doi:10.2533/chimia.2017.186 Chimia 71 (2017) 186–189

Chiral Cyclopentadienyl Ruthenium Complexes as Versatile Catalysts for Enantioselective Transformations

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[§]SCS-Metrohm Award for best oral presentation in Organic Chemistry

Abstract: Ruthenium complexes, in particular cyclopentadienyl ruthenium (II) derivatives, catalyze a vast number of transformations in the field of homogenous catalysis. Herein we describe the first synthesis of efficient chiral cationic cyclopentadienyl ruthenium (II) catalysts and their application in enantioselective cycloisomerizations yielding 4*H*-pyrans. A tremendous counterion effect on the selectivity was observed and subsequently explored, giving rise to a complementary set of neutral cyclopentadienyl ruthenium (II) complexes able to catalyze asymmetric cyclobutene formations.

Keywords: Asymmetric catalysis · Cycloisomerization · Cyclopentadienyl ligand · Ruthenium

David Kossler *was born in Giessen and grew up in the southwestern part of Germany. He studied chemistry with a focus on organic chemistry and biochemistry at the Ruprecht-Karls University Heidelberg, receiving his Diploma in 2012 under the guidance of Prof. Helmchen, working in the field of iridium-catalyzed asymmetric allylic substitution. Afterwards he joined the group of Prof. Cramer at the Ecole Polytechnique Fédérale de Lausanne to pursue his PhD. In 2017 David will join the Baran group at the Scripps Research Institute, La Jolla as an SNF postdoctoral fellow.*

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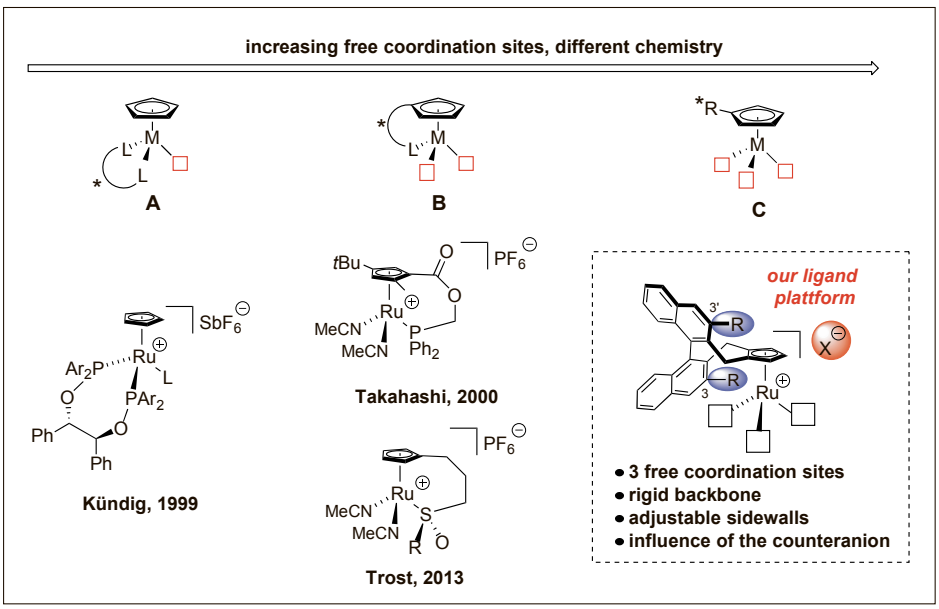
Introduction

