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Coordination Chemistry Reviews 250 (2006) 1023–1031

COORDINATION CHEMISTRY REVIEWS

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Review

Paramagnetic organometallic Cr(II)/Cr(III) redox-active catalysts

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Received 26 August 2005; accepted 29 November 2005

Contents

Abstract

The synthesis and reactivity of well-defined paramagnetic organometallic complexes of the first-row transition metals is an area of increasing research, as new applications of these species are discovered. While most inorganic chemists studying paramagnetic organochromium compounds have been investigating their application for olefin polymerization, redox-active chromium catalysts have been developed for C–C bond forming reactions for organic synthetic applications. In particular, a variety of chiral ligands have been introduced for the coupling of organic halides and aldehydes by chromium reagents, the Nozaki–Hiyama–Kishi (NHK) reaction. This article describes some of the coordination chemistry of Cr(II) and Cr(III) that led to these asymmetric NHK catalysts and that continues to underpin the unique reactivity profile of these reagents, as well as reviewing recent progress in the development of these and other paramagnetic organometallic catalysts based on more than one oxidation state of chromium.

Keywords: Paramagnetic complexes; Asymmetric catalysts; Chromium; Reduction-oxidation reactions

1. Introduction

In the past decade, several important advancements have been made in catalysts involving paramagnetic, redox-active organometallic chromium complexes. In keeping with the theme of this issue of *Coordination Chemistry Reviews*, this review will focus on organometallic compounds, and specifically paramagnetic Cr complexes that alternate between two oxidation states as part of their catalytic cycle. Particular attention will be paid to the most well-developed application in this area, the Nozaki–Hiyama–Kishi (NHK) reaction, which couples organic halides and aldehydes and is based on the Cr(II)/Cr(III) redox pair. The scope of this article precludes coverage of the many examples of paramagnetic catalysts that involve only a single oxidation state of chromium, such as Cr(III) catalysts for olefin polymerization [1], asymmetric ring-opening of epoxides [2], or asymmetric hetero-Diels–Alder reactions [3].

Despite the relatively exotic nature of paramagnetic organometallic species, the asymmetric applications featured in this review are undeniably at the forefront of current catalysis

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doi:10.1016/j.ccr.2005.11.019

research. As new catalytic applications involving paramagnetic first-row transition metal complexes are developed, there has been an increasing interest in the synthesis of well-defined compounds with tunable ancillary ligands to help understand the relevant structure–activity relationships [4]. This review is intended as a guide to those interested in the rational design of catalysts for these as-yet understudied systems. For each of the types of applications involving redox-active paramagnetic organochromium catalysts, emphasis is placed on well-defined complexes that have been isolated and characterized. While ligand design considerations are always critical for organometallic catalysis, the reactivity of paramagnetic first-row transition metal complexes in particular is dictated on a large number of interdependent factors. The ligand σ- and π-bonding properties, the metal's oxidation and spin state(s), coordination number, and ligand geometry can all play a role in influencing the reactivity of the complex. However, many of these factors can be understood using relatively simple Ligand Field Theory (LFT) considerations. Indeed, inorganic chemists have been striving to understand transition metal reactivity for many decades now, and this review will attempt drawing parallels to earlier work by chromium chemists that may help illuminate some recurring structural motifs and reactivity trends of relevance to current catalytic applications.

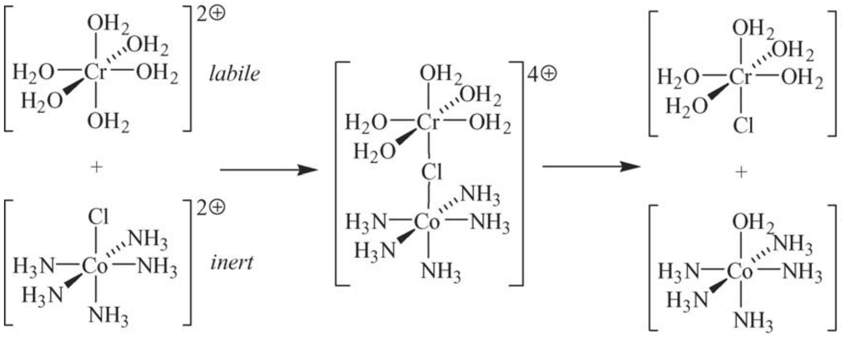
2. C–C bond formation with Cr(II)/Cr(III)

2.1. Activation of organic halides with $Cr^{2+}_{(aq)}$

Considering that they differ only by a single electron, the discrepancy in the rate constants for water exchange between $[Cr(H_2O)_6]^{2+}$ and $[Cr(H_2O)_6]^{3+}$ of over 10 orders of magnitude is astounding [5]. The incredible differences in reactivity between $Cr^{2+}_{(aq)}$ and $Cr^{3+}_{(aq)}$ and related transition metal complexes was the focus of much research after World War II [6], leading to the development of Ligand Field Theory. By successfully accounting for a wide variety of spectroscopic and reactivity trends based on straightforward arguments of the occupancy and relative energies of the valence d-orbitals, the impact of LFT on the study of transition metal complexes can be compared to the influence of Valence Bond Theory in organic chemistry. Both LFT and VBT gave experimental chemists a convenient back-of-the-envelope conceptual framework to explain their results and predict new reactivity.

