Communication

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Chiral Cationic Cp^{x}Ru(II) Complexes for Enantioselective Yne-Enones Cyclizations

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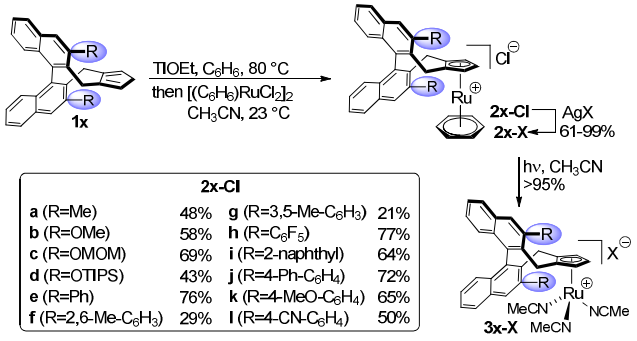
Supporting Information Placeholder

ABSTRACT: The cyclopentadienyl (Cp) group is a ligand of great importance for many transition-metal complexes used in catalysis. Cationic CpRu^{II} complexes with three free coordination sites are highly versatile catalysts for many atom-economic transformations. We report the synthesis of a family of Cp^{x}Ru^{II} complexes with chiral Cp ligands keeping the maximum number of available coordination sites. The cationic members are efficient and selective catalysts for enone-yne cyclizations *via* formal hetero-Diels-Alder reactions. The illustrated transformation proceeds in less than one hour at -20°C and provides pyrans in enantioselectivities of up to 99:1 er. Unsaturated ester or Weinreb-amide substrates directly yield the iridoid skeleton.

The cyclopentadienyl (Cp) ligand is of fundamental importance for organometallic chemistry and as such found in countless transition-metal catalysts.[1] For instance, CpRu^{II} and Cp*Ru^{II} fragments are established powerful catalysts enabling many synthetically versatile and atom-economic transformations.[2] In contrast to other ligand classes, chiral Cp^x ligands enabling enantioselective transformations lag behind.[3] When the transformation does not require all three coordination sites of the Ru(II)-based catalyst, enantioselective reactions are achieved by employing a tethering strategy[4] or an exogenous source of chirality.[5] This enhanced transmission of stereochemistry comes at the expense of a reduced number of available coordination sites on the ruthenium center. However, a significant number of cationic CpRu^{II} catalyzed reactions need all three coordination sites for functionality.[2] Hence, a tethering approach fails to produce a reactive catalyst, thus requiring the design of chiral Cp^x ligand backbones. We recently developed two chiral Cp^x ligand systems[6] showing good performance for Rh^{III}-catalyzed enantioselective C-H functionalizations of aryl hydroxamates.[7-8] Further exploration of these ligands as steering element on Ru complexes would be a major step to close the gap in asymmetric Ru-catalysis. Herein, we report the preparation of chiral Cp^{x}Ru^{II} complexes and demonstrate their potential in enantioselective cyclizations giving chiral pyrans.

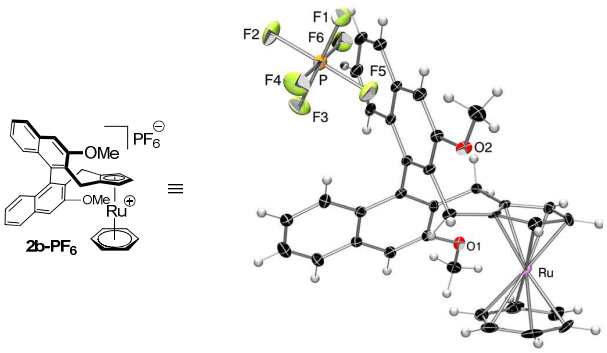
The first hurdle of using chiral Cp ligand scaffolds in Ru-catalysis consisted in the securing access to the corresponding complexes by a reliable preparative method. The majority of synthetic methods for the targeted piano-stool CpRu complexes require a large excess of the corresponding cyclopentadiene precursor.[9] While this is tolerable for CpH and Cp*H, it is prohibitive for the more complex chiral Cp^x ligands. Despite many attempts, Mann's protocol using CpTl,[10] which was used as well for the synthesis other chiral Cp ruthenium(II) complexes,[3n] proved to be the best method (Scheme 1). The use of [(C_6H_6)$RuCl_2$] instead of the more common [(cymene)$RuCl_2]_2$ reduced the formation of undesired ruthenocene byproducts and provided in moderate to good yields of complexes **2aCl-2lCl**. At this stage, the chloride ion could be exchanged by salt metathesis for any desired anion, mainly for very weakly coordinating anions such as PF_6^- or SbF_6^-. Crystallized arene complex **2b-PF$_6$** showed the expected geometry with a good shielding from the chiral Cp^X ligand (Figure 1).[11] Subsequently, the cationic complexes were dissolved in acetonitrile and photolyzed under ambient conditions, inducing a decomplexation of the benzene ligand in exchange for three acetonitrile molecules. Complexes **3** are in their solid state stable orange powders.