The cyclopentadienyl (Cp) ligand and its pentamethyl substituted derivative (Cp*) are important ligands in organometallic chemistry, and complexes with many transition metals are known. In particular, cyclopentadienyl ruthenium (II) complexes catalyze a variety of different transformations.[1] Aside from the Cp ligand, three coordination sites are available in these complexes. To render these catalysts chiral, several approaches are possible (Scheme 1): a) Employment of an exogenous source of chirality, *e.g.* a chiral diphosphine. These catalysts have proven to be very selective chiral Lewis acids in hetero-Diels–Alder reactions.[2] b) A complementary strategy makes use of tethering the Cp to the metal, either inducing planar[3] or point-chirality.[4] Complexes of this type have been predominantly used for allylic substitutions. Both approaches occupy coordination sites, alter the electronic properties of the ruthenium center, and increase the steric bulk around the metal, potentially hampering reactivity. For instance, cycloisomerizations represent a cornerstone of ruthenium-catalyzed reactions and often require three available coordination sites at the metal center for turnover, excluding the aforementioned strategies. A suitable catalyst requires the Cp ligand as the only source of chirality.



Scheme 1. Different approaches to chiral CpRu(II) complexes.

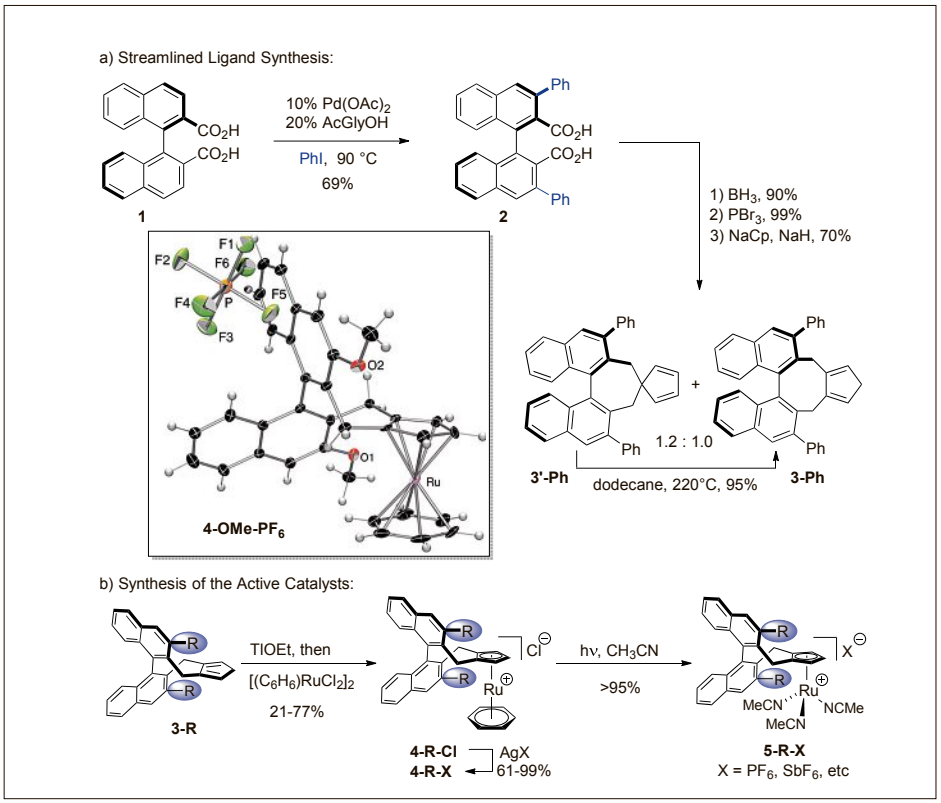
Our group has a longstanding interest in the development of chiral cyclopentadienyl ligands (termed Cp^x).[5] Although initially designed for rhodium-catalyzed C–H functionalizations,[6] the Cp^x ligand family derived from (*R*)-BINOL has proven to also be successful in iridium-catalyzed processes.[7] Herein we describe the development of Cp^{x}Ru(II) catalysts, incorporating the same rigid backbone derived from (*R*)-BINOL with adjustable sidewalls (R) as handles to fine-tune the catalyst. Furthermore, as CpRu(II)$^+$ is a cationic fragment, the corresponding counterion represents another modifiable parameter to modulate the catalytic properties.