The explanation of why high spin octahedral d^4 complexes with $t_{2g}^3e_g^1$ electronic configurations are labile while octahedral d^3 complexes ($t_{2g}^3e_g^0$) are inert is an integral part of most undergraduate inorganic chemistry courses dealing with transition metal reactivity. While these principles remain central to many coordination chemists (including presumably most of the readers of this journal), it is worth pointing out that LFT considerations are not typically employed even by inorganic chemists when discussing reactivity in current organometallic chemistry. To those interested primarily in catalysis or the synthetic organic application of transition metal reagents, the central ideas of LFT may be even more foreign. And yet these principles are especially critical for those wishing to harness the reactivity of paramagnetic first-row transition metal complexes.

A famous example of the use of the enormous variation in ligand exchange rates observed for $Cr^{2+}_{(aq)}$ and $Cr^{3+}_{(aq)}$ is shown in Eq. (1), which was used to provide critical evidence for the inner-sphere mechanism of electron transfer [7]. When the labile high spin d^4 Cr(II) complex $[Cr(H_2O)_6]^{2+}$ and the inert low spin d^6 Co(III) compound $[Co(NH_3)_5Cl]^{2+}$ react in aqueous solution, the chloro ligand on cobalt can displace one of the aqua ligands to form the illustrated bridging complex. Following transfer of an electron from Cr(II) to Co(III) through the bridging chloro group, the relative rates of ligand exchange of the two metals are reversed. As a result, the labile d^7 Co(II) complex surrenders the chloro ligand to the inert d^3 Cr(III) center. While the Co(II) rapidly dissociates its ammine ligands to form $[Co(OH_2)_6]^{2+}$, the Cr(III) $[Cr(H_2O)_5Cl]^{2+}$ complex retains all of its ligands, including the chloro group. Lack of incorporation onto Cr of added radioactively labeled chloride ions in solution provided additional proof for the proposed inner-sphere electron transfer mechanism [7].



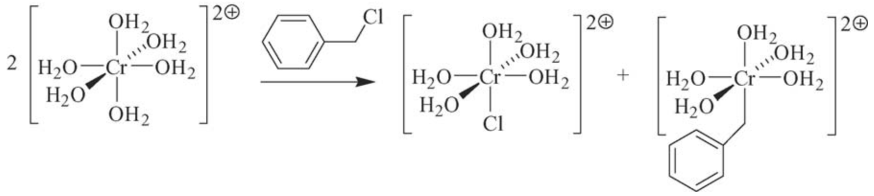
(1)

LFT and inner-sphere electron transfer are the backdrop for Eq. (2), the activation of benzyl chloride with $Cr^{2+}_{(aq)}$ to give two Cr(III) species, $[Cr(Cl)(H_2O)_5]^{2+}$ and $[Cr(CH_2Ph)(H_2O)_5]^{2+}$, performed by Anet and Leblanc in 1954 [8]. From the perspective of organometallic chemistry, almost every characteristic of the Cr(III) benzyl species runs contrary to the expected requirements of a stable transition metal alkyl complex. During this period, the research groups of Wilkinson and Fischer were using the 18 electron rule as a guide to prepare stable diamagnetic complexes in low formal oxidation states, with

$$[Cr(OH_2)_6]^{2+} + R{-}X \xrightarrow{\text{slow}} [Cr(X)(OH_2)_5]^{2+} + R\cdot$$
$$[Cr(OH_2)_6]^{2+} + R\cdot \xrightarrow{\text{fast}} [Cr(R)(OH_2)_5]^{2+}$$

Scheme 1. Mechanism of alkyl halide activation by $Cr^{2+}_{(aq)}$.

π-acceptor ancillary ligands and usually an overall neutral charge [9]. But the feature of the Cr(III) benzyl compound that perhaps remains most surprising to current organometallic chemists is the presence of water. The organometallic complexes of early transition metals in particular must be synthesized, isolated, and stored under rigorously anhydrous conditions. Not only is $[Cr(CH_2Ph)(H_2O)_5]^{2+}$ prepared in aqueous solution, the Cr–C bond remains intact despite the five molecules of water bound directly to the metal center. Of course, from a coordination chemistry viewpoint, the complex is merely one of a vast catalog of inert Cr(III) octahedral aqueous complexes, albeit one with an atypical anionic ligand. The Cr(III) benzyl complex serves as a prime example of how paramagnetic organometallic complexes may usefully be viewed as bridging between Werner-type coordination compounds and classic low oxidation state organometallics [10].



