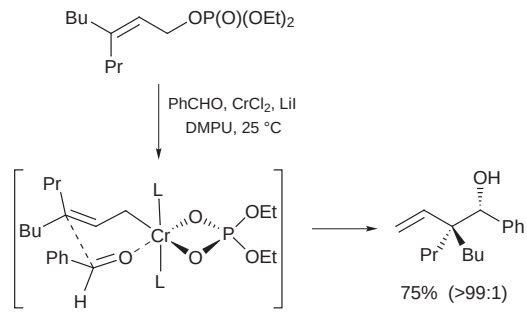
A further and unanswered complex physical question involves the exact nature of chromium salts in solution. Whereas Cr(II) chloride can be successfully utilized to form *in situ* the putative organochromium(III) reagents, the action of several reducing agents on Cr(II), depending on the method of preparation, may lead to the formation of low-valent chromium species, a common aspect of other transition metals, having different structures and modes of action.

Comprehensive reviews dealing with the preparation and applications of low-valent chromium species were reported by Saccomano[3] and one of us[4] covering the literature up to 1991. Since then, numerous articles and specific revisions, notably the applications of these protocols as key steps in some syntheses of natural products, have also been published. The purpose of this article is to provide the reader with a concise description and critical analysis of the more recent developments in this fascinating chemistry, such as the application to processes other than Barbier-type reactions, newer radical reactions, the introduction of a catalytic method, or an electrochemically-driven coupling. It is not within the scope of *Chem. Soc. Rev.* to provide a full, rather comprehensive account of a particular area, but it is hoped that the present article will be a springboard for further reading.

2 Stoichiometric reactions

As previously mentioned, allyl halides are favorite substrates of the chromium-mediated addition reactions. γ-Monosubstituted organochromium reagents will usually react through the (*E*)-allyl organometallic species, and it is therefore irrelevant which allyl halide is used because both isomers converge to the same product. The loss of stereochemical integrity could occur during the formation of the allyl radical intermediate, or perhaps by the η^1–η^3 haptotropic rearrangement of the allyl metal species.[8] Such a rearrangement can be faster or slower than their addition to aldehydes, and this fact critically affects *syn/anti* selectivity.

In contrast with these stereoconvergent processes, γ-disubstituted allyl derivatives react with aldehydes and $CrCl_2$ in a stereodivergent manner to afford homoallylic alcohols with high stereoselectivity (Scheme 1).[9] The use of LiI is essential



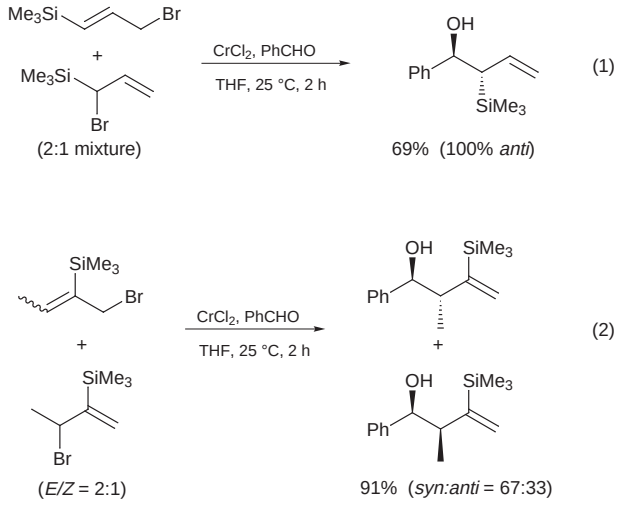
Scheme 1

because without this additive low yields were obtained. The presence of the two substituents at the γ-position slows down the equilibration between the (*E*)- and (*Z*)-organochromium(III) intermediates, which results in retention of the geometrical integrity in the coupling step. The stereochemical outcome can be rationalized assuming a chair transition state. It should be noted that allylic phosphates, and not halides, were used as electrophiles but this leaving group is not responsible for the high stereoselection. In fact (*E*)- and (*Z*)-monosubstituted allylic phosphates both stereoconverge to the *anti* alcohol as major diastereoisomer.

Stereoconvergence has been observed in the reactions of silyl-substituted allylchromium reagents and the coupling occurs through the most substituted end of the organometallic species (Scheme 2, eqn. (1)).[10] However, the trimethylsilyl group imparts high levels of regio- and stereoselectivity. Importantly, reversal of the *anti* diastereoselectivity occurs in the reactions of silyl-substituted crotyl halides at the 2-position, which clearly contrasts with simple crotylchromium reagents (Scheme 2, eqn. (2)).

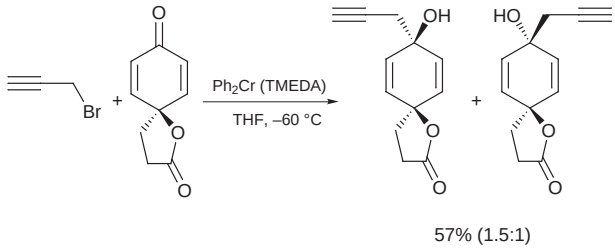
The coupling of aldehydes with $(Me_3Si)_2CBr_2$ in the presence of $CrCl_2$ in DMF at room temperature gives rise to 1,1-bis(trimethylsilyl) alkenes.[11] Likewise, the synthetically useful vinylstannanes can be readily prepared by a direct synthesis involving the coupling of aldehydes with the alkylchromium reagent derived from $Me_3SnCHBr_2$. Again, it is necessary to use LiI as an additive.[12]

