Mild complexation protocol for chiral Cp⁻Rh and Ir complexes suitable for \textit{in situ} catalysis †

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A practical complexation method for chiral cyclopentadienyl (Cp⁻) iridium and rhodium complexes is described. The procedure uses the free CpH with stable and commercially available rhodium(I) and iridium(I) salts without base or additive. The conditions are mild and do not require the exclusion of air and moisture. A salient feature is the suitability for \textit{in situ} complexations enhancing the user-friendliness of Cp⁻ ligands in asymmetric catalysis. DFT-calculations confirm an intramolecular proton abstraction pathway by either the bound acetate or methoxide. Furthermore, the superior facial selectivity of the proton abstraction step enabled the development of TMS-containing trisubstituted Cp⁻ ligands which display improved enantioselectivities for the benchmarking dihydroisoquinolone synthesis.

Introduction

Cyclopentadienyl (Cp) coordinated transition-metal complexes are a very important class of catalysts enabling a broad range of versatile and atom-economic transformations. During the last decade, the dominance of Cp and Cp* (pentamethylcyclopentadienyl) has been challenged by new designer Cp ligands. Modulation of the electronic and steric properties of the Cp ligands has become a key focus for reaction optimization. These ligands display superior performance such as enhanced reactivity, improved regioselectivity and diasteroselectivity. Moreover, the rise of chiral Cp ligands (Cp⁻) enabled the development of enantioselective processes.

While the synthesis of simple classical Cp⁻ and Cp complexes with late transition-metals is well established, accessing the corresponding metal Cp complexes of more elaborate – especially chiral – Cp derivatives remains problematic and suffers from a number of undesirable attributes (Fig. 1). For instance, the increased value of tailored cyclopentadienes requiring multi-step syntheses imposes the use of the CpH derivative as the limiting reactant, making protocols that use multiple CpH equivalents prohibitively inefficient. A frequently largely reduced crystallinity and/or enhanced solubility limit purification options of reaction mixtures from suboptimal reaction outcomes. Until now, the most reliably and broadly applicable method involves the use of stoichiometric amounts of highly toxic thallium bases, often paired with toxic benzene as solvent. Alkali bases were inferior and caused often complex reaction outcomes. A complementary method used chloride based metal salts without a base. The released hydrochloric acid during the complexation is incompatible with some sensitive functional groups of designer Cp scaffolds. We have developed a complementary complexation strategy capitalizing on β-carbon elimination of cyclopentadienyl carbinols as Cp-ligand precursors. While this method consists of an improvement, it requires the synthesis of the ligand precursor.

Fig. 1 Characteristics and drawbacks of complexation strategies for cyclopentadienyl ligands.
by an additional synthetic step. Moreover, it is limited to highly substituted and hindered Cp variants. In consequence, the development of a robust and general complexation platform for a broad range of tailored chiral Cp ligands remains an important task in improving utility and user friendliness of the resulting Cp metal catalysts.

Herein, we report a mild and convenient method to access key Rh(i) and Ir(i) Cp complexes upon simply mixing a stable and easily accessible metal precursor with CpH in protic solvents. The protocol qualifies as well for user friendly in situ catalyst assembly.

Results and discussion

We started our investigations towards a mild and general complexation with cyclopentadiene 1a. A set of common rhodium precursors was screened for reactivity under a variety of conditions and additives (Table 1). The common [Rh(cod)Cl]2 did not react at all (entries 1 and 2). As well, no reaction was observed for [Rh(cod)OAc]2 in toluene (entry 3). In contrast, running the reaction in methanol produced the desired Cp complex 2a in modest yield (entry 4). Switching the rhodium source to [Rh(cod)OMe]2 resulted in a fast and clean conversion yielding 2a in 88% yield (entry 5). Ethanol and TFE proved to be as efficient as methanol (entries 6 and 9), whereas bulkier alcohols display largely decreased reaction rate and yields (entries 7 and 8). HFIP mainly led to degradation (entry 10). The use of THF as solvent completely inhibited the reaction (entry 11). Notably, the complexation protocol works as well very smoothly for penta-substituted Cp** substrate (2l). Such true chiral Cp* analogues have been so far refractory substrates for complexation, hampering application in catalysis. Previously, any classical complexation methods failed for this substrate, making β-carbon elimination strategy from tert-carbinols the only viable method. Importantly, the illustrated complexation strategy is equally viable to access the corresponding Cp*Ir complexes. The complexation employing commercially available [Ir(cod)OMe]2 complex provided the