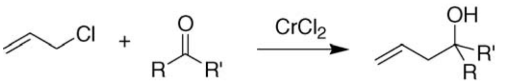
(2)

The mechanism of the reaction was explored in seminal work by Kochi, who determined that the reaction proceeded in two steps, as shown in Scheme 1. The inner-sphere reaction between the organic halide and $Cr^{2+}_{(aq)}$ generates the Cr(III) halide complex and an alkyl radical in the rate-determining step. The organic radical then reacts rapidly with a second equivalent of $Cr^{2+}_{(aq)}$ to form the Cr(III) alkyl compound [11]. The approximate rate of the alkyl radical trapping process was determined using radical clock experiments. While the $Cr^{2+}_{(aq)}$ system generates Cr(III) alkyl complexes only with very highly activated organic substrates such as $PhCH_2Cl$ or $CHCl_3$, it was demonstrated that more reactive Cr^{2+} complexes could be formed by introducing ligands such as ethylenediamine [12] or tetraazamacrocycles [13]. The enhanced activity achieved by adding N-donor ligands is consistent with the increased electron density donated by these ligands leading to a more powerful Cr(II) reductant, influencing the rate determining step of the organic halide activation process.

Subsequent reactivity studies of the Cr(III) alkyl complexes, generated from organic halides or via other synthetic routes [14], demonstrated that the $[Cr(R)(H_2O)_5]^{2+}_{(aq)}$ species showed remarkably high rates of ligand exchange for the aqua ligand *trans* to the alkyl due to the σ-donor strength of the R group. This labile ligand allowed the preparation of neutral $[Cr(R)(acac)_2(L)]$ complexes with treatment of the $[Cr(R)(H_2O)_5]^{2+}_{(aq)}$ species with 2,4-pentanedione [15]. The key factor for the application of the activation of alkyl halides for organic synthesis lies in the second step of the process shown in Scheme 1. But while the rapid and essentially irreversible reaction of Cr(II) with organic radicals to give inert, highly functional group tolerant Cr(III) alkyl complexes would eventually prove critical, no C–C bond forming reactions were feasible with the Cr(III) alkyl complexes in aqueous solution.

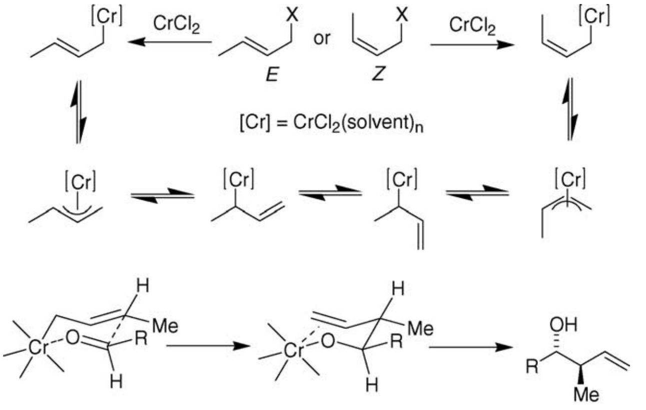
2.2. Stoichiometric coupling reactions with $CrCl_2$

In 1977, Hiyama and co-workers demonstrated that $CrCl_2$ in THF could be used to add allyl halides to aldehydes or ketones to give homoallyl alcohols after aqueous work-up, as shown in Eq. (3) [16]. The use of an aprotic donor solvent is critical, as the reaction of allyl halides and $Cr^{2+}_{(aq)}$ in aqueous solution leads to protonation of the Cr(III) allyl intermediate rather than insertion of aldehydes. Even in aprotic solvents, the in situ Cr(III) allyl species will eventually undergo homocoupling if generated in the absence of carbonyl complexes. Less reactive allylic substrates required the use of DMF as a solvent, to enhance both the solubility of the Cr(II) salt and its reducing power, similar to the increased reactivity noted by Kochi when ethylenediamine is added to the $Cr^{2+}_{(aq)}$ system. Even in the initial communication, the remarkable selectivity of the $CrCl_2$ reagent for both of the organic substrates was noted. In particular, the Cr(III) allyl intermediate reacts preferentially with aldehydes, with ketones reacting only much more slowly, and nitriles and esters remaining unreacted. Even in DMF, the $CrCl_2$ reagent alone remains a relatively mild reductant, and will not reduce alkyl, aryl, or alkenyl halides.



(3)

The stereoselectivity of the reaction of $CrCl_2$ with aldehydes and *substituted* allyl halides provided valuable insights into the mechanism of this reaction. The C–C bond formed in these reactions is with the more highly substituted terminal carbon of the allyl moiety. Crotyl halides afford the anti configured allyl alcohol, with the same product being observed regardless of whether the initial allyl halide has an E or Z configuration. These observations are consistent with the mechanism shown in Scheme 2. Once attached to the Cr(III) center, the allyl group can isomerize via different possible η^1 and η^3 binding modes. When the allyl ligand is coordinated η^1, the aldehyde can coordinate to the Cr atom in the vacant site in the *cis* position relative to the allyl group. In the critical C–C bond forming event, steric interactions will direct both the allyl methyl substituent and the



Scheme 2. Mechanism of stereoselective coupling of crotyl halides and aldehydes.