Results and Discussion

Ligand Synthesis and Complexation

Recently, we reported an improved synthesis of the Cp^x ligand required for the transformations shown in this work (Scheme 2a).[8] Starting from *bis*-carboxylic acid **1**, we took advantage of recent developments in *ortho*-directed C–H activation,[9] allowing the installation of two phenyl groups. Reduction of carboxylic acid **2** and subsequent substitution yielded the corresponding benzylbromide. The Cp moiety was attached to yield ligand **3-Ph**. Spiro isomer **3'-Ph** was thermally isomerized to the desired fused derivative.

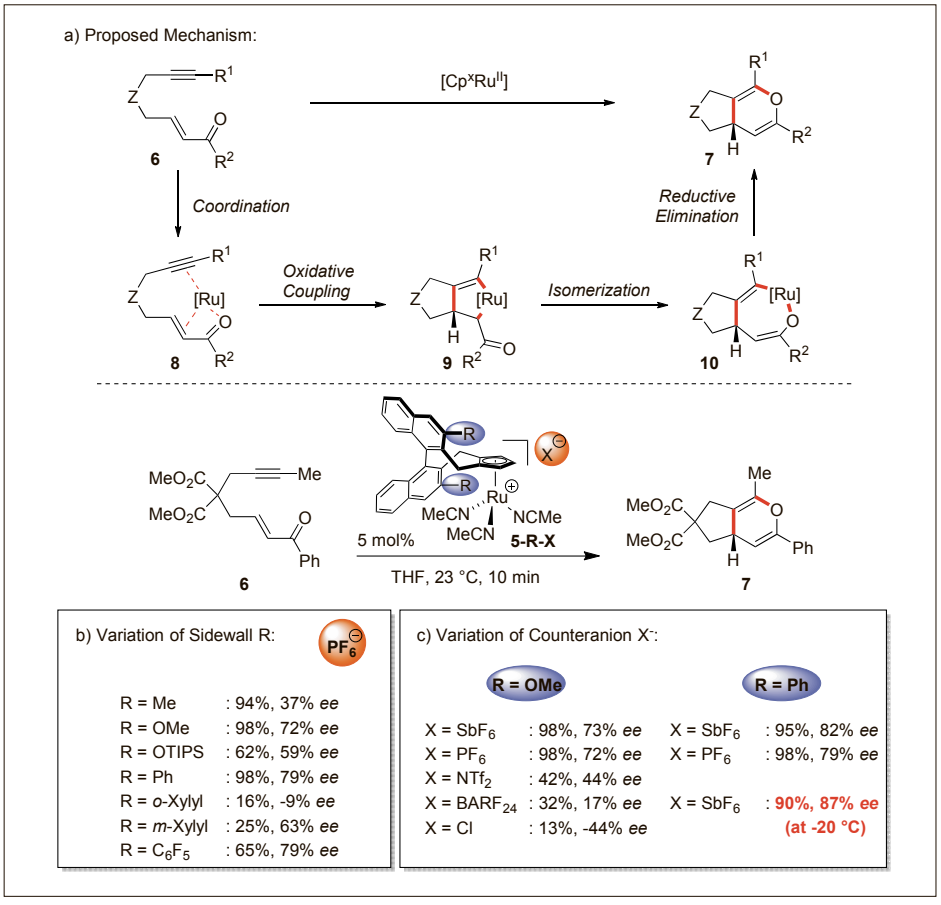
With a set of ligands, varying at the substituent R, the complexation to the ruthenium metal was performed (Scheme 2b).[10] The resulting chloro-complexes **4-R-Cl** are air- and moisture-stable. The counterion was exchanged *via* salt-metathesis. UV light promoted decomplexation of benzene in acetonitrile was carried out giving trisacetonitrile complexes **5**. These labile ligands are readily substituted by the substrate during a desired catalytic reaction. The designed shielding of one side of the metal is evident in the crystal structure of **4-OMe-PF$_6$**, depicted in Scheme 2.