An important improvement of the Nozaki–Hiyama reaction of allyl and propynyl halides has been the development of a low-temperature version.[13] The protocol is based on the fact that the redox potential of Cr(II) can be altered by the presence of electron-rich ligands. Consequently, a Ph_2Cr–tetramethylethylenediamine complex mediates addition reactions of either allyl iodides or bromides to aldehydes, ketones and enones at a



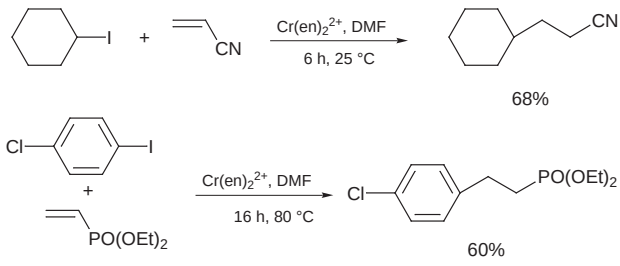
Scheme 2

temperature as low as −60 °C. The reagent is readily prepared by addition of PhMgBr to $CrCl_2$ in THF in the presence of TMEDA. The use of such a complex leads to a considerable rate enhancement (reactions are usually complete within 30 min *versus* several hours following the standard protocol) and a wide tolerance of sensitive substrates. Scheme 3 illustrates the selective 1,2-addition to a spirodienone, which would otherwise be cleaved under regular Nozaki–Hiyama reaction conditions.



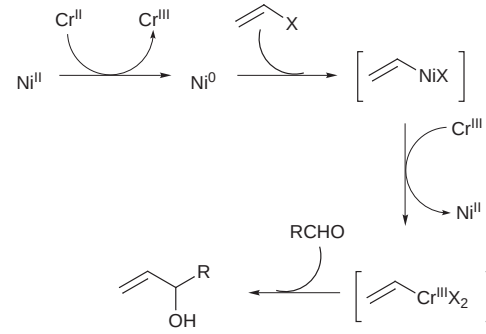
Scheme 3

In previous studies it has been demonstrated that free radicals generated from organic halides and (ethylenediamine)-chromium(II) complexes can be trapped by electron-withdrawing alkenes to afford the corresponding coupling products in moderate to good yields.[14,15] The coupling reactions work well in DMF, a solvent in which Cr(II) is a stronger reducing agent, either with alkyl or aryl halides, although the trapping of benzyl radicals by alkyl-substituted alkenes (*e.g.* cyclohexene) was unsuccessful leading almost exclusively to bibenzyl formation. Likewise, 1-iodo-4-nitrobenzene failed to react with methyl methacrylate and neither coupling nor reduction products were obtained. Alkyl halides react faster than aryl derivatives and sometimes the reactions proceed slowly at room temperature, especially with bromides, but can be accelerated by heating the reaction mixture. Acrylates as well as vinyl sulfones and phosphonates can be equally utilized as deficient alkenes (Scheme 4).



Scheme 4

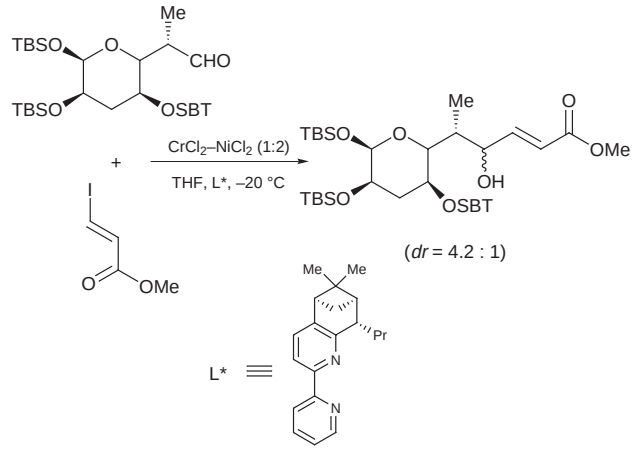
The positive effects of complexation with nitrogenated ligands were also investigated by Kishi and his associates during their synthetic studies, in which the key bond-forming step involves an intermolecular Cr(II)–Ni(II)-mediated coupling and only a catalytic amount of Ni(II) is needed. The most plausible mechanism accounting for the catalytic role of nickel(II) is shown in Scheme 5. The process may be initiated by



Scheme 5

reduction of $NiCl_2$ to nickel(0) by two equivalents of $CrCl_2$ followed by oxidative addition of the unsaturated halide (or a related substrate) to afford an organonickel(II) reagent. This species may then undergo transmetallation with Cr(III) to give the corresponding organochromium(III) reagent, which then reacts with the carbonyl compound. The nickel(II) generated in the oxidative addition step reenters the catalytic cycle.[3,4,6]

In view of the intermediacy of coordinating transition metal species, Kishi *et al*. suggested that a chiral ligand could enhance the rate of coupling and induce a higher level of stereoselection.[16] However, a suitable ligand for this purpose must form labile complexes with Ni(II), but sufficiently strong with Cr(II). After a preliminary screening, dipyridyls with a substituent at the 6-position were found to be the ligands of choice. In the presence of $NiCl_2$ as catalyst the coupling proceeded rapidly even at −20 °C and the unwanted homocoupling reaction was completely suppressed (Scheme 6). Even ketones react with