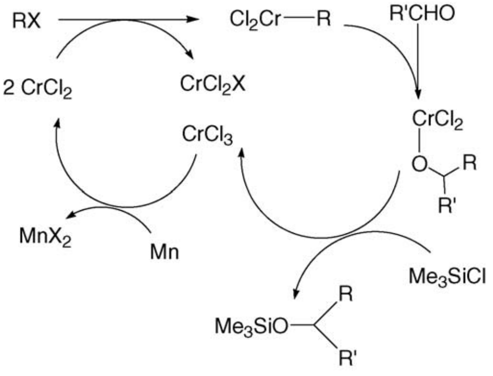
aldehyde R group into equatorial positions of the chair-shaped transition state, leading to the anti configuration.

In 1986, the scope of C–C bond forming reactions mediated by the Cr(II)/Cr(III) redox pair was greatly extended by almost simultaneous reports from the groups of Nozaki and Kishi [17]. After observing that the activity of commercially available $CrCl_2$ seemed to vary dramatically depending on the source or batch, both groups found that the range of organic halides to be activated could be extended by adding catalytic amount of $NiCl_2$. The $CrCl_2$ reduces the $NiCl_2$, and the reduced Ni species serves to activate less reactive substrates such as alkenyl or aryl halides. Transmetallation of the organic group from Ni to Cr gives the Cr(III) alkyl complex responsible for the following aldehyde insertion step. Similarly, the ability of Co complexes to generate alkyl radicals from alkyl halides (a critical feature of the bioinorganic chemistry of Vitamin B_{12}) led to the successful use of Co co-catalysts to permit the use of alkyl halides as substrates for the Cr-mediated coupling with aldehydes [18].

This improved methodology proved to be one of the key features in Kishi's celebrated total synthesis of palytoxin [19]. A staggeringly complex marine natural product with 63 stereogenic centers, palytoxin remains the largest secondary metabolite to be synthesized to date [20]. The Ni(II)/Cr(II) system was found to be superior to all other bond forming reactions for the coupling of alkenyl halides and aldehydes in the late stages of the assembly of palytoxin [21]. The ability of the Ni(II)/Cr(II) system to activate a range of organic halides, its selectivity in coupling aldehydes, its broad functional group tolerance, and its demonstrated utility in the key C–C bond forming steps of highly complicated organic molecules led to the enthusiastic adoption of the "Nozaki–Hiyama–Kishi" (NHK) reaction by natural products total synthesis chemists. The application of this methodology has been the subject of two excellent reviews in 1999 by Wessjohann and Scheid [22] and Fürstner [23], and a more recent comprehensive 'Organic Reactions' chapter by Takai [24], one of the original developers of the NHK reaction.

2.3. Catalytic-in-Cr Nozaki–Hiyama–Kishi reactions

Synthetic organic chemists using the Cr(II)/Ni(II) system for C–C bond forming reactions discovered that often 4–16 equivalents of $CrCl_2$ were required for optimal product yield. While the unique reactivity profile of the reagent justified its overstoichiometric use in the late stages of elaborate natural product total syntheses, more practical applications of the methodology would become feasible if the amount of $CrCl_2$ could be reduced to catalytic quantities. To achieve this goal, two separate challenges had to be addressed. The strong Cr–O bond in the inert Cr(III) alkoxide product resulting from aldehyde insertion into the Cr(III) alkyl species would have the be cleaved to release the product alcohol. In addition, a stoichiometric reductant would have to be used to transform the Cr(III) products back to the active Cr(II) form so that the next organic halide substrate could be activated.



Scheme 3. Proposed cycle for catalytic-in-Cr Nozaki–Hiyama–Kishi reaction.

The first catalytic-in-Cr Nozaki–Hiyama–Kishi reactions were reported by Fürstner and Shi in 1996, using Me_3SiCl to break the Cr(III)–OR bond and give the desired alcohol product as the corresponding silyl ether, and Mn powder as the stoichiometric reductant [25]. Scheme 3 illustrates the possible catalytic cycle that was suggested by Fürstner and co-workers for their multicomponent system. An important requirement for the success of the catalytic reaction is that all of the various reagents present must be mutually compatible. For instance, while many metal powders and other chemical reductants are capable of reducing Cr(III) to Cr(II), the stoichiometric reductant must not be so powerful that it consumes the sensitive organic substrates. The cycle shown in Scheme 3 shows the same excellent functional group tolerance, yields, and selectivity as the stoichiometric NHK reaction. Air stable $CrCl_3$ can be used as a catalyst precursor since it is reduced in situ, obviating the need for more expensive and sensitive $CrCl_2$. Catalyst loadings can be substantially reduced by using more soluble cyclopentadienyl substituted catalyst precursors, although the more electron rich Cr(II) center in the presumed CpCrCl intermediate leads to potential side reactions (see Section 2.5). The catalytic version was also shown to be compatible with Ni co-catalysts in order to activate aryl, heteroaryl, alkenyl, and alkynyl halides.

2.4. Catalytic and asymmetric NHK

By coupling an aldehyde to an organic halide, the NHK reaction creates a chiral secondary alcohol. If the key C–C bond forming step can be influenced by chiral ligands on the Cr atom, the reaction could be rendered enantioselective. There had been a few early reports of the introduction of chiral ligands to achieve this goal [26], but the overstoichiometric amount of $CrCl_2$ required for the NHK reaction acted as a strong disincentive to the exploration of this possibility.