Initially, a variety of achiral cyclopentadiene substrates were tested (Scheme 1). For instance, tBu2CpH, Me2CpH and Cp**H participated in a smooth and rapid complexation, giving the desired CpRh(cod) complexes 2b–2d in excellent yields. Solely, bulky and electron-deficient Ph2CpH required longer reaction time and gave reduced yields of 2e. With the observed success for the achiral Cp ligands, we have successfully tested the complete portfolio of the most useful chiral Cp ligands for this transformation. In detail, mannitol-derived Cp ligand 2a** was isolated in 85% yield. The mild conditions at ambient temperature were compatible with the acetal group. Similarly, readily accessible cyclopentane-fused cyclopentadiene 1f and the most versatile methoxy-bearing Cp**H 1g** engaged in complexations giving 2f and 2g in very high yields. Moderate solubility of the Cp**H 2g required some heating. Bulkier isoproxy-derivative (2h) reacts at ambient temperature, whereas substrates with larger groups (2i–2j) require gentle heating for optimal reactivity without compromising the high yield. Bulky tri-substituted cyclopentadiene 1k gave corresponding complex 2k in significantly improved yields compared to the thallium-process. Notably, the complexation protocol works well as very smoothly for penta-substituted Cp** substrate (2l).

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Rh]</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>[Rh(cod)Cl]2</td>
<td>toluene</td>
<td>&lt;5</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(cod)Cl]2</td>
<td>MeOH</td>
<td>&lt;5</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
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<td>toluene</td>
<td>&lt;5</td>
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</tr>
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<td>28</td>
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<td>0</td>
</tr>
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</table>

* Conditions: 40 μmol 1a, 24 μmol [Rh], 0.2 M in indicated solvent at 23 °C for 60 min. † Determined by 1H-NMR with an internal standard. ‡ Partial cleavage of the acetal (30%) was observed.

Scheme 1 Conditions: 0.1 mmol 1x, 0.06 mmol [Rh(cod)OAc]2 or [Ir(cod)OMe]2 in toluene/MeOH (1:1) (0.2 M) at 23 °C. (a) 0.4 mmol 1x, 0.1 mmol [Rh(cod)OAc]2; (b) 24 h; (c) 70 °C; (d) [Ir(cod)OMe]2 instead of [Rh(cod)OAc]2.
desired complexes (3a, 3f-3g) in good yields. Compared to illustrate examples with rhodium, the complexation is slower with iridium and requires gentle heating. For more reluctant cases, the reaction can be performed with more reactive [Ir(cod)OAc]₂, which is prepared in a single step from [Ir(cod)Cl]₂.¹²

To foster further understanding of the mechanism of complexation, DFT computations (at the PBE0-dDSc/TZ2P//M06/def2-SVP theoretical level, see ESI for computational detail) of different possible pathways were performed.¹³ Two potential pathways exist, which involve reactions of pentamethylcyclopentadiene with either a Rh(OAc) (pathway A, Scheme 2) or alternatively a Rh(OMe) (pathway B, Scheme 2) fragment. Each pathway begins with the thermodynamically favorable cleavage of the solvated Rh(cod)OAc dimer (as determined from the crystal structure)¹⁴ to form a Rh(cod)(OAc)(MeOH) monomer (Int1). From this point the two pathways diverge. Methanol can either be directly dissociated in process endergonic process costing ~12 kcal mol⁻¹ (Int1 → TS1, pathway A). Int2 then forms reaction complex Int3 in the presence of the Cp*-

![Pathway A](image)

![Pathway B](image)

**Scheme 2** Potential reaction profiles proceeding form the [Rh(COD)OAc]₂ to RhCp*(COD). Each of the reaction pathways is characterized by roughly similar energetic profiles. Computations at the PBE0-dDSc/TZ2P//M06/def2-SVP level (see ESI for details).
very close in energy (+24.1 vs. +23.8 kcal mol⁻¹) and maybe both accessible under the mild reaction conditions utilized. Since the transformation works cleaner and in higher yields with [Rh(cod)OAc]₂ compared to [Rh(cod)OMe]₂ (which would only allow for pathway B), involvement of pathway A is assumed. Alternatively, the better solubility and potentially easier dimer of [Rh(cod)OAc]₂ may account for the superiority of this precursor complex.

Besides the illustrated practical utility of the complexation strategy, our method offers two significant additionally advances. First, it enables new opportunities in complex ligand design previously unfeasible substitutions. Secondly, the facile complexation allows for the first time true in situ complexation and catalysis. In our attempt to pursue the concept of late-stage diversification and adjustability of the steric demand of a common ligand platform, we found that deprotonation of Cp³H with BuLi and subsequent trapping with TMSCl uniformly provided a single regio- and diastereomer (Scheme 3). X-Ray crystal structure analysis of intermediate 1m confirmed that the TMS group occupies the position off the C₂-symmetry axis of 1a at the more accessible face (See ESI†).