Scheme 6

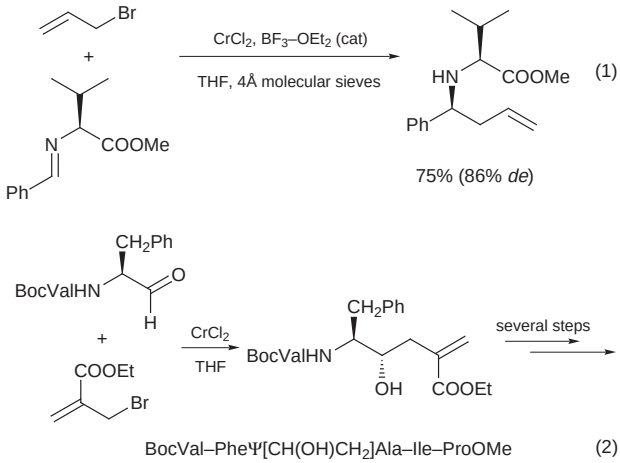
iodoolefins at an appreciable rate. It should be noted that the coupling took place in the presence of pyridine, but not with 2,2'-dipyridyl, 1,10-phenanthroline or CHIRAPHOS (bis(diphenylphospino)butane). Chiral pyridines were also tested but these ligands gave poor diastereomeric ratios. Furthermore, the authors anticipate that the results may suggest that the stability and/or reactivity of the Cr- *versus* Ni-complexes correlates to the ability of the ligands to adopt a nonplanar conformation. This surmise was reinforced by the observation that coupling was effective in the presence of (*S*)-BINAPH, but did not progress with CHIRAPHOS.

It is also evident that Scheme 6 shows an example of double stereodifferentiation: the starting aldehyde itself is chiral. The

coupling in the presence of the enantiomeric ligand gave an approximate diastereomeric ratio of 1 : 1.9 at room temperature, so that the chiral centre(s) present in the sugar has an effect on the stereoselection.

In a further study it has been shown that 4-*tert*-butylpyridine is a beneficial additive in the Nozaki–Hiyama–Kishi coupling reaction.[17] The use of this substance allows for homogeneous reactions, improves reproducibility, and avoids homocoupling side reactions. Thus, solutions of $CrCl_2$(98–67%)–$NiCl_2$(2–33%) in THF–4-*tert*-butylpyridine (4 : 1) or in DMF–4-*tert*-butylpyridine (3 : 1) can be prepared by stirring the mixture at room temperature for 5–15 min, though in both solvent systems a suspension of $NiCl_2$ is observed. It is unclear what is the role of this additive, but the authors suggest that it facilitates the selective solubilization of Cr(II) over Ni(II) because 4-*tert*-butylpyridine alone does not provide a homogeneous solution of $CrCl_2$. Likewise, an improved workup using chromium ion chelators, such as ethylenediamine or sodium or potassium serinate, produces a better yield.

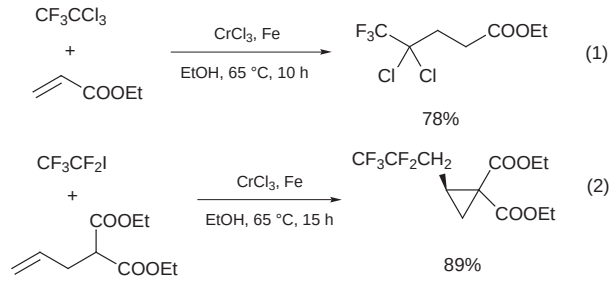
Italian authors have reported the coupling of allylchromium reagents with alkyl and aryl imines in the presence of a Lewis acid catalyst. The diastereoselectivity is in general poor, but better results were obtained in the reaction of allylchromium and the imine derived from benzaldehyde and (*S*)-valine (Scheme 7, eqn. 1).[18] In a related work, the Cr(II)-mediated allylation of *N*-protected α-amino aldehydes led to a versatile synthon, which could further be converted into a polypeptide containing a hydroxyethylene isostere, which allows a variation of the amino acid sequence found in naturally-occurring peptides (Scheme 7, eqn. 2).[19] Although this Cr(II)-promoted



Scheme 7

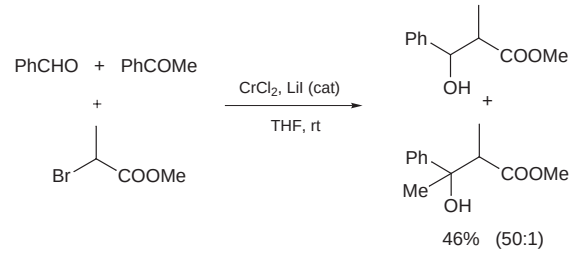
allylation of oligopeptide aldehydes proceeds with moderate stereoselectivity, the use of other allylating reagents such as allylsilanes, allylstannanes or allylcuprates gave poor yields along with a complex reaction mixture. In contrast, allylzincs gave comparable yields and also a comparable stereoselectivity to that of chromium reagents.

In an interesting work, Chinese researchers have reported the chromium-mediated activation of polyfluorohaloethanes, which add to electron-deficient alkenes to give the corresponding coupling products in good yields.[20] It should be pointed out that reactions can be conducted in hot ethanol and low-valent chromium was generated from anhydrous $CrCl_3$ and the inexpensive iron (Scheme 8, eqn. (1)). The latter metal has found so far limited applications in organic synthesis since activated iron should be an acid-washed, finely divided material that oxidizes rapidly in air.[21] This methodology has also been applied to the preparation of polyhaloalkylmethyl-substituted electrophilic cyclopropanes (Scheme 8, eqn. (2)).[22] The reaction with this Cr–Fe redox system proceeds apparently by two steps combining radical addition and cyclopropanation.