The situation was dramatically altered after the catalytic-in-Cr NHK reaction was developed. The first catalytic *asymmetric* NHK reaction was reported by Cozzi and Umani-Ronchi in 1999, using complex **1** shown in Fig. 1 [27]. This initial communication was followed by a series of different applications of this catalyst [28], which have been reviewed by Cozzi and co-workers [29]. An interesting feature of this system is that for the coupling of crotyl bromide and benzaldehyde, the amount of syn configured allyl alcohol steadily increases relative to the expected anti product as the amount of chiral salen ligand is increased, reaching a maximum of 83/17 syn/anti when two equivalents of salen are present per Cr atom.

Fig. 1 shows other chiral catalysts that have been successfully employed in catalytic asymmetric NHK reactions. The salen ligand in Berkessel et al. [30], catalyst **2** is prepared from a C_2-symmetric diamine with a rigid backbone: the enantioselective synthesis of the diamine in four steps from norbornadiene has recently been reported [31]. Paterson et al. used **2** in a catalytic asymmetric NHK reaction in the synthesis of analogues of the anti-cancer agent laulimalide [32].

In addition to the chiral salen ligands, several groups have developed asymmetric NHK catalysts with ligands containing chiral oxazoline groups. The tridentate carbazole ligand **3** of the Nakada group has two oxazoline moieties [33]. The oxazoline amide ligand **4** was one of many prepared and screened by Sigman and co-workers [34]. In a synthetic approach designed to engender stereochemical ligand diversity, two amino acid derivatives were used to prepare an amine functionalized oxazoline, which was then capped with a third amino acid, with ligand **4** being based on phenylalanine, valine, and proline. The papers outlining the development of Kishi's sulfonamide ligand **5** provide an excellent example of the use of well-defined chromium complexes in rational catalyst design, and are discussed in detail in Section 3.2 [35,36].

2.5. *Pinacol coupling reactions*

In the NHK reaction, the Cr(II)/Cr(III) redox process is critical for the SET activation of the organic halide and the trapping of the radical generated as a relatively inert Cr(III) alkyl complex. The subsequent steps involving the aldehyde substrate (coordination, insertion, and release of the resulting alkoxide) are all restricted to intermediates solely in the Cr(III) oxidation state. However, Cr(II) complexes may also engage in SET reactivity directly with readily reduced aldehydes, as shown in Scheme 4. Inner-sphere electron transfer from Cr(II) to the C–O π^*-orbitals of the coordinated organic substrate generates a radical anion bound to a Cr(III) center. Formation of a C–C bond between two such species results in a pinacol coupling reaction. The resulting diol can be either the achiral *meso* isomer or the chiral *dl* isomer, with the type and extent of this diastereoselectivity depending on the steric interactions in the transition state. The use of chiral ligands on the metal might introduce further enantioselectivity, preferentially forming the *d* or *l* chiral complex, although obviously no enantioselectivity is possible if the achiral *meso* product is formed.

The possibility of pinacol coupling depends greatly on the relative redox potentials of both the Cr(II) source and the organic substrate. Aromatic aldehydes have low-lying C–O π^*-orbitals and are more prone to SET reduction than more electron rich aliphatic aldehydes. Introducing more electron donating ligands on Cr can lead to pinacol coupling competing with alkyl halide activation in NHK reactions. When Cp_2Cr or $CpCrCl_2(THF)$ were employed as NHK catalyst precursors, Fürstner and Shi found that significant amounts of diol product were produced when aromatic aldehydes were used instead of aliphatic aldehydes, a side reaction that was not observed in the corresponding stoichiometric or catalytic reactions using $CrCl_2$ [25].

The catalytic pinacol coupling of aromatic aldehydes using Fürstner's methods was explicitly examined by Svatoš and Boland [37]. The catalytic cross-coupling reactions of aldehydes and acetals of acrolein were reported by Boeckmann and Hudack [38]. Takai et al. have developed a range of intriguing catalytic and stoichiometric reactions involving pinacol coupling

