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The Open d-Shell Enforces the Active Space in 3d Metal Catalysis: Highly Enantioselective Chromium(II) Pincer Catalysed Hydrosilylation of Ketones

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Bis(oxazolinyldimethylmethyl)pyrrol (PdmBox) stereodirecting ligands provided the key to the chromium(II)-catalysed highly enantioselective hydrosilylation of ketones. A rare square planar, chiral chromium(II) alkyl complex was found to serve as a potent precatalyst for the reduction of a broad range of aryl alkyl and dialkyl ketone derivatives. The stereoelectronic preference of the open d^4 shell of chromium(II) firmly locks the molecular catalyst in a square planar geometry giving rise to two blocked quadrants of the coordination sphere. This earth-abundant base metal catalytic platform produces the corresponding chiral alcohols in excellent isolated yields with up to 98 %ee under mild reaction conditions (–40 °C to rt) and at low catalyst loadings (as low as 0.5 mol%).

Applications of chromium salts or well-defined chromium complexes in homogeneous catalysis[1] include *inter alia* the asymmetric Nozaki-Hiyama-Kishi-reaction,[1b,d,2] poly-[3] and oligomerizations[4] of olefins or cross-coupling reactions.[5] However, chromium-catalyzed reductions of C=O bonds have not been investigated in a systematic fashion so far. In particular, there are no reports on enantioselective versions of the latter catalysed by chromium complexes.

We have recently explored a range of 3d metal-catalysed stereoselective transformations and investigated the associated mechanistic pathways.[6] Our studies have shown that application of conjugated, rigid and planar *N,N,N* pincer-type ligands in combination with 3d metals in their formal M^{II} oxidation state furnished catalytic systems of unprecedented activity and selectivity.[2c,6c,e,7] In these cases, the rigidity of the stereodirecting ligand gave rise to a structurally well-defined coordination sphere which was thought to deliver the observed high enantioselectivity.

The conjugated π-electron system of the rigid chiral pincers rendered these ligands redox non-innocent which in some cases gave rise to competitive one-electron radical chemistry.[6f, 7g] To overcome this limitation we recently developed the non-conjugated but more flexible bis(oxazolinyldimethyl-methyl)pyrrole ("PdmBox") ligand.[8] Initial attempts of transferring chiral information by 3d metal(II) complexes using this re-designed ligand family gave rise to modest enantioselectivities.[9] A careful structural investigation revealed that this outcome could be attributed to the preferential formation of tetrahedral M^{II} complexes (for M = Mn, Fe and Co), featuring an arrangement of the oxazoline substituents which is unfavourable for efficient enantio-discrimination. We envisioned that the desired square-planar coordination, which provides a geometrically suitably structured active space for chirality transfer (Figure 1), could be enforced stereoelectronically by the open d-shell of the metal centre. This would be expected for the (high spin) d^4 as well as d^8 configuration of the divalent group 6 and 10 metal ions.

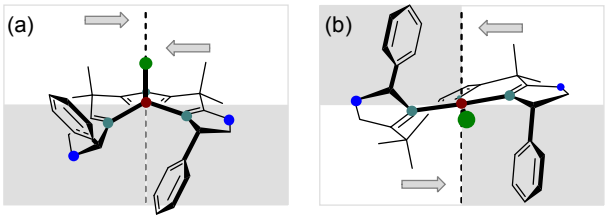

Figure 1. Illustration of the metal-induced stereo-electronic shaping of the active space in tetrahedral (a) *vs.* square-planar (b) PdmBox (3d) metal complexes. Arrows highlight the sterically favoured substrate binding sites.

The exceptional inertness of square-planar PdmBox d^8-nickel(II) complexes in the hydrosilylation of ketones led us to investigate their presumably isostructural PdmBox d^4-chromium(II) congeners and, based on previous experience with 3d metal reduction catalysis, chose the chromium(II) alkyls as potential pre-catalysts.