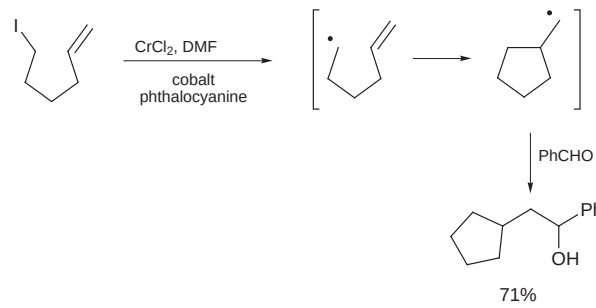
Scheme 8

A recent contribution highlights the use of $CrCl_2$ in Reformatsky reactions,[23] old processes that enjoy a new renaissance in synthetic organic chemistry. Reactions are run in THF at room temperature in the presence of LiI, and can be applied to aldehydes and ketones. Aldehydes exhibit excellent selectivities (≥ 50 : 1) *versus* methyl ketones and larger ketones (≥ 200 : 1). Methyl ketones also react preferentially in the presence of higher ketones (Scheme 9).



Scheme 9

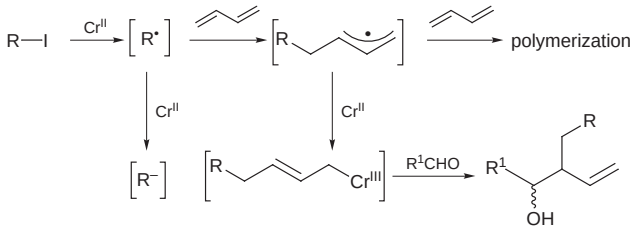
The reactivity of alkylchromium reagents, generated from halides and tosylates, towards aldehydes has been largely studied by Takai and coworkers.[3,4,7] Reactions can be conducted in DMF under mild conditions in the presence of cobalt catalysts, such as vitamin B_{12} or cobalt phthalocyanine. These species are thought to form an organocobalt intermediate which cleaves to an alkyl radical that further adds to Cr(II) to give the alkylchromium reagent. Curran and his associates utilized this hypothesis to develop a tandem carbon–carbon bond-forming reaction involving a sequence of 5-*exo*-trigonal cyclization, transmetallation to organochromium species and coupling to an aldehyde (Scheme 10).[24]



Scheme 10

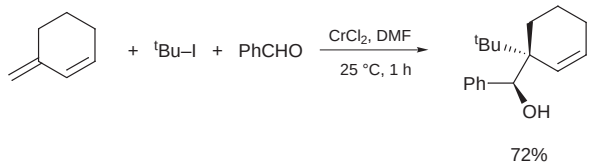
The sequential generation of radical and anionic species can be harnessed to devise a three-component coupling of alkyl iodides, 1,3-dienes, and carbonyl compounds.[25] The use of $CrCl_2$ as a mild reductant constitutes the driving force and controls the selectivity as illustrated in Scheme 11.

Reactions are performed in an aprotic solvent such as DMF in which the reduction of alkyl halides by $CrCl_2$ proceeds more easily. Even under such conditions, however, primary alkyl iodides are converted preferentially into alkyl chlorides because the rate of substitution by the chloride ion is faster than that of



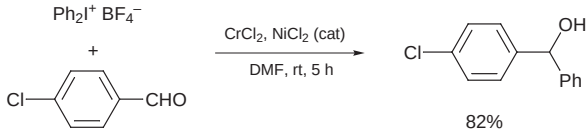
Scheme 11

one-electron reduction with Cr(II). Only secondary and tertiary alkyl radicals will survive for a sufficient lifetime to undergo intermolecular addition to a 1,3-diene to form radical or anionic species. The competitive radical polymerization does not occur because the one-electron reduction of the allyl radicals is fast affording the reactive allylchromium reagents. The overall process is highly selective: two regioisomeric homoallylic alcohols are obtained, both of them as a mixture of two stereoisomers. The major regioisomer contains essentially one stereoisomer which displays an *anti* geometry. Nevertheless, coupling with cyclic systems, having a fixed double bond, proceeds stereospecifically affording only one stereoisomer (Scheme 12).



Scheme 12

Another interesting result from Takai and his group describes for the first time the umpolung reactivity of diaryliodonium salts.[26] These substances are precursors of aryl cation equivalents and because of their electron-deficient character, they undergo arylation with numerous nucleophiles. However, in the presence of $CrCl_2$ plus a catalytic amount of $NiCl_2$, the iodonium reagents are converted into arylchromium(III) species, thereby behaving as aryl anion equivalents, that can react with aldehydes. Benzyl alcohols are obtained in good yields in DMF solution, and the reaction works well either with aromatic or aliphatic aldehydes (Scheme 13). In some cases, by-products



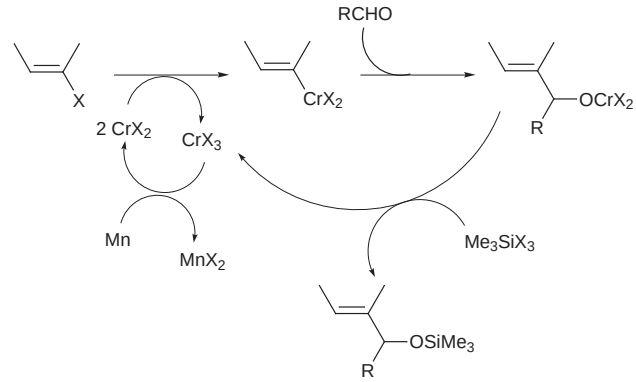
Scheme 13

such as iodoarenes and arenes resulting from reductive dehalogenation are also obtained. Steric effects are quite important and pivalaldehyde does not react under these conditions.