Scheme 2. Synthesis of Cp^x-ruthenium(II) complexes.

Enantioselective 4H-Pyran Formation

In order to benchmark these newly synthesized catalysts **5**, we applied them in a formal [4+2] cycloaddition of yne-enones **6** to produce valuable chiral pyrans **7**. A racemic reaction was reported by Trost.[11] According to the proposed mechanism and experimental evidence, all three coordination sites are required in the catalytic cycle, as it involves the isomerization of a carbon-bound to an oxygen-bound ruthenium enolate (**9** to **10**, Scheme 3a).



Scheme 3. Optimization of the enantioselective pyran formation.

The transformation proceeds rapidly at room temperature. The effect of different ligands were evaluated after a reaction time of 10 min (Scheme 3b). A small methyl group (R = Me) gave a high yield but a low enantiomeric excess of only 37% *ee*, indicating insufficient shielding of one side of the catalyst. Switching to a more sterically demanding OMe group improved the enantioselectivity to 72% *ee*. However, increasing the size of the sidewall further led to substantial loss in re-

activity and selectivity (**5-OTIPS-PF$_6$**). A phenyl group was the optimal choice, maintaining a high yield and enhanced the enantioselectivity to 79% *ee*. In order to further optimize this lead catalyst structure we synthesized derivatives bearing substituted phenyl groups, and large influences on both reaction parameters were found. Surprisingly, *ortho*-substituents rendered the catalyst almost unreactive and unselective (**5-*o*-Xylyl-PF$_6$**). *Meta*-substitution delivered a moderately selective catalyst but the steric bulk lowered the efficiency (**5-*m*-Xylyl-PF$_6$**). By fluorinating the phenyl ring an electronic effect was anticipated, however only a slightly diminished yield of the pyran product was observed.[10]

With the two best performing ligands (R = OMe and R = Ph), the influence of the counterion was investigated next (Scheme 3c). Triflimide and BARF$_{24}^-$ anions were detrimental to the catalyst performance. Surprisingly, the covalently bound chloride anion delivered the opposite enantiomer of pyran **7**. The hexafluoroantimonate counterion (**5-OMe-SbF$_6$**), surpassed the parent PF$_6^-$ bearing catalyst. The counterion effect translated well to the phenyl ligand (**5-Ph-SbF$_6$**) increasing the enantiomeric excess to 82% *ee*. Lowering the reaction temperature to –20 °C increased the enantioselectivity further, and gave 87% *ee*, highlighting the superb reactivity of the Cp^{x}Ru(II) system.

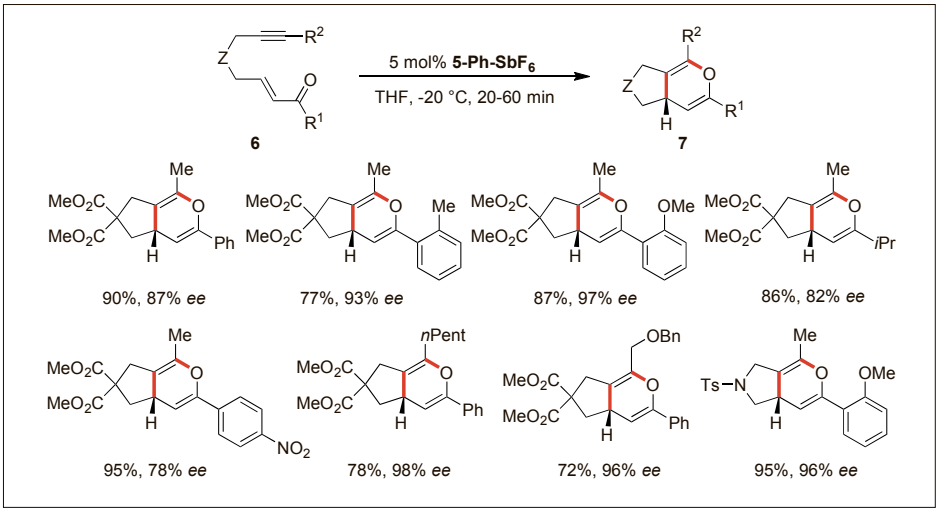
The scope of the cycloaddition was found to be rather broad. Substituted aromatic groups in position R^1 were well tolerated, giving mostly enantioselectivities above 90% *ee*. Alkyl groups reacted with no substantial loss of enantioselectivity. With regards to alkyne substitution, both linear alkyl chains as well as more functionalized groups, displayed exceedingly high selectivities. Replacing the malonate tether with a tosylamide group had no influence on the reaction outcome (Scheme 4).