The chromium(II) complexes of this type were readily accessible following a standard two-step protocol: Initial lithiation of the protioligand followed by addition of (tmeda)$CrCl_2$ gave chlorido complexes **1a**,**b**.[10] Subsequent alkylation of these compounds with a dialkyl magnesium

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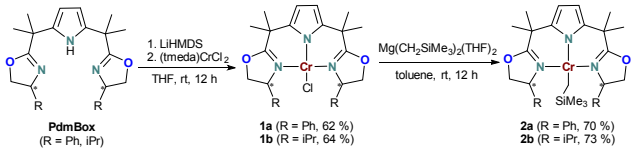
source $MgR_2(THF)_2$ (R = CH_2SiMe_3) produced precatalysts **2a**,**b** in moderate overall yields (Scheme 1).



Scheme 1. Synthesis of PdmBox chromium(II) chlorido (**1a,b**) and alkyl (**2a,b**) complexes.

In addition to a characterization by EA, MS, NMR and determination of the magnetic moment in solution (*vide infra*), we were able to obtain single crystals suitable for X-ray diffraction for both classes of compounds (**1b**, **2b**, Figure 2).

The coordination geometry around the chromium centre is best described by a slightly distorted square-planar arrangement with calculated geometry factors of $\tau_4 = 0.14$ (for **1b**) und $\tau_4 = 0.09$ (for **2b**) ($\tau_4 = 0$ describes an ideal square-planar coordination).[11] This square-planar geometry is the expected behaviour for d^4-chromium(II) complexes and is facilitated by a twist/torsion of the pyrrole-backbone due to the inherent flexibility of the ligand. A close structural resemblance of both molecular structures is observed, indicating that co-ligand exchange only has a minor impact on the structural parameters of the complex. All bonds were in the expected range for chromium(II) complexes with tridentate pincer ligands.[3c, 4c, 12] Both compounds feature the typical short M-N bond length for the anionic nitrogen as opposed to the neutral oxazoline N donors. In addition, a noticeable *trans*-influence of the alkyl ligand is detected.

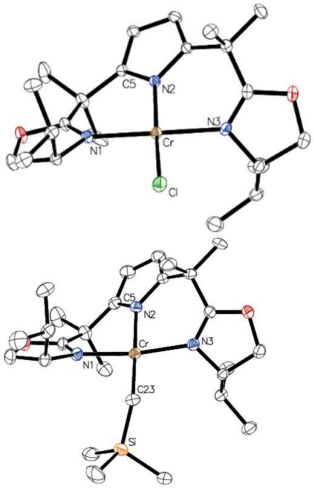
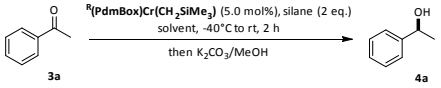


Chart 2. Molecular structures of chlorido complex **1b** and alkyl precatalyst **2b** were determined by X-ray diffraction. Displacement ellipsoids have been set at 30% probability level, hydrogen atoms have been omitted for clarity. Selected bond lengths [Å] and angles [°]: **1b:** Cr-Cl 2.3305(6), Cr-N(1) 2.0735(18), Cr-N(2) 2.0144(17), Cr-N(3) 2.079(2); N(1)-Cr-Cl 95.43(5), N(1)-Cr-N(3) 169.87(8), N(2)-Cr-N(3) 86.47(7), N(2)-Cr-N(1) 86.79(7), N(2)-Cr-Cl 170.70(6), N(3)-Cr-Cl 92.43(6); torsion angle N(1)-Cr-N(2)-C(5) -20.4(2). **2b:** Cr-N(1) 2.081(6), Cr-N(2) 2.066(6), Cr-N(3) 2.084(6), Cr-C(23) 1.843(8), N(1)-Cr-C(23) 95.4(3), N(1)-Cr-N(3) 168.9(2), N(2)-Cr-N(3) 84.5(2), N(2)-Cr-N(1) 84.4(2), N(2)-Cr-C(23) 177.1(3), N(3)-Cr-C(23) 95.7(3); torsion angle N(1)-Cr-N(2)-C(5) -37.44(6).

The solid state structural data is complemented by the magnetic susceptibilities observed in solution (μ_{eff} = 4.75 μ_b for **1a**, μ_{eff} = 4.70 μ_b for **1b** and μ_{eff} = 4.73 μ_b for **2a**) determined by Evans' method.[13] Such values reflect the presence of a paramagnetic d^4-*high spin* complex, being in the same range as the theoretical spin-only value (μ_{so} = 4.90 μ_b) and matching other reported chromium(II) complexes.[4d, 12a]

Table 1. Optimization of the reaction conditions for the chromium(II) catalysed hydrosilylation of ketones.



