

Chromium(II) chloride: A Reagent for Chemo-, Regio- and Diastereoselective C–C-Bond Formation

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Chromium(II) reagents are powerful one-electron reducing agents ($\text{Cr}^{3+}/\text{Cr}^{2+}$, $E^\circ = 0.41\text{V}$). The application of these compounds in organic synthesis has never been as popular as the oxidations with chromium(VI) reagents, which basically every chemist has already carried out himself. During the last years, however, chromium(II) chloride (CrCl_2) has increasingly been used in the later stages of total synthesis projects, where mild conditions and a highly chemo-, regio- and diastereoselective reaction was needed. Nowadays CrCl_2 is commercially available from several suppliers. Sometimes better results are obtained when a reagent, which behaves analogously to CrCl_2 , is freshly prepared from anhydrous chromium(III) chloride and lithium aluminium hydride in tetrahydrofuran (THF) [1, 2]. This way a dark brown suspension is obtained, which can be stored in the refrigerator for weeks without loss of activity. Since chromium(II) salts have a high affinity to oxygen, they must be handled under protecting gas. Normally an excess of CrCl_2 is necessary for good conversions.

Pure CrCl_2 is a colourless, hygroscopic solid with a melting point of 824°C (the commercially available material is a grey powder). In aqueous solution it forms octahedral complexes of blue colour (d^4 with Jahn-Teller distortion; the name of the element chromium is based on the high tendency to form coloured compounds).

The following sections will give examples of different chemical transformations that can be achieved with CrCl_2 [2, 3].

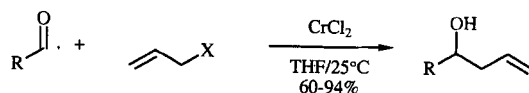
1 The Beginning

The first applications of CrCl_2 in organic chemistry were simple reductions in aqueous solution, C–C-bond formation was involved in exceptional cases only [3a, 3b]: In 1916 Traube and Passarge reported the conversion of maleic or fumaric acid to succinic acid [4a]. Beside such reductions of electron-deficient olefins [4], later studies covered the dehalogenation of α -halocarbonyls to carbonyls [5], vicinal dihalides to olefins [6], dibromo-*o*-xylenes to *o*-quinodimethides [7], the reduction of benzoquinones to hydroquinones [8] and the generation of allenes [1b, 9] from geminal dibromo- cyclopropanes in a Doering–Moore–Skatebøl-like reaction.

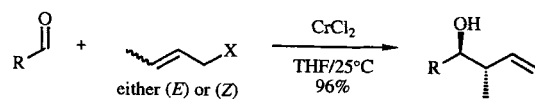
Other sources for chromium(II), like chromium(II) sulfate, chromium(II) acetate, chromium(II) perchlorate and chromium(II) amine complexes, were used in singular cases only [3a, 3b, 10].

2 Synthesis of Homoallylic Alcohols

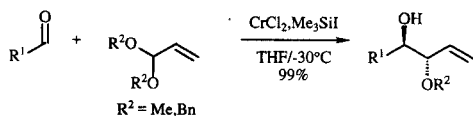
A milestone in the application of CrCl_2 was the usage of aprotic solvents that made possible effective C–C-coupling with activated halides. First it was discovered, that benzylic [1b, 11] (and allylic [9, 12]) halides can be dimerized under these conditions. In 1977 Hiyama succeeded in coupling allylic halides with aldehydes and ketones in a Barbier-type reaction [1a]. Nowadays this formation of homoallylic alcohols is referred to as the *Hiyama* reaction.



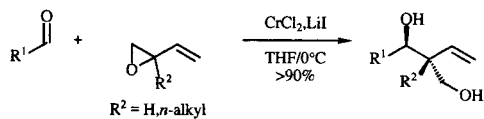
In this context it is worth mentioning that in the absence of allylic halides only aromatic aldehydes in protic solvents showed pinacolic coupling with CrCl_2 [13]. Other carbonyl compounds are completely inert towards CrCl_2 . With α,β -unsaturated aldehydes in the *Hiyama* reaction exclusively 1,2-addition was observed. Ketones were much less reactive, but provided product. Nitriles, esters, epoxides [14], sulfones [15], vinylhalides [1b, 16a] and special, hindered allylic halides [16] were not affected. The higher substituted γ -carbon of the allyl group was attached to the carbonyl carbon. With crotyl substrates simple diastereoselection was observed. From either *cis*- or *trans*-1-bromo-2-butene only one diastereomer was formed [1a] (different from allylboranes and allylsilanes!). Heathcock was later able to assign the product to the *anti*-isomer [17]. A mechanistic proposal for these reactions was provided by Mulzer [2, 18].