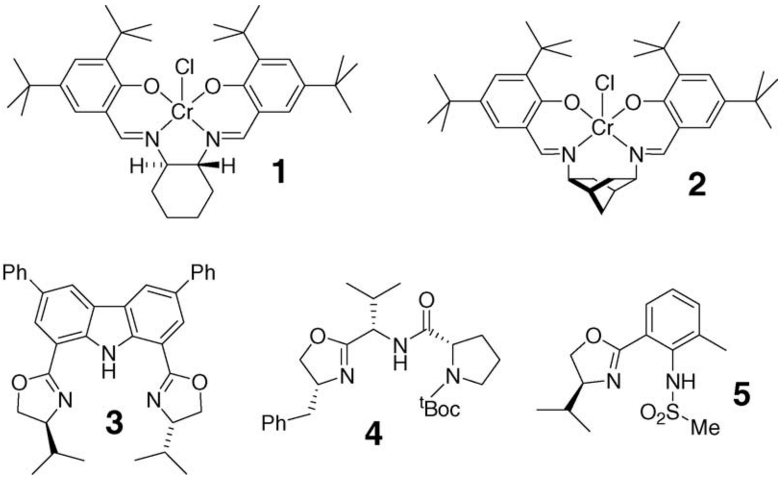
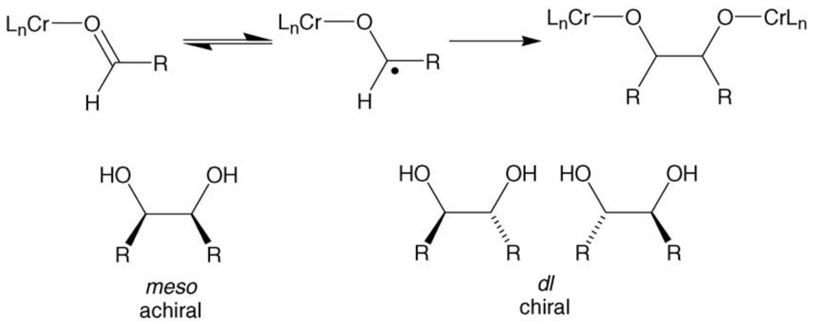


Fig. 1. Chiral complexes and ligands for asymmetric NHK catalysts.



Scheme 4. Pinacol coupling reaction.

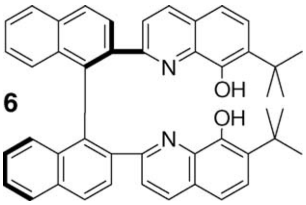

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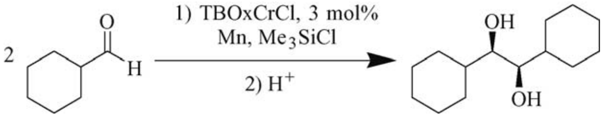
Fig. 2. Chiral TBOx ligand used for selective catalytic pinacol coupling.

and cross-coupling steps where the initial SET activation of the organic halide by Cr(II) initiates a sequence of free-radical chemistry before the eventual trapping step forms the reactive Cr(III) intermediate [39]. Groth and co-workers have recently published an extensive study of ligand effects in the diastereoselectivity of pinacol cross-coupling between α,β-unsaturated carbonyl complexes and aldehydes [40].

Yamamoto and co-workers have reported a well-defined Cr complex bearing chiral ligand **6** capable of catalyzing the pinacol coupling reaction in a manner that is both highly diastereoselective for the chiral *dl* diol, and highly enantioselective in generating the (*R*,*R*) isomer [41]. The chiral TBOx ligand **6** used employs two quinolinato units attached to a resolved axially chiral binaphthyl linker, as shown in Fig. 2. The X-ray crystal structure of the [Cr(TBOx)(EtOH)$_2$]Cl salt shows the tetradentate ligand adopts a cis-β configuration around the metal, distinct from the trans form preferred by the corresponding chiral salen complexes, or the C_2-symmetric cis-α geometry [42]. Not only does this pre-catalyst achieve high yields, *dl* selectivity and enantiomeric excesses with aromatic aldehydes with different steric and electronic properties, it also represents the first example of an aliphatic pinacol coupling reaction, as shown in Eq. (4).



(4)

3. Ligand design considerations

3.1. Well-defined complexes and rational catalyst design

The remarkable progress that has been achieved in the last 10 years in Cr(II)/Cr(III) catalysts for C–C bond forming reactions has been due almost entirely to the efforts of organic chemists. The development of asymmetric NHK catalysts in particular has provided ample evidence of the strength of the empirical approach to catalyst optimization. This strategy would appear to be a mandatory requirement of the multicomponent catalytic system. In a typical procedure, to a suspension of $CrCl_3$ in an aprotic donor solvent is added sequentially Mn powder, the chiral ligand in its protonated form, and a hindered amine base to facilitate the deprotonation of the ligand and its coordination to Cr. Then the aldehyde, the organic halide, and Me_3SiCl are added. When TLC monitoring of the reaction indicates completion, the reaction is quenched and the desired silyl ether organic product is extracted, converted to the alcohol and purified [27].

Given the demonstrated success of this methodology and the inherent complexity of the multicomponent catalyst system, the potential for using well-defined paramagnetic Cr(II) and Cr(III) compounds to examine the individual reactions that make up the proposed catalytic cycle may seem distinctly unpromising. Compounding these difficulties are the intrinsic difficulties facing chemists who would attempt to examine individual species in catalytic processes. These problems are famously formulated in Halpern's rules (as recently quoted by Finke based on Bergman's summary): "if you can isolate it, it is probably not the catalyst; if it is metastable and you can detect it, it *could* be the catalyst; and if it is highly unstable and undetectable, then it probably *is* the catalyst" [43].