3 Catalytic reactions

It is fair to say that the most important goal in modern organometallic chemistry is the introduction of multicomponent catalysis for reductive bond formations,[27] since this strategy enables the assembly of various structural frameworks avoiding the use of an excess of toxic and expensive reagents.

Although chromium is an *essential element* in trace amounts, chromium anions are described as *toxic* and, from a physiological viewpoint, this is probably due to generating Cr(III) bound in a special site from which it will not exchange. In fact the effects of chromium and other transition metals on the immune system have been reported.[28] Consequently, the development of equally efficient alternate methods that diminish the need for stoichiometric chromium halides has obvious significance. Recently, Fürstner and Shi have been able to accomplish this objective with the use of the triplet $CrCl_3$–trimethylchlorosilane–Mn which renders Nozaki–Hiyama-type reactions catalytic in chromium.[29] The nucleophilic addition of an aldehyde to the intermediate organochromium reagent forms the corresponding chromium alkoxide. The latter impedes a catalytic cycle because of the inherent oxophilicity of Cr(III). However, these authors reasoned that σ-bond metathesis with a more oxophilic element, such as silicon, would permit ligand exchange, thereby liberating Cr(III). Finally, Cr(III) could be reduced by a massive metal having the appropriate redox potential. In principle, Zn, an inexpensive and rather nontoxic element, could satisfy this requirement; however, this metal may also insert into reactive halides and, more importantly, zinc halides generated during the course of the reaction have a sufficient Lewis acidity to react with enolizable aldehydes. Manganese was chosen as the best substitute for zinc in view of the low acidity of manganese salts and the fact that insertion reactions will only occur with highly activated manganese (Scheme 14).[21]

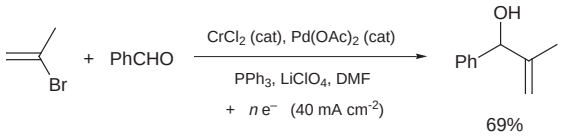


Scheme 14

It should also be noted that the catalytic cycle depicted in Scheme 14 will proceed regardless of whether it starts with Cr(II) or Cr(III). Accordingly, catalytic reactions were also highly effective using chromium metallocenes such as Cp_2Cr or $CpCrCl_2$, and with the latter reagents carbon–carbon bond formation took place with less than 1 mol% of chromium.[29]

A highly stereoselective synthesis of *anti* diols involves the chromium(II)-catalyzed reaction of acrolein acetals with aldehydes.[30] Anew, the catalytic system consists of a mixture of $CrCl_2$, Mn powder and TMSI, which is generated by use of TMSCl and NaI. Diols were obtained in good yields with excellent diastereomeric ratios (*anti* : *syn* > 10 : 1). However, diminished yields and diastereoselectivities were observed for α,β-unsaturated aldehydes, mainly due to pinacol coupling. Likewise, modest facial selectivity was obtained in the case of chiral aldehydes bearing an α heteroatom, a fact attributable to the absence of coordination with the chromium reagent.

An electrochemically-driven catalytic coupling has also been devised by Grigg and his associates.[31] Reactions of both aryl and vinyl halides with aromatic aldehydes were conducted in a thermostatted electrochemical cell in DMF, and in the presence of a catalytic combination of Cr(II) and Pd(0). The supporting electrolyte, $LiClO_4$, also serves as the oxophilic mediator capable of cleaving the O–Cr(III) bond, thereby liberating Cr(III) that is further reduced to Cr(II) on the electrode surface (Scheme 15). As in the case of other cocatalysts, the Pd(0) first undergoes oxidative addition to the substrate and the resulting organopalladium(II) species likely undergoes a subsequent transmetallation with Cr(II). The current density is a critical

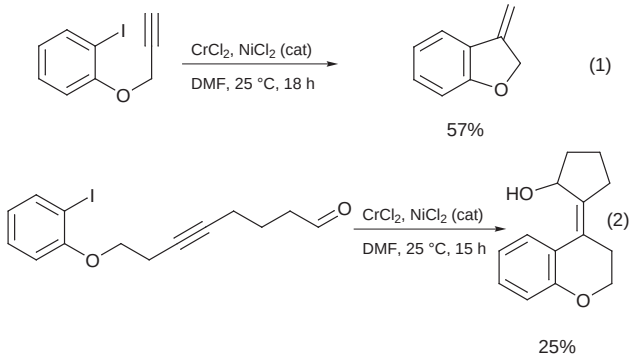


Scheme 15

parameter that must be carefully controlled to avoid side reactions such as biaryl formation. Anyway, the importance of this contribution lies in the fact that electrons (or electrochemically-generated solvated electrons) might be utilized as the ultimate reducing agents.

4 Cyclizations and construction of natural fragments

Employing Kishi's conditions, namely the Cr(II)-mediated–Ni(II)-catalytic coupling, Hodgson and Wells described an interesting cyclization of both iodoaryl-substituted alkynes and alkynals to afford five- and six-membered rings under mild conditions (Scheme 16).[32] It is interesting to note that only the

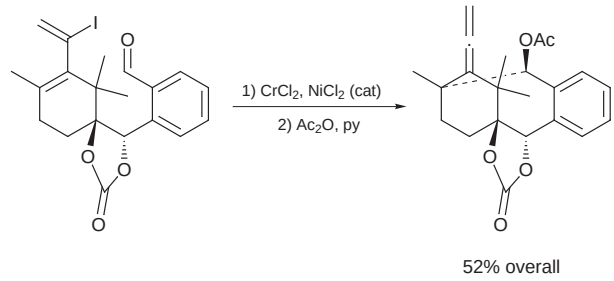


Scheme 16

products resulting from *syn*-vicinal difunctionalization of the triple bond were detected as evidenced by NOE studies. The mechanism of this carbometallation, involving an alkyne rather than aldehyde addition, occurs anew by oxidative addition of low-valent nickel followed by intramolecular *syn*-arylnickelation of the triple bond prior to transmetallation to Cr(III) with retention of geometry, and further nucleophilic attack on the aldehyde moiety, if present.