Scheme 1. Synthesis of the chiral Cp^{x}Ru^{II} complexes 3.

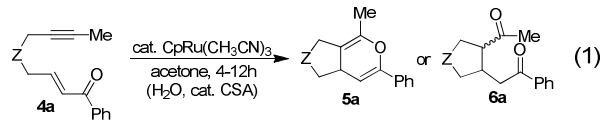


2x-Cl			
a (R=Me)	48%	**g** (R=3,5-Me-C_6H_3)	21%
b (R=OMe)	58%	**h** (R=C_6F_5)	77%
c (R=OMOM)	69%	**i** (R=2-naphthyl)	64%
d (R=OTIPS)	43%	**j** (R=4-Ph-C_6H_4)	72%
e (R=Ph)	76%	**k** (R=4-MeO-C_6H_4)	65%
f (R=2,6-Me-C_6H_3)	29%	**l** (R=4-CN-C_6H_4)	50%

Figure 1. X-ray crystal structure of Cp^{x}Ru(C_6H_6)PF_6 (**2b-PF$_6$**).

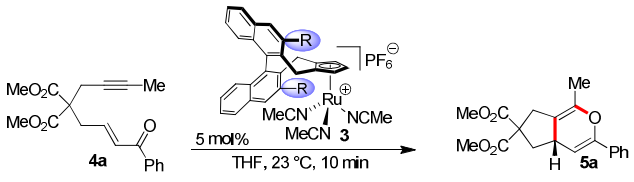


Next, we gauged the potential of these Cp^xRu^{II} complexes in a challenging benchmark transformation. We selected Trost's cyclization reaction of yne-enone **4a** providing 4*H*-pyran **5a** or diketone **6a**, depending upon the reaction conditions (Eq. 1, Z=C($CO_2Me)_2$).[12] The transformation requires all three coordination sites of the ruthenium center and the addition of one equivalent of triphenylphosphine immediately inactivated the catalyst.



We initially evaluated several Cp^xRu^{II} complexes with substrate **4a** (Table 1). The reaction went to completion within 10 minutes at ambient temperature in THF. From the tested PF_6-bearing complexes **3a**-**3l**, 3,3'-methoxy derivative **3b** gave good reactivity and an enantioselectivity of 86:14 (Entry 2), only surpassed by the 3,3'-phenyl congener **3e** with 89.5:10.5 er (Entry 5). Consequently, ligands with different substituted 3,3'-arenes were tested and a tremendous impact on the catalyst performance was found. An *ortho*-substituted arene shut down the reactivity (Entry 6), while *meta*-substitution just slightly diminished the enantioselectivity (Entry 7). The large influence of the substitution at the *para*-position of the arene substituent is noteworthy. A *p*-biphenyl or *p*-methoxyphenyl ligand led to almost complete loss of selectivity (Entries 10 and 11). The *p*-cyanophenyl substitution totally inactivated the catalyst (Entry 12). We speculate that the cyano group of **3l** coordinates to the ruthenium center, abolishing its catalytic performance. Although 2-naphthyl or pentafluorophenyl groups resulted in selectivities comparable to **3e**, they render the complexes somewhat less reactive (Entries 8 and 9).

Table 1. Screening of different Cp^xRu complexes 3[a]

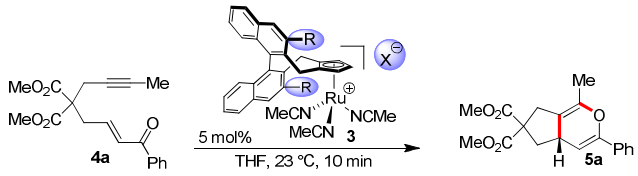


entry	**3-PF_6**	R	conv. (%)[b]	**5a** (%)[b]	er[c]
1	**3a**	Me	100	94	68:32
2	**3b**	OMe	100	98	86:14
3	**3c**	OMOM	18	11	33:67
4	**3d**	OTIPS	67	62	79.5:20.5
5	**3e**	Ph	100	98	89.5:10.5
6	**3f**	2,6-Me-C_6H_3	24	16	45.5:54.5
7	**3g**	3,5-Me-C_6H_3	25	25	81.5:18.5
8	**3h**	C_6F_5	74	65	89.5:10.5
9	**3i**	2-naphthyl	24	22	87.5:12.5
10	**3j**	4-Ph-C_6H_4	35	27	55.5:44.5
11	**3k**	4-MeO-C_6H_4	30	29	45:55
12	**3l**	4-CN-C_6H_4	<5	<5	22.5:77.5

[a] Conditions: 25 µmol **4a**, 1.25 µmol **3**, 0.13 M in THF, 23 °C, 10 min. [b] Determined by ^{1}H-NMR with an internal standard. [c] Determined by HPLC with a chiral stationary phase.