Enantioselective Cyclobutene Formation

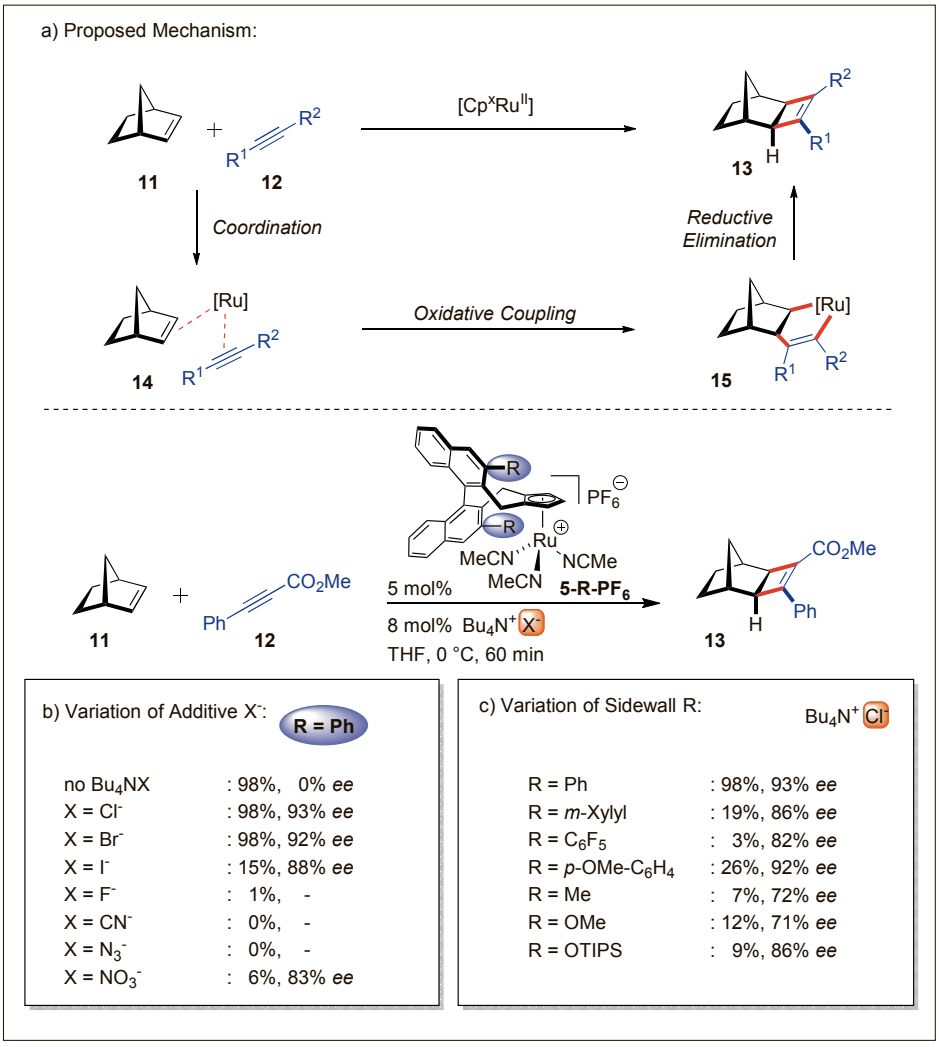
The impact of different counteranions on reactivity and selectivity prompted us to investigate this effect further, with particular emphasis on covalently bound anions, like chloride, thus obtaining a chiral congener of the well-established Cp*Ru(COD)Cl catalyst (COD = cyclooctadiene). These neutral CpRu(II) type complexes represent another major class of homogenous ruthenium catalysts, disclosing a broader spectrum of potentially applicable reactions.[12]