#	R [a]	Solvent	Silane	Conv. [%][b]	ee [%][b]
1[c]	Ph	toluene	$(EtO)_2MeSiH$	>99	87
2	Ph	toluene	$(EtO)_2MeSiH$	>99	95
3[d]	Ph	toluene	$(EtO)_2MeSiH$	>99	95
4	*i*Pr	toluene	$(EtO)_2MeSiH$	>99	75
5	Ph	toluene	$(EtO)_3SiH$	>99	83
6	Ph	toluene	$nBuSiH_3$	>99	84
7	Ph	toluene	PMHS[e]	58	84
8[f]	Ph	toluene	$PhSiH_3$	>99	70
9[f]	Ph	toluene	Ph_2SiH_2	0	nd
10[f]	Ph	toluene	Me_2PhSiH	0	nd
11	Ph	*n*-pentane	$(EtO)_2MeSiH$	>99	90
12	Ph	*n*-hexane	$(EtO)_2MeSiH$	>99	90
13	Ph	Et_2O	$(EtO)_2MeSiH$	>99	90
14	Ph	THF	$(EtO)_2MeSiH$	>99	86
15	Ph	tmeda	$(EtO)_2MeSiH$	>99	80
16	Ph	DCM	$(EtO)_2MeSiH$	0	nd
17	Ph	MeCN	$(EtO)_2MeSiH$	0	nd

[a] *(S)*-enantiomer for R = *i*Pr, *(R)*-enantiomer for R = Ph. [b] Determined by chiral HPLC. [c] Reaction was perfomed at rt. [d] Reaction was perfomed with 0.5 mol% catalyst loading. [e] PMHS = Poly(methylhydrosiloxane). [f] Work-up with NaOH in *i*PrOH. All reactions were performed at 0.12 mmol scale.

An initial assessment of the activity of this system with acetophenone **3a** as the benchmark substrate and $(EtO)_2MeSiH$ as the silane showed full conversion in less than 15 min at rt and gave a promising enantioselectivity of 87 %ee ([Cr] = 5 mol% of **2a**). The fast reaction rate led us to investigate this transformation at reduced temperatures (Table 1). Employing the phenyl derivative of the PdmBox ligand (complex **2a**), we were able to improve the selectivity for this reaction to 95 %ee while warming from -40 °C to rt over a period of two hours. Despite its similar activity, the isopropyl substituted derivative **2b** produced a significantly reduced selectivity and no further improvements could be achieved by a variation of the silane (Table 1, entries 2 and 3-8). While excellent conversions and a somewhat diminished enantiomeric excess were observed for the more reactive silanes, no product formation was detected for Ph_2SiH_2 and Me_2PhSiH. These findings could suggest that the silane is involved in the rate-determining step of the catalysis or that catalyst activation is dependent on a suitable silane source (*vide infra*).

A solvent screening revealed that although (aromatic) low polarity solvents (toluene, *n*-pentane, *n*-hexane) give rise to