However, complexation of non-C₂-symmetric ligands poses inherent selectivity issue due to a notoriously difficult facial discrimination in the complexation step of the flat Cp anion. In consequence, the typical thallium ethoxide complexation method is not suitable due to its lack of facial discrimination of the deprotonation. This results in inseparable mixture of diastereoisomers. Along the same lines, chloride containing rhodium salts mainly resulted in desilylated complexation stereoisomers. Along the same lines, chloride containing rhodium salts mainly resulted in desilylated complexation of alkene ligands on the metal (axis with respect to the chiral selector backbone). Consequently, on a substrate bound to the metal, the small fragment (Rsmall) would minimize the interactions with the TMS function, while the bulkier part (Rlarge) would stay in the open area of the Cp*. The bulk of the silyl group forces an orientation closer to the chiral selector which

The proximity of the bulky trimethylsilyl group to the steering pseudoaxial methyl group of 3m leads to extended side-walls. Comparison of the X-ray crystal structures of 3a (3d) and 3m visualizes well the enhanced shielding caused by the installed ligand feature (Fig. 2). While the TMS group slightly influences the chiral backbone, it has a profound effect on the orientation of alkene ligands on the metal (axis with respect to the chiral selector backbone). Consequently, on a substrate bound to the metal, the small fragment (Rsmall) would minimize the interactions with the TMS function, while the bulkier part (Rlarge) would stay in the open area of the Cp*. The bulk of the silyl group forces an orientation closer to the chiral selector which

Scheme 3 Regio- and diastereoselective silylation yields trisubstituted Cp* ligands 1m–1o.

Fig. 2 Overlay of the X-ray crystal structures reveals the influence of the TMS group on the axis of the olefin ligand (faint blue: parent Cp*-complexes without TMS group).
could result in an enhanced interaction and improved discrimination. Hence, the introduction of the TMS as extended side wall could help pre-organization around the metal center thus improving enantio- and regioselectivity compared to the parent ligand.

The performance of complex 2m was benchmarked in the enantioselective dihydroisoquinolinone synthesis.\(^\text{18}\) Compared to the previously best performing catalyst (having the diphenyl acetal which is cumbersome to access), an equivalent selectivity was obtained for styrene as the coupling partners (Scheme 5). Dihydroisoquinolinone 6b, a precursor for chiral 1,3,2-diazaphospholenes,\(^\text{19}\) was obtained in 80% yield with high 93 : 7 er. Importantly, a significant selectivity improvement was observed in reactions with challenging cyclic olefins. Complex 2m outperformed all previously reported complexes.\(^\text{20,21}\) Reaction with 1,3-cyclohexadiene afforded 6c in 95 : 5 er (91.5 : 8.5 previously). Similarly, reactions with cyclopentene and dihydrofuran-5-one gave 6d (95 : 5 er) and 6e (97 : 3 er) in significantly improved enantioselectivity. Notably, norbornene reacted with an excellent selectivity of 99 : 1 er, outperforming Perekalin’s planar enantioselectivity. Notably, norbornene reacted with an excel-

Scheme 5 Conditions: 0.1 mmol 4, 0.2 mmol 5, 5 µmol 2m, 5 µmol (BzO)₂ in EtOH (1 M) at 23 °C.

The development of protocols for an in situ complexation, meaning the addition of the Cp²H ligand (or a suitable surrogate) and the metal salt altogether with the substrates and additives for the desired catalysis is a high priority, due to its simplicity and accessibility to non-specialists. The outlined complexation has several advantageous characteristics. It proceeds sufficiently fast in almost quantitative manner under mild conditions. The only generated by-products are either catalytic amounts of alcohols (common solvents) or carboxylic acids. In particular for rhodium(III)-catalyzed functionalization, carboxylic acids or carboxylates are frequently added additives that are essential for reactivity.\(^\text{22}\) We examined four different benchmark reactions for their in situ complexation suitability (Scheme 6). For instance, the enantioselective formation of dihydroisoquinolone 6a by the in situ approach proceeded in comparable yield and enantioselectivity compared to the usage of the preformed Cp²-rhodium catal-

Scheme 6 Application of in situ Cp²Rh-catalyst assembly under different benchmark reactions. Ar = 3,5-CF₃-C₆H₃, R = CH(iPr)₂.
Conclusions

In summary, we disclosed a convenient and general complexation method to access chiral Cp* iridium and rhodium complexes. The method has large advance over previous methods as it uses the free Cp*H in combination with stable and commercial rhodium(i) and iridium(i) salts without the addition of base or any additive. Moreover, the conditions are mild and the reactions can be conductive without precautions to exclude air and moisture. DFT-calculations revealed two potential pathways with a low energy barrier in which either a bound methoxide or acetate is involved in an intramolecular proton abstraction of the coordinated cyclopentadiene. Moreover, the selectivity and mildness of the complexation method enabled the development of new TMS-containing Cp* ligands which displayed superior selectivity for benchmarking dihydroisooquinolone synthesis. Another salient feature is its suitability for in situ complexation which significantly enhances the user-friendliness of Cp* ligands. This holds the potential to open the versatile catalytic application with designer ligands to a broader community.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

17 CCDC 1869889 (3a), CCDC 1869894 (1m), CCDC 1869888 (3m) and CCDC 1869893 (3o) contains the supplementary crystallographic data for this paper.†