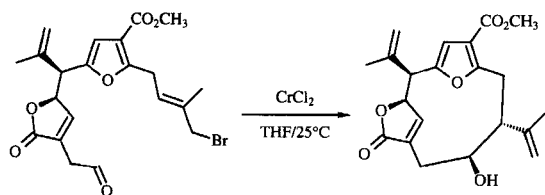
Only in the case of bulky aldehydes like pivalylaldehyde the *syn*-product dominated. Apart from halogens also geminal dichlorides [16], tosylates [1a], phosphates [19], acrolein dimethyl- or dibenzylacetals [20] reacted, the latter formed monoprotected *anti*-1,2-diols (*Umpolung* of acrolein).



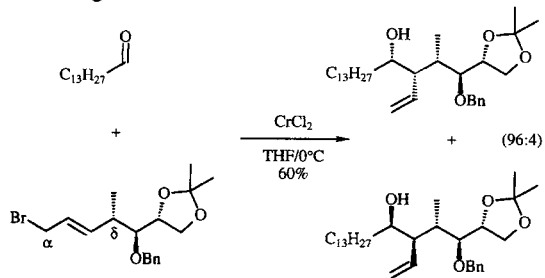
1,3-Diols were generated from vinylic epoxides [21].



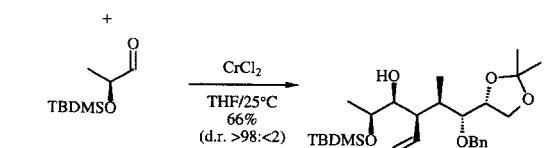
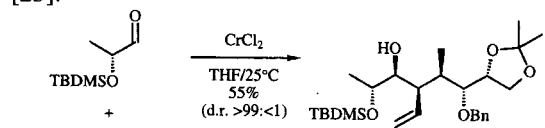
The interesting case of substrate controlled diastereoselectivity directed by remote stereocenters was reported by Paquette in his synthesis of furanocembranolides [22].



Reagent-induced and double stereodifferentiation was investigated by Mulzer [23]. In the allylic bromides the stereogenic center in the δ -position turned out to be the directing element.



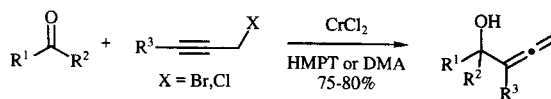
When both compounds were chiral, the stereodirecting influence of the chromium reagent usually dominated. These principles were applied in total synthesis by Mulzer and others [23].



3 Synthesis of α -Allenic Alcohols

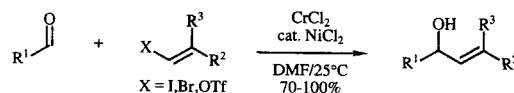
The reaction described in section 2 could be extended to propargylic bromides and chlorides. Goré and coworkers found that in contrast to analogous organomagnesium and zinc

compounds, α -allenic alcohols were formed preferentially [24]. Hexamethylphosphorous triamide (HMPT) was the solvent of choice to suppress the formation of the homo-propargylic alcohols as side products. Later Knochel performed such reactions with polyfunctional compounds (esters, nitriles, alkyl chlorides) in *N,N*-dimethylacetamide (DMA) where he observed excellent chemo- and regioselectivity [25].