As mentioned above the intramolecular coupling of carbonyls with organic halides represents a convenient methodology for the stereocontrolled preparation of cyclic fragments present in numerous natural products and their analogs.[3–5,33] Perhaps one of the most striking applications of this methodology and the paradigm of Cr(II)–Ni(II)-mediated reactions was the total synthesis of palytoxin[33] involving several chromium-induced steps. The recent literature is full of elegant examples including synthetic approaches to enediyne antibiotics,[33] taxane and taxamycin precursors,[17,33] a total synthesis of brevetoxin B,[33] or a one-pot access to two different aldol fragments of the cytotoxic epothilones,[34] a remarkable new class of antitumor agents.

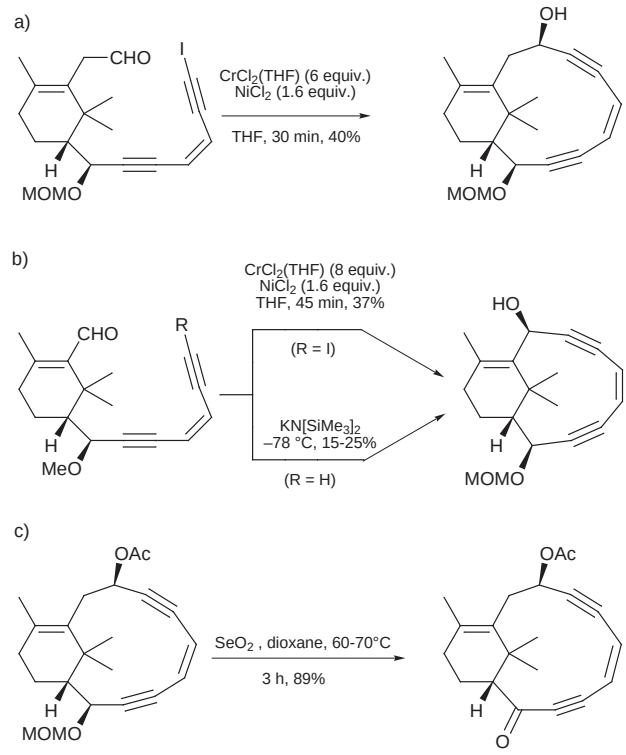
Scheme 17 shows an unprecedented S_N2' intramolecular coupling leading to a C9–C12 eight-membered ring closure of a *seco*-taxoid precursor.[35] It is noteworthy that the stereochemistry of the starting material is a crucial factor and determines the steric course. When the precursor having *cis* stereochemistry (referred to the protected 1,2-diol function) was subjected to the Cr(II)–Ni(II)-mediated coupling in DMSO at 20 °C for 4 days, no cyclization product was observed but a diene, resulting from iodine–hydrogen exchange, could be isolated in 65% yield. This result means that iodine–metal exchange took place



Scheme 17

but the subsequent attack on the aldehyde group did not occur. However, the above-mentioned conditions applied to the *trans* iodovinyl aldehyde gave, after further acylation, the allenic derivative depicted in Scheme 17, whose structure was unequivocally established by X-ray crystallography. The authors reasoned that an oxygen–metal complexation should favor a chair-like six-membered transition state, proposed for the sterochemical outcome of Nozaki–Hiyama reactions,[3,4] a condition that can be reached in the *trans* isomer, but not in the case of its *cis* counterpart owing to angular distortions and nonbonding repulsive interactions between the *gem*-dimethyl group and the eclipsed aromatic moiety.

The preparation of taxamycins, an enediyne family of anticancer antibiotics, entails an intramolecular Nozaki–Kishi ring closure of iodoaldehydes.[36] Scheme 18 shows the synthesis

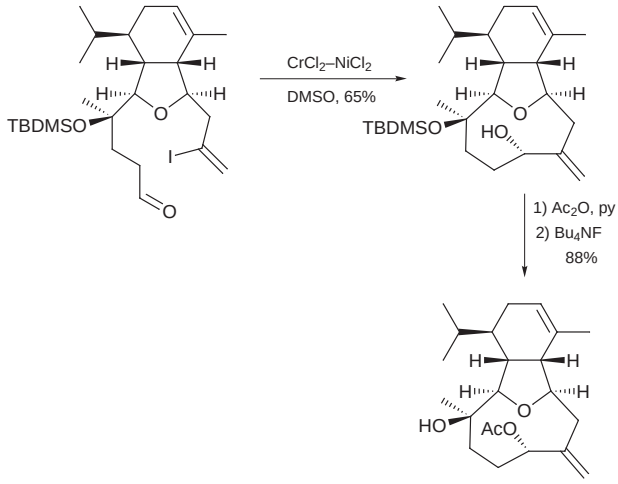


Scheme 18

of (a) taxamycin-12 and (b) taxamycin-11. Reactions were run in THF using the $CrCl_2$(THF) complex which gave the best results. Attempts to generate Cr(II) species *in situ* by reduction of $CrCl_3$ with $LiAlH_4$, plus a catalytic amount of $NiCl_2$ afforded low yields of taxamycins. The coupling in the presence of SmI_2, an excellent one-electron transfer donor, was unsuccessful.