It is important, however, to note the two counterexamples to these rules that Finke cites, namely olefin polymerization catalysts and olefin metathesis catalysts [43]. Similar to the current catalytic NHK system, both olefin polymerization and metathesis catalysts were initially poorly defined multimetallic mixtures of transition metal halide salts and highly reactive organometallic species. For the d^0 Mo and W, Schrock olefin metathesis catalysts in particular, entirely new synthetic inorganic methodologies had to be developed before the well-defined catalyst species could be prepared [44]. As new applications of paramagnetic first-row transition metal complexes continue to be developed, a similar improvement in synthetic inorganic routes will have to accompany work on well-defined compounds to investigate these reactions [4].

While the sheer number of reagents involved in the catalytic NHK reaction would appear to hinder attempts to investigate this process, it is actually indicative of how this system is fundamentally different than the catalytic reactions like olefin hydrogenation which originally prompted the enunciation of

Halpern's rules. Most of the intermediates in the NHK reaction are inert, octahedral Cr(III) d^3 complexes. It is their very lack of reactivity that contributes to both their excellent selectivity and functional group tolerance, and which requires the various components of Fürstner's catalytic system to drive the otherwise unresponsive Cr(III) intermediates around the cycle. With the appropriate ancillary ligands and in the absence of the reagent required to push the complex along to the next step, the various Cr(III) intermediates proposed in Fürstner's catalytic cycle are expected to be viable targets for independent synthesis, isolation, and characterization. While the presence of unpaired d-electrons in paramagnetic organochromium compounds hinders the application of NMR for their characterization, improvements in the availability and power of single-crystal X-ray diffraction methods have made crystallographic structural determinations of paramagnetic complexes almost routine. For Cr(II)/Cr(III) redox catalysts, electrochemical, and UV–visible spectrophotometric techniques should be particularly valuable.

A particularly promising line of inquiry is the development of clean routes to prepare paramagnetic Cr compounds in situ so that their reactivity can be quantitatively evaluated. In this manner, a series of ligands with systematically varied steric and electronic properties can be screened in order to learn about the ligand effects operating for that particular step in the catalytic cycle, with the information gained being used in the next iteration of ligand design. An excellent example of this approach in paramagnetic organochromium chemistry is Gibson's use of arene elimination reactions of $Cr(p\text{-tolyl})Cl_2(THF)_3$ with Schiff bases to generate catalyst precursors for olefin polymerization [45]. Detailed structure–activity relationships could be obtained by interrogating each reaction individually, which then could be combined to rationally design an improved catalyst for a given reaction.

3.2. *Sulfonamide Cr complexes for asymmetric catalytic NHK reactions*

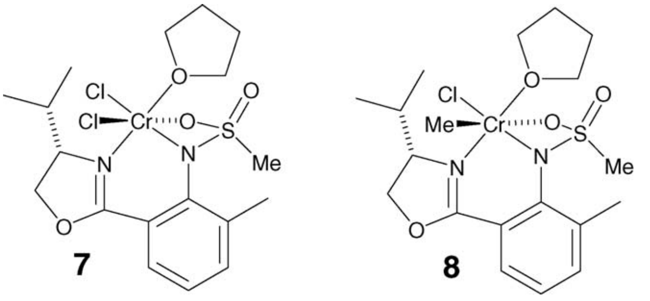


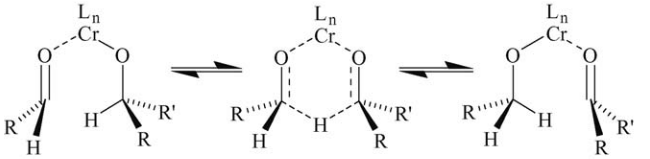
Fig. 3. Structures of dichloro **7** and chloro methyl **8** Cr(III) complexes with ligand **5**.

It is somehow strangely fitting that the best example to date of the "inorganic" approach to rational design of an NHK catalyst is provided by the work of Kishi. As in the initial work on the reaction to address a specific synthetic challenge in the total synthesis of palytoxin [21], the development of ligand **5** emerged from the desire for an asymmetric catalyst to aid in the synthesis of halichondrin B and related analogues [35]. In one of the series of consecutive communications in 2002, Kishi and co-workers describe in illuminating detail how chiral ligands were screened in stoichiometric-in-Cr reactions to couple organic substrates that approximated the synthetic problem faced in the halichondrins. From the initial lead structure, the ligand **5** was optimized, with the introduction of the sulfonamide group and the *ortho*-methyl substituent proving to be particularly crucial. The Cr(III) dichloro **7** and Cr(III) methyl chloro **8** complexes bearing ligand **5** were prepared and structurally characterized by single crystal X-ray diffraction. As shown schematically in Fig. 3, the two complexes **7** and **8** are remarkably similar, with the sulfonamide ligand adopting a tridentate facial coordination mode, and a molecule of THF occupying the site trans to the oxazoline N-donor atom. Of particular interest is the Cr–O bond length of the coordinating sulfonamide group. When trans to a chloro ligand in **7**, the length is 2.11 Å, but when trans to a methyl ligand in **8**, the bond length is 2.28 Å, presumably due to the trans effect of the strong σ-donor. This crystallographic study provided an excellent basis for the mechanistic rationale forwarded to account for the observed enantioselectivity, based on the coordination of the aldehyde in the position occupied by the THF molecule in complexes **7** and **8**. Gratifyingly, isolated complex **8** was reacted directly with the aldehyde, and the major enantiomer of the expected product was found to correspond to that obtained in the halichondrin model reaction. Ligand **5** was then employed successfully in a stoichiometric asymmetric NHK reaction to prepare the actual desired halichondrin fragment [35].