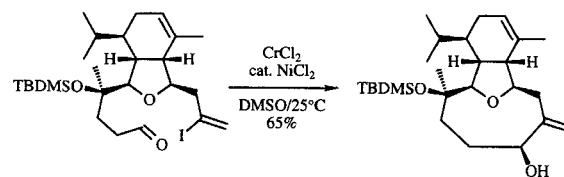


4 Synthesis of Allylic Alcohols

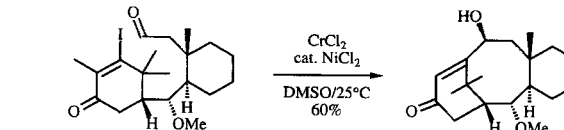
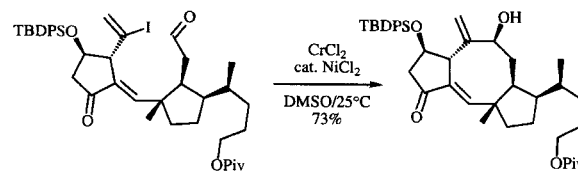
In 1977 it was stated, that aryl and vinyl halides do not react under the conditions of the *Hiyama* reaction [1a, 16a]. In 1983 the CrCl_2 -mediated additions of vinyl iodides to aldehydes were first described by Takai [26a]. But the success of the reaction heavily depended on the source of the CrCl_2 . 1986 Kishi [27] and Takai [26b] independently reported that nickel dichloride (NiCl_2) was a crucial cocatalyst for this reaction – traces of nickel in the CrCl_2 were responsible for a successful reaction (oxidative addition of the non-activated sp^2 -halide to nickel(0) and subsequent transmetalation to chromium). Now vinyl bromides and vinyl triflates could be used in the *Takai-Kishi* reaction, too. The configuration of double bonds remained unchanged during these reactions [27a].



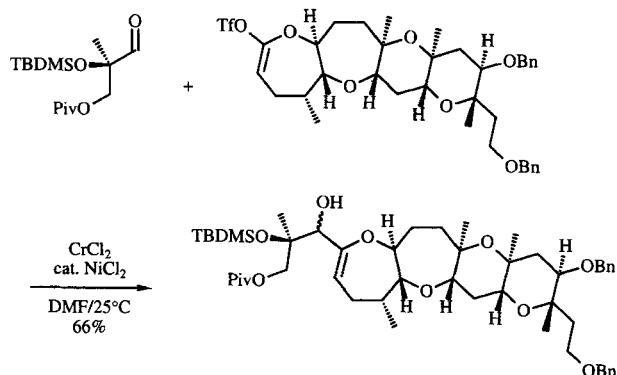
There are numerous synthetic applications, for example the formation of a nine-membered ring in Overman's synthesis of a eunicellin diterpene [28g]. In the *Takai-Kishi* reactions often *N,N*-dimethylformamide (DMF) or dimethylsulphoxide (DMSO) were used as solvents.



The synthesis of eight-membered rings was investigated by Kishi in the total synthesis of (+)-opiobolin C [29] and in the synthesis of the taxane skeleton [30].

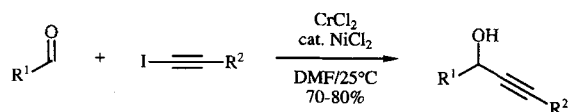


Another application is found in Nicolaou's synthesis of brevetoxin B, where an enol triflate derived from a lactone was coupled [31].

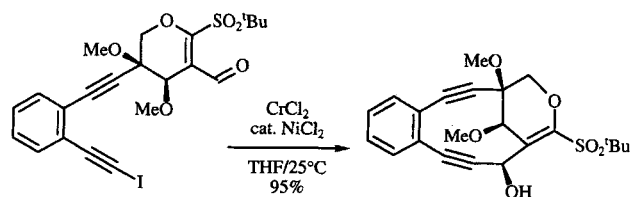


5 Synthesis of Propargylic Alcohols

Starting from alkynyl iodides with CrCl_2 alkynylchromium(III) compounds are formed in situ – they undergo chemoselective 1,2-addition to aldehydes [32]. The nickel-effect described in section 4, was also observed [27b, 33]. Unlike with lithium or magnesium alkynides, aldehydes were clearly preferred over ketones in the addition reaction.

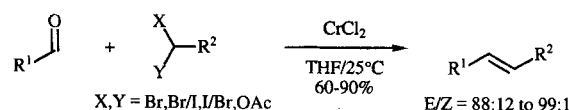


Most applications are found on the field of endiynes [33]. One recent example was provided by Beau [33h].