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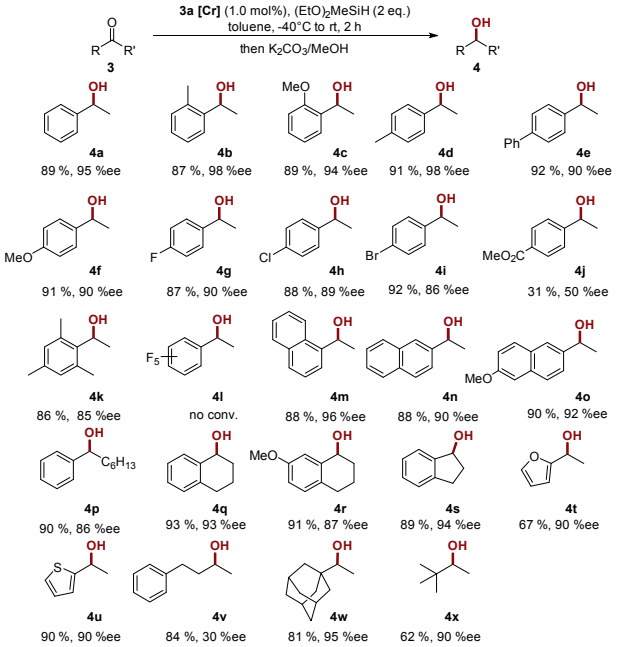
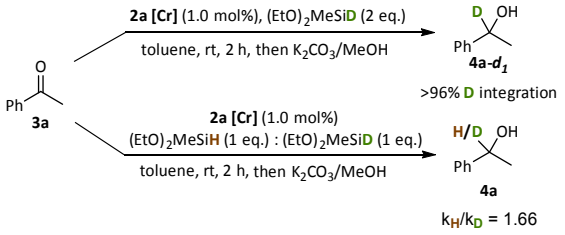
slightly higher enantioselectivities, coordinating and polar solvents such as tetrahydrofuran or even tmeda can in principle afford the product in good selectivity and excellent yield (Table 1, entries 10-14). This behaviour contrasts with that of many other ketone hydroelementation catalysts which generally prefer low polarity and weakly coordinating solvents.[28,31] No conversion was observed in dichloromethane and acetonitrile, presumably due to rapid precatalyst decomposition in these solvents (Table 1, entries 15 and 16). Notably, the activity of the chromium catalyst allowed a reduction of the catalyst loading down to 0.5 mol% (at 3 mmol scale) without impairing the enantioselectivity.

With the optimized reaction conditions in hand, we explored the substrate scope of the chromium(II)-catalysed ketone reduction (Scheme 2): A broad range of *o*- and *p*-substituted aryl methyl ketones was tolerated, furnishing the chiral alcohols in good to excellent yields and enantioselectivities up to 98 %ee (entries **4a**-**i**). In the case of very electron-poor aryl groups, a reduced yield and selectivity was detected, finally leading to no conversion in the extreme case of the C_6F_5 aryl substituent (cf. entry **4l**). Naphthones and aryl alkyl ketones with a linear alkyl chain were converted readily with good to excellent enantiodiscrimination, as were cyclic derivatives (entries **4m**-**s**, up to 96 %ee) as well as heterocyclic substrates, highlighting the potential of the presented method. In addition, the protocol proved useful even in the case of dialkyl ketones, provided that the substituents featured sufficiently dissimilar steric bulk (entries **4v** *vs*. **4w**,**x**).



Scheme 2. Substrate scope of the chromium(II)-catalysed hydrosilylation of ketones. The reactions were performed on a 0.52 mmol scale and all values refer to the isolated products. Selectivities have been determined by chiral HPLC or GC.

A series of control experiments was carried out in order to identify the nature of the elementary steps and the rate-determining kinetics. The activity of the catalyst in the hydrosilylation of acetophenone **3a** remained unaffected by presence of the radical traps triphenylmethane and 9,10-dihydroanthracene, suggesting heterolytic rather than homolytic bond activation and absence of radical intermediates. Similarly, hydrosilylation of acetophenone **3a** using deuterated $(EtO)_2MeSiD$ gave a high degree of D incorporation at the C1 carbon after work-up with K_2CO_3/MeOH and no deuteration of the methyl group (Scheme 3, top). This manifests the role of the silane as the sole hydrogen atom source.



Scheme 3. Deuterium labelling study of the chromium(II)-catalysed reduction of **3a** (top) and determination of the kinetic isotope effect for this reaction by a competitive hydrosilylation experiment (bottom).

The $^1H/^2H$ kinetic isotope effect (KIE) of this transformation was determined in a competitive experiment employing equimolar amounts of hydrosilane and deuterosilane in the chromium(II)-catalysed hydrosilylation (Scheme 3, bottom). From the fraction of the deuterated product, we calculated a significant KIE of k_H/k_D = 1.66, indicating that E-H/D bond scission is a major contribution to the rate-limiting step of the catalytic pathway in this particular derivative (*vide infra*).