It is worthy of mention that taxamycin-11 could also be obtained by base-induced cyclization of the acetylene precursor with 2 equiv. of potassium hexamethyldisilazide at −78 °C. The latter protocol, however, gave lower yields of cyclized material. Finally, allylic oxidation with SeO_2 in dioxane gave the desired ketone, characteristic of taxoid systems (Scheme 18c).

Macrocyclization induced by a Cr(II)–Ni(II) system has been utilized in an enantioselective total synthesis of an eunicellin diterpene, a family of marine metabolites.[37] The construction of the oxonane ring was accomplished by treating the iodoaldehyde precursor with $CrCl_2$–$NiCl_2$ in DMSO (Scheme 19). The resulting tricyclic ether was obtained in 65% yield with an excellent stereoselectivity (> 20 : 1). Further acetylation followed by cleavage of the silyl ether gave the desired diterpene in 88% yield.



Scheme 19

In a total synthesis of pinnatoxin A,[38] a toxic substance with a pronounced biological activity as a Ca^{2+}-channel activator, the key step was a Cr(II)–Ni(II)-mediated coupling again. The synthetic strategy, depicted in Scheme 20, involves the intermolecular reaction of an aldehyde with a vinyl iodide, which afforded a mixture of diastereomeric allylic alcohols. Removal of the primary TBS group and further oxidation furnished a single diketo-aldehyde. A second Cr(II)–Ni(II)-mediated coupling was also conducted in the presence of a bispyridinyl ligand. It should be pointed out that the vinylchromium species adds selectively to the aldehyde moiety even in the presence of sensitive groups such as a carbamate carbonyl, and enone, and a ketone.

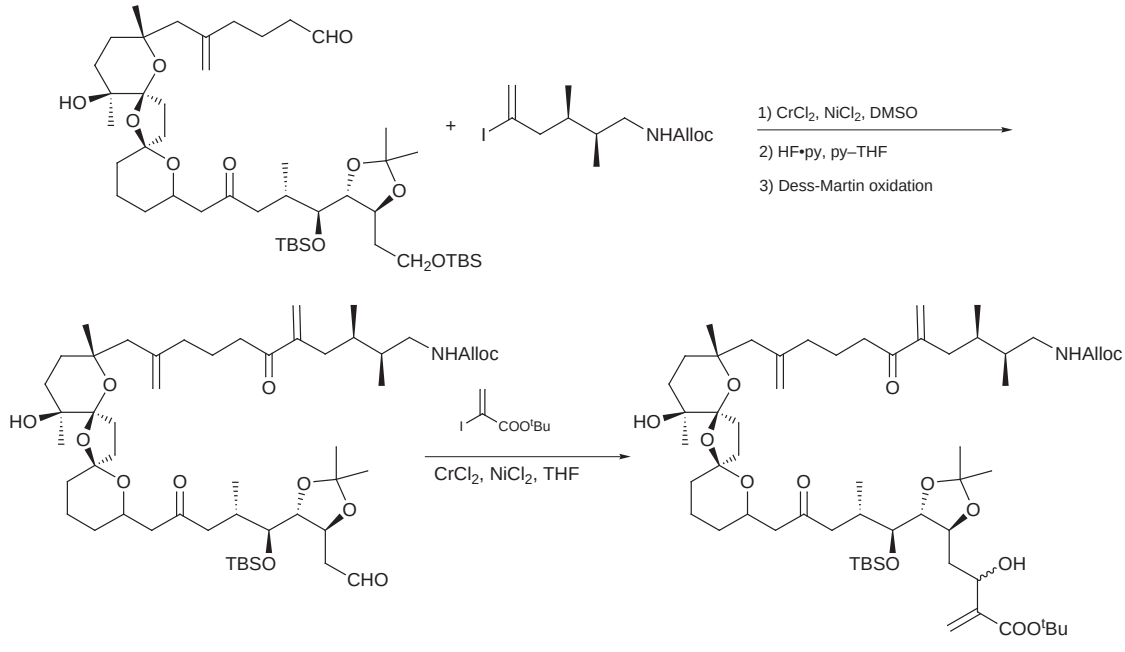
A previous paper by Kishi and his associates described the total syntheses of halichondrin B and norhalichondrin B,[39] a family of complex polyether macrolides with pronounced *in vitro* and *in vivo* antitumor activity. Remarkably, the synthetic strategy contains more than one Cr(II)-mediated coupling. During the synthesis of the right half of the halichondrin B, the coupling of two segments was accomplished by an intermolecular Nozaki–Kishi reaction to yield a ~6 : 1 mixture of the two possible allylic alcohols, which were then subjected to base-induced cyclization to produce the tetrahydropyran system in 50–60% overall yield. It should be pointed out that the starting mesylate was found to be quite labile, but survived under the mild conditions of the Cr(II)–Ni(II) coupling. The tetrahydropyran was deprotected, the alcohol functionality was oxidized (Dess–Martin), and the resulting aldehyde was subjected to a further Cr(II)–Ni(II)-mediated coupling with a vinyl iodide, followed by Dess–Martin oxidation, removal of the MPM group, and lactonization (Scheme 21).