Next, the role of the counterion was evaluated (Table 2). The nature of the anion has a considerable effect on both, the reactivity and the enantioselectivity. The best reactivities were observed with PF_6^- and SbF_6^- (Entry 1 and 2). Triflimide and the $BARF_{24}$ anion were less reactive and selective (Entry 4 and 5). Surprisingly, the complex with a covalently bound chloride gave the opposite enantiomer of **5a** in 28:72 er, although with significantly reduced reactivity (Entry 6), requiring four hours for the reaction to go to completion (Entry 7). At present, the underlying effect of this reversed selectivity is not clear and subject to more detailed investigations. The observed trend in selectivity translated to the more selective phenyl-bearing complex **3e**. With the SbF_6^- anion, a slightly higher enantioselectivity of 91:9 was obtained (Entry 8). Conducting the cyclization at -20°C for 1 h increased the selectivity further and provided **5a** in 90% yield and 93.5:6.5 er (Entry 9).

Table 2. Counterion effect on the selectivity[a]

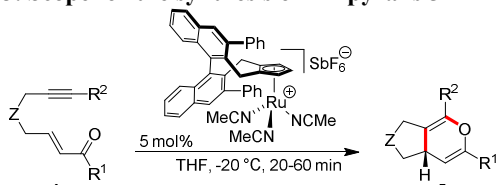


entry	R	X	conv. (%)[b]	**5a** (%)[b]	er[c]
1	OMe	PF_6	100	98	86.5:13.5
2	OMe	SbF_6	100	98	86:14
3	OMe	BF_4	29	22	30.5:69.5
4	OMe	NTf_2	42	42	72:28
5	OMe	$BARF_{24}$	35	32	58.5:41.5
6	OMe	Cl	13	13	28:72
7[d]	OMe	Cl	100	80	30.5:69.5
8	Ph	SbF_6	100	95	91:9
9[e]	Ph	SbF_6	100	90[f]	93.5:6.5

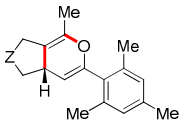
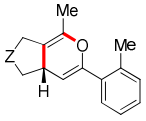
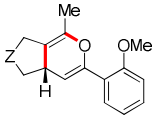
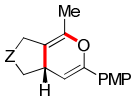
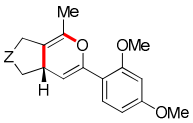
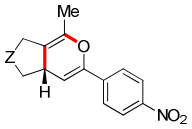
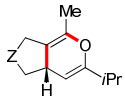
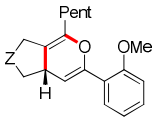
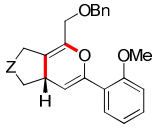
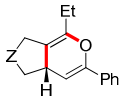
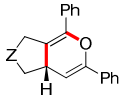
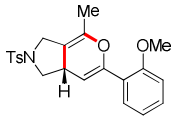
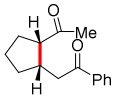
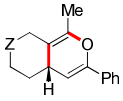
[a] Conditions: 25 µmol **4a**, 1.25 µmol **3**, 0.13 M in THF, 23 °C, 10 min. [b] Determined by ^{1}H-NMR with an internal standard. [c] Determined by HPLC with a chiral stationary phase. [d] for 4 h. [e] 0.1 mmol scale at -20°C for 1 h. [f] isolated yield.

The scope for the enantioselective ruthenium-catalyzed pyran formation was subsequently established with the aforementioned optimized conditions (Table 3). A variety of arene groups R^1 are tolerated and provide the cyclized product **5** in good yields and selectivities (Entries 1-6). Besides arenes, the reaction retains most selectivity with R^1 being an alkyl group (Entry 7). The substituent R^2 can be changed for longer or functionalized alkyl chains keeping the good reaction characteristics (Entries 8-10). A phenyl group in this position slightly reduces the selectivity and requires a reaction temperature of 0°C (Entry 11). Moreover, the malonate tether could be replaced without loss of selectivity by a NTs group (Entry 12) or by a simple methylene bridge (Entry 13). Pyran **5n** is very labile and was therefore hydrolyzed to diketone **6n** for isolation. A larger tether reduced the reaction performance with the current catalyst (Entry 14).