We selected a ruthenium-catalyzed formal [2+2] cycloaddition of strained bicyclic alkenes **11** with internal alkynes **12** yielding chiral *exo*-cyclic cyclobutenes **13**, as an attractive benchmark reaction (Scheme 5a).[8] This scaffold enables rich follow-up chemistry based on the inherent ring strain of the products.[13] The transformation is well investigated with the Cp*Ru(COD)Cl catalyst,[14] but no enantioselective ruthenium-catalyzed version has been known. The proposed mechanism commences with the coordination of the alkene **11** and an unsymmetrical substituted alkyne **12** to the ruthenium catalyst, followed by an enantio-determining oxidative cyclization. In contrast to the earlier described pyran formation no isomerization occurs at this stage, but instead reductive elimination furnishes cyclobutene **13**.

Initial optimization revealed that propiolates are suitable substrates. The reaction proceeds rapidly in THF at 0 °C with only a slight excess of norborene. To evaluate



Scheme 4. Scope for the enantioselective pyran formation.

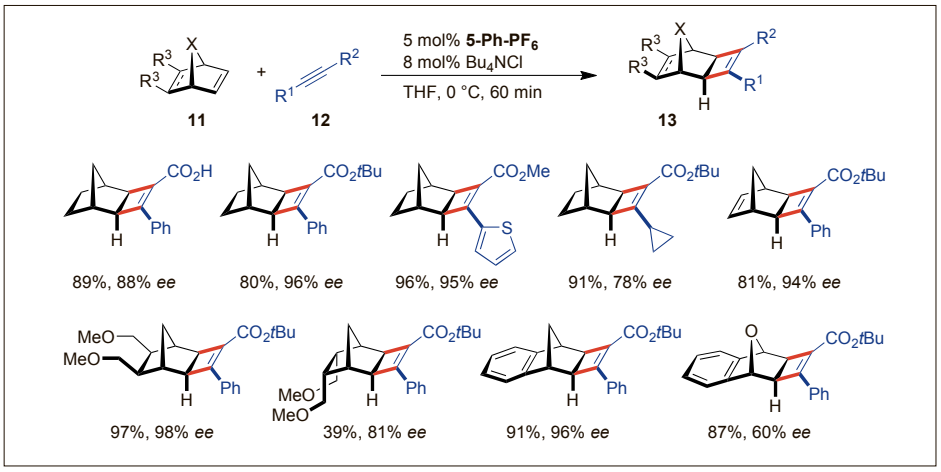


Scheme 5. Optimization of the enantioselective cyclobutene formation.

counterion effects, we premixed a catalyst bearing a weakly coordinating counterion (**5-Ph-PF$_6$**) with the tetrabutylammonium salt of a given strongly coordinating anion (Scheme 5b).[15] The *in situ* exchange to form the corresponding neutral [RuX] species occurs within seconds, and can be followed by the formation of a deep red solution. When no additive was employed, the cationic complex **5-Ph-PF$_6$** produced **13** cleanly, however, in racemic form. Remarkably, addition of chloride delivered cyclobutene **13** with an excellent enantiomeric excess of 93% *ee*. Consequently, the other halides were examined. Bromide led to a competent catalyst of similar performance, while iodide diminished the yield of **13**. Fluoride and pseudohalides acted as catalyst poisons. With chloride as the optimal additive, the ligand substituents R were re-evaluated (Scheme 5c). The phenyl group (R = Ph) once again proved to be superior to other Cp^x ligands, particularly in terms of efficiency, underpinning the privileged structure of this particular scaffold for Cp^{x}Ru(II) catalysis.