Remarkably, coupling of the right half moiety of halichondrin B with the left half (in the form of an iodo derivative) was also successfully effected by a Cr(II)–Ni(II) reagent. The synthesis of norhalichondrin B was performed in the same way and gave a yield comparable with that of halichondrin B.

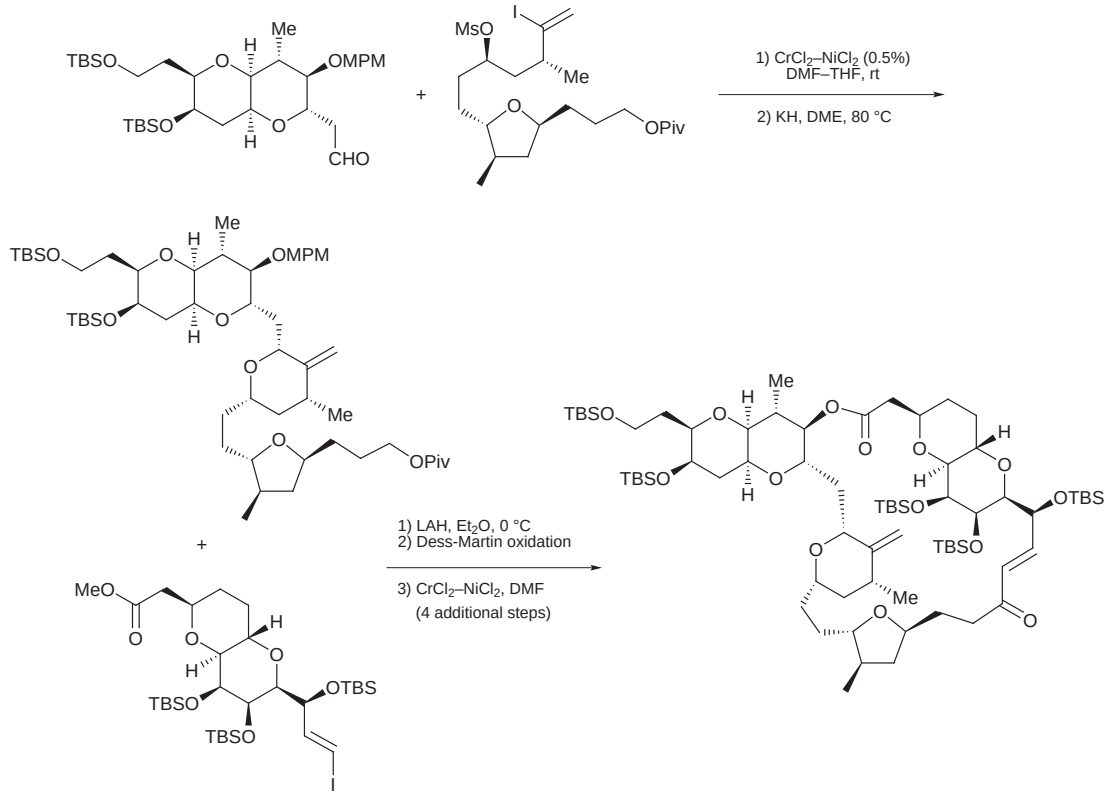
An additional example from carbohydrate chemistry also illustrates the enormous versatility of this low-valent chromium-based methodology for the construction of carbon–carbon bonds. Unsaturated keto carbocycles (pseudosugars) can be obtained by means of an intramolecular Nozaki–Kishi reaction of ω-haloaldehydes (Scheme 22).[40] Preliminary attempts to cyclize the unsaturated aldehyde under Barbier-type conditions, either with magnesium or lithium, were unsuccessful and no reaction was detected at room temperature, while at 40 °C, β-elimination took place. However, the Cr(II)–Ni(II) system promoted the cyclization and gave a mixture of anomeric alcohols in 61% yield. Further oxidation of these allylic alcohols furnished the desired enone which was also debenzylated to give gabosine I in 74% yield.

5 Conclusions

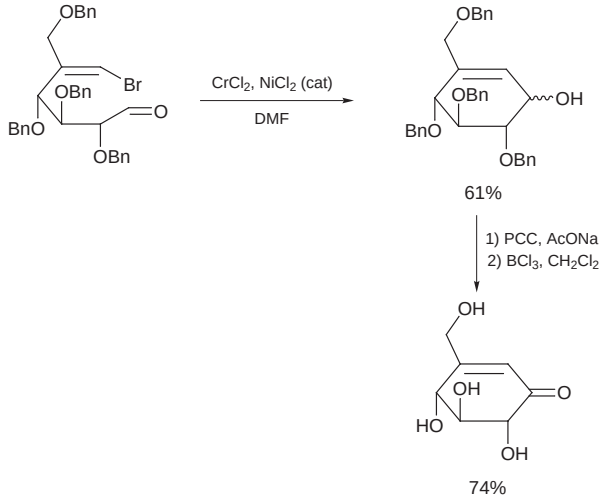
The selected examples described through this article illustrate the continuing interest and potential of Cr(II)-based couplings, often in the presence of other metal catalysts. It is noteworthy the recent introduction of elegant and versatile catalytic methods that require a few mol% of chromium, and have therefore an important environmental significance. Complexa-



Scheme 20



Scheme 21



Scheme 22

tion with nitrogen ligands does enhance the redox potential of Cr(II), a fact that can be harnessed to evaluate the effect of a chiral ligand in asymmetric versions. The wide functional group compatibility and mildness of this methodology make it an ideal process to be utilized for the construction and carbon homologation of complex skeleta through inter- and intramolecular pathways.

6 Acknowledgements

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