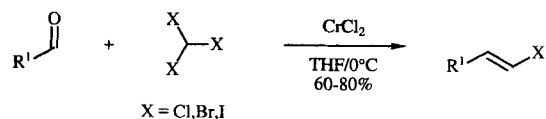
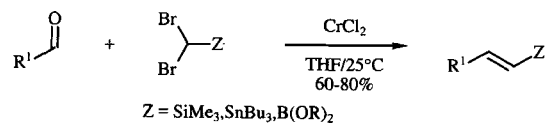


6 Olefination Reactions

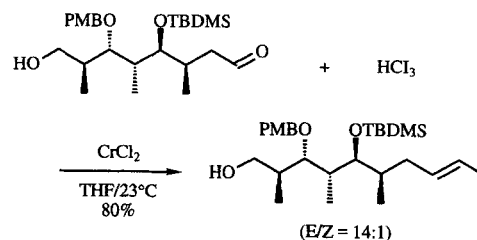
1,1-Dihaloalkanes and CrCl_2 form an 1,1-dichromium reagent that reacts with aldehydes to furnish olefins with good (*E*)-selectivity and in good yields [34a]. The reaction could be extended to the more readily available α -acetoxy bromides [34b].



An extension of this methodology provided versatile functionalized olefins like vinylsilanes [35], vinylstannanes [36], vinylboronic esters [37] and vinyl halides [38].



The formation of vinyl iodides in the presence of a free hydroxyl group in Evans' synthesis of rutamycin B [39a] is just one example [39b, 28f].

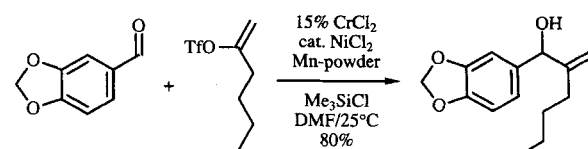


7 Miscellaneous

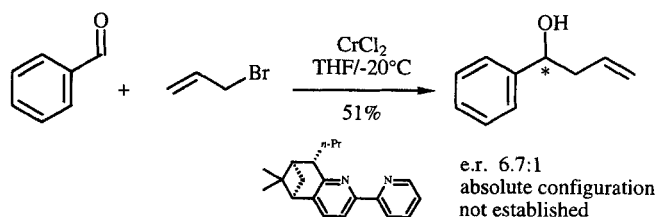
A nickel-chromium catalyst was used by Trost for the cycloisomerization of 1,6-enynes, 1,7-enynes [40a] and 1,6-enallenes [40b]. Intramolecular carbometallations of alkynes applying nickel cocatalysts were described by Hodgson [41]. With unactivated alkyl halogenides (i.e. not allylic-, benzylic- or propargylic halogenides) *Hiyama* reactions proceeded well in the presence of cobalt catalysts [41], an effective intramolecular carbometallation was also possible.

8 Future Prospects

One major drawback of the *Hiyama* and *Takai-Kishi* type reactions is the fact, that in practice instead of two equivalents per halogen a huge excess of CrCl_2 is required. Due to the toxicity of the chromium and nickel salts this reaction can neither be applied to large-scale synthesis nor to pharmaceutical chemistry. Fürstner attended this problem and developed a reaction catalytic in chromium, using manganese as nontoxic reducing agent and trimethylsilyl chloride to release the chromium(III) from the intermediate [43]. Here iodides, bromides and triflates reacted, the manganese also tolerated functional groups like esters, ethers and acetals.



The second problem not mastered so far are asymmetric *Hiyama* or *Takai-Kishi* reactions. Recently Kishi investigated several chiral ligands [44].



Since the research on this sector was just initiated, we can look forward to the further development in this field. Maybe we will be able to include catalytic and asymmetric *Hiyama* or *Takai-Kishi* reactions in our synthetic planning in the close future.

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In der Rubrik „Das Reagenz“ erscheinen demnächst:

- Ruppert's Reagent Trifluormethyltrimethylsilane (C. Lamberth, Basel, Sandoz Agro AG)
- Dess-Martin-Periodinan (DMP) (A. Speicher, V. Bomm, T. Eicher, Saarbrücken)
- Betmip (1-Triphenylphosphorylideneaminomethyl)benzotriazole, a Unique $\text{CH}_2=\text{N}-\text{PPh}_3^+\text{X}^-$ -Equivalent for Organic Synthesis (A. R. Katritzky, J. Jiang, Gainesville/Florida)
- Acylated Cyanatoarenes – Reagents for Convenient Cyanations (K. Buttke, H.-J. Niclas, Berlin-Adlershof)