The following paper described the development of a catalytic process built on the preceding foundation of well-defined stoichiometric chemistry [36]. Again, a wealth of fascinating detail was provided outlining the catalyst optimization process. The well-defined Cr sulfonamide catalysts proved to be compatible with all three types of Cr(II)/Cr(III) mediated C–C bond forming reactions involving organic halides and aldehydes, coupling allyl chlorides without additional metal co-catalyst, alkenyl iodides with a Ni co-catalyst, and primary alkyl halides with a Co co-catalyst. Subsequent reports by the Kishi's group have described the use of sulfonamide Cr catalysts to couple aldehydes and 2,3-dihalopropene using Co or Fe co-catalysts [46], and the intriguing replacement of Me_3SiCl with Cp_2ZrCl_2 in multicomponent asymmetric NHK catalysts [47].

3.3. *Mechanistic studies*

Some very interesting mechanistic issues regarding the NHK reaction have been raised by Wessjohann and co-workers. As shown in Eq. (5), once the Cr(III) alkoxide has been formed by coupling the allyl halide and the aldehyde, it can be prone to a further reversible reaction with excess aldehyde present in solution. The process is known as the OMPV equilibrium, since the forward process is an Oppenauer oxidation and the reverse is a Meerwein–Ponndorf–Verley reduction. The allyl ketone resulting from the OMPV equilibrium can reduce the overall yield of the desired alcohol product [48]. Of even greater significance from a rational catalyst design viewpoint, the reversible nature of the equilibrium scrambles the stereocenter in the chiral alcohol that the asymmetric NHK reaction is designed to create enantioselectively. Wessjohann has produced evidence that not only might the OMPV process be interfering with what would otherwise be highly selective chiral Cr catalysts, the high ee's reported for some of the compounds in Section 2.3 might actually be due to the OMPV process displaying significant chiral induction, rather than the inherent enantioselectivity of the C–C bond forming step itself [49].



(5)

In a review article, Wessjohann and Scheid also expressed doubt about the kinetic ability of the Me_3SiCl reagent to break the Cr–OR bond in inert octahedral Cr(III) complexes [22]. As a possible alternative, they suggested that in the catalytic NHK reaction, Mn may in fact reduce the Cr(III) alkoxide species to the more labile Cr(II) complex prior to reaction with the silyl chloride to produce the observed silyl ether product. Yet another alternative is presented by the work of Jacobsen on Cr-based catalysts for the asymmetric ring-opening of epoxides with Me_3SiN_3 using catalyst **1** [2]. Careful investigation of the kinetics of this reaction revealed that among other peculiar mechanistic features, trace water was converting Me_3SiN_3 to the corresponding acid, and that it was actually the trace amounts of HN_3 that were responsible for the cleavage of the Cr–OR bond in the Cr(III) salen alkoxide intermediate. The resulting alcohol then reacted with Me_3SiN_3 to give the final silyl ether and regenerate the trace HN_3 catalyst. Interestingly, Shaughnessy and Huang have demonstrated a catalytic NHK reaction that uses lutidinium chloride rather than Me_3SiCl to liberate the alkoxide, demonstrating the feasibility of a proton catalyzed system analogous to Jacobsen's asymmetric epoxide ring-opening work [50].

4. Concluding remarks

In addition to the Cr(II)/Cr(III) based systems discussed in this review, other well-defined redox-active paramagnetic organochromium catalysts are currently in the process of being developed. Non-organometallic epoxidation catalysts based on Cr(salen) oxo species have recently been reviewed [51], and Theopold and co-workers have communicated some exciting initial experimental and computational work on the epoxidation activity of well-defined $CpCrCl_2O$ and Cp^*CrCl_2O oxo compounds derived from O_2 oxidation [52]. The industrial use of Cr-based catalysts for the selective trimerization of ethylene to 1-hexene is generally considered to proceed via metallacyclic intermediates, but whether the active catalyst involves a Cr(I)/Cr(III) or a Cr(II)/Cr(IV) redox couple is still unclear [53], although recent results from Bercaw and co-workers provides compelling evidence for the viability of the Cr(III) based precatalysts [54]. Another reaction involving metallacyclic intermediates and the Cr(I)/Cr(III) redox cycle is the report of Takahashi et al. on the reactivity of in situ generated chromocyclopentadienes with unsaturated substrates to form various cyclic organic products [55]. While this work is currently stoichiometric and relies on transmetallation from Cp_2Zr complexes, when viewed in conjunction with the olefin trimerization catalysts it underscores the need for further exploration of the synthesis and reactivity of well-defined Cr(I) complexes [56].

Note added in Proof

Kishi and co-workers have developed new substituted bipyridine and phenanthroline ligands that improve the yield and selectivity of Ni/Cr-mediated NHK reactions for both catalytic and asymmetric catalytic applications:

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