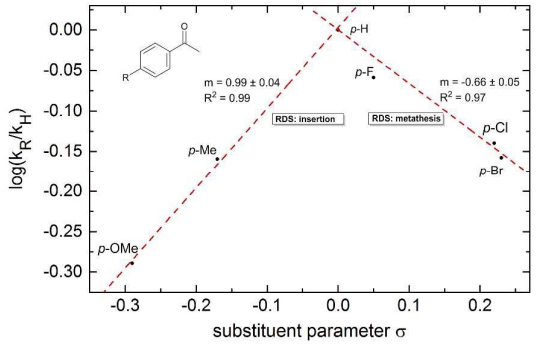


Figure 3. Hammett correlation for the chromium-catalysed hydrosilylation of various *p*-substituted acetophenone derivatives (R = H, F, Br, Cl, Me, OMe). Substituent constant values were taken from reference 14.

Finally, we evaluated the electronic properties of the rate-limiting step by means of a Hammett analysis. Relative reaction rates of six *p*-substituted acetophenone derivates (R = H, F, Cl, Br, Me, OMe) were determined in a competitive experiment by ^{13}C NMR spectroscopy.[15] Interestingly, the Hammett correlation produced a non-linear curve which can be subdivided into two linear segments. For substrates with electron-donating groups the reaction parameter was found to be positive ($\rho = +0.99 \pm 0.04$), which is generally interpreted in

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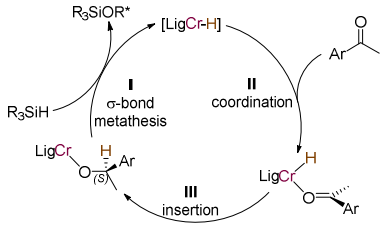
terms of a build up a negative charge in the active complex of the rate-limiting step. In contrast, substrates with electron-withdrawing groups gave rise to a negative reaction parameter ($\rho = -0.66 \pm 0.05$), which can be attributed to build-up of a positive charge in the active complex of the rate-limiting step. The non-linear Hammett correlation with a maximum rate for a derivative with a small Hammett substituent constant is typical of a single mechanism with a change in the rate-limiting step depending on the electronic properties of the substrate. Thus, the positive reaction parameter of the electron-rich derivatives is in accordance with a rate-determining insertion step, whereas the negative reaction parameter of the electron-poor derivatives agrees well with a rate-limiting metathesis process. This is consistent with a deactivation of electron-rich ketones compounds towards hydride insertion and an activation of the corresponding alkoxides with respect to a metathesis step. On the other hand, insertion is expected to be fast for electron-poor ketones, with the metathesis step being decelerated in this case. The hypothesis of a change in the rate-limiting step is also supported by KIE analysis in the two distinct kinetic regimes: compared to acetophenone a somewhat larger KIE is observed for the *para*-bromo derivative (k_H/k_D = 1.78) as opposed to a significantly reduced KIE for a ketone featuring a *para*-methoxy substituent (k_H/k_D = 1.18). The large KIE for σ-bond metathesis is in line with our previous work[6b,g] and we envision that the smaller values for electron-rich ketones can be attributed to a critical associative formation of a chromium-hydride ketone complex (*vide infra*) in the rate-determining step.



Scheme 4. Mechanistic proposal for the chromium(II)-catalyzed hydrosilylation of ketones.

Based on these initial mechanistic experiments presented herein and our previously reported results in the related iron(II)- and manganese(II)-catalyzed hydrosilylations, we propose a catalytic cycle consisting of three critical steps (Scheme 4):[6b,e,7a] After activation of the chromium(II) alkyl precatalyst and formation of a hypothetical Cr(II)-H species, ketone coordination (I) and insertion into the Cr-H bond (II) occurs. Subsequent σ-bond metathesis regenerates the hydride and releases the product (III). This proposed direct hydride transfer pathway is consistent with labelling- and Hammett correlation studies as well as the absence of radical intermediates.

In conclusion, we have designed and isolated the first chromium(II)-based precatalyst for the highly enantioselective hydrosilylation of a broad range of ketones containing various functional groups. This work emphasizes the application of chromium in enantioselective catalysis besides the NHK reaction. Further investigations towards the extension of this catalyst to other substrates and additional studies of the reaction mechanism are currently underway in our laboratories.

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Conflicts of Interest

There are no conflicts to declare.

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