The generality of the reaction was then explored (Scheme 6). On the alkyne substituent R^2, a free propiolic acid was tolerated, but esters gave higher enantioselectivities. In addition to phenyl substituents, heteroaromatic systems and alkyl residues can be used at R^1. For the alkene component, the norbornene derivatives showed a strong influence of spatial substitution, with the *exo*-substrate giving virtually quantitative yield and excellent 98% *ee*. An oxygen bridge was tolerated, however this reduced the enantioselectivity.

Norbornadiene (nbd) delivered the expected cyclobutene product. In addition ruthenium complex **14** was isolated (Fig. 1). Nbd coordinates to the ruthenium center as a bidentate ligand and **14** is believed to be the resting state of the catalyst. Structurally, chloride occupies a position under the naphthyl-backbone. The enantioselection of the formal [2+2] reaction can be rationalized with the structure of complex **14**. With the cationic Cp^{x}Ru(II) complexes having three coordination sites available, one alkene and two alkynes can coordinate simultaneously. A random insertion of one alkyne leads to a racemic product. With the neutral [Cp^{x}RuCl], one coordination site is occupied by chloride, and only a single alkyne and alkene can coordinate at once. These two coordination sites are sterically different, allowing for a highly ordered transition state. The recovered neutral catalyst **14** can be reused for subsequent transformations, giving the same enantioselectivity with no need for addition of a chloride source. The trapping procedure with nbd turned out to be general and reactions with other alkenes can be quenched with norbornadiene after complete conversion, facilitating the isolation of approximately 40% of the employed ruthenium catalyst.



Scheme 6. Scope for the enantioselective cyclobutene formation.

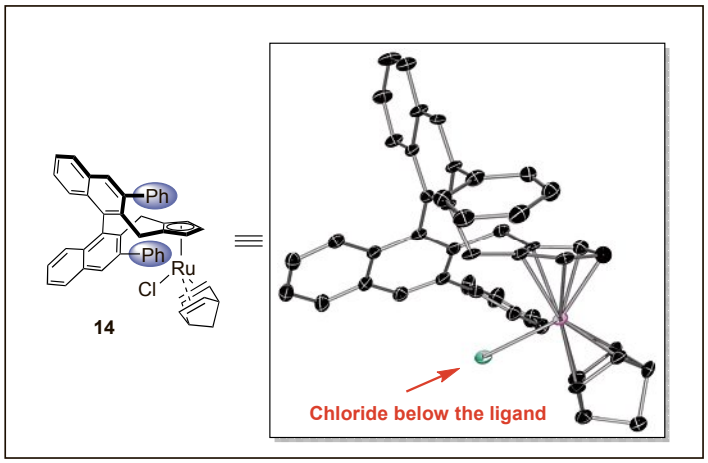


Fig. 1. ORTEP representation of complex **14**.

Conclusions

A new set of chiral Cp^{x}Ru(II) complexes were introduced, mimicking the versatile CpRu(MeCN)$_3$PF$_6$ catalyst. Excellent enantioselectivities were obtained for a cycloisomerization yielding 4*H*-pyrans. In addition, we streamlined the synthesis of the best performing Cp^x ligand utilizing a C–H functionalization approach. A counterion effect was explored leading to a class of neutral Cp^{x}RuCl(II) catalysts, competent for asymmetric formal [2+2] cycloadditions. A method for catalyst recovery employing norbornadiene allows the recycling of the precious ruthenium complexes.

Acknowledgments

David Kossler is grateful to Metrohm and the Swiss Chemical Society for being awarded with the SCS-Metrohm best oral presentation award. We thank the Ecole Polytechnique Fédérale de Lausanne for financial support.

Received: February 3, 2017

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