Table 3. Scope for the synthesis of *4H*-pyrans 5[a]



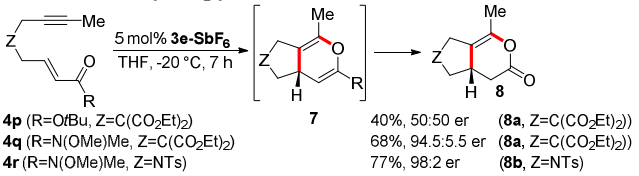
entry	**4**	**5**	yield (%)[b]	er[c]

1[e]	**4b**	**5b**		71	97:3
2	**4c**	**5c**		77	96.5:3.5
3	**4d**	**5d**		87	98.5:1.5
4	**4e**	**5e**		86	91:9
5	**4f**	**5f**		94	98.5:1.5
6	**4g**	**5g**		95	89:11
7	**4h**	**5h**		86	91:9
8	**4i**	**5i**		78	99:1
9	**4j**	**5j**		72	98:2
10	**4k**	**5k**		53	95.5:4.5
11[d]	**4l**	**5l**		95	82:18
12	**4m**	**5m**		95	98:2
13	**4n**	**6n**		90 (7.5:1 dr)	95.5:4.5
14[f]	**4o**	**5o**		36	71:29

[a] Conditions: 0.10 mmol **4** (Z=C(CO_2Me)$_2$), 5.0 µmol **3e-SbF$_6$**, 0.13 M in THF, -20 °C, 20-60 min. [b] Isolated yields. [c] Determined by HPLC with a chiral stationary phase. [d] at 0 °C. [e] 10.0 µmol **3e-SbF$_6$**. [f] 10.0 µmol **3b-SbF$_6$**, 23°C, 24 h.

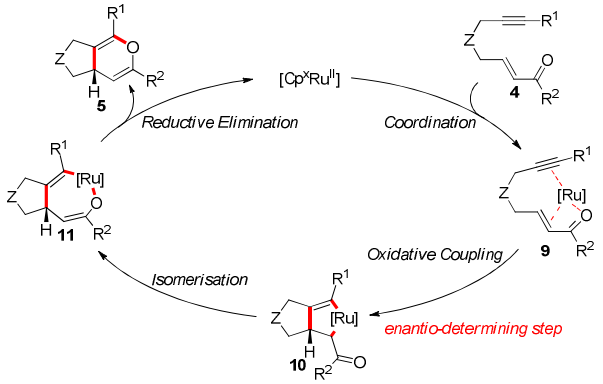
Besides enones, α,β-unsaturated ester **4p** and amide **4q** were viable substrates (Scheme 2). The intermediately formed ketene acetal **7** could not be isolated, and instead was directly hydrolyzed lactone **8a**. Dihydropyranone **8a** consists of the full iridoid skeleton found in a large number of natural products.[13] The *tert*-butyl ester **4p** did not provide any enatioinduction to give **8a** as a racemic mixture. In contrast, α,β-unsaturated Weinreb-amides **4q** and **4r** are converted to **8a** and **8b** in a very good selectivity of 94.5:5.5 er, respectively 98:2 er. The absolute configuration of the cyclization was assigned by X-ray crystallography of **8b** to be (*S*).[11]

Scheme 2. Dihydropyranones from esters and amides.



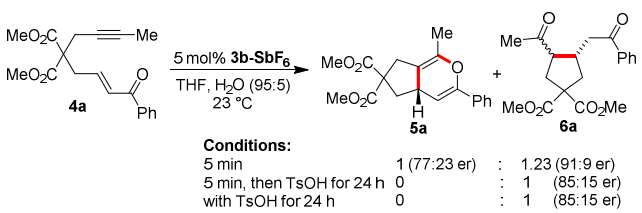
Based on the preceding reports,[14] the following mechanism for the pyran cyclization is likely (Scheme 3). Initial coordination of the alkyne and olefin moiety of substrate **4** to the cationic Cp^{x}Ru^{II} complex initiates the catalytic cycle. Enantiodetermining oxidative cyclization of **9** leads to ruthenacyclopentene **10**. Isomerization of the *C*-bound enolate to the corresponding *O*-bound enolate[15] forms ruthenaoxacycloheptadiene **11**. In turn, reductive elimination delivers the pyran **5**, closing the catalytic cycle.

Scheme 3. Proposed mechanism and enantiodetermining step in the formation of pyran 5.



To gain further insights on the formation of the diketone product **6**,[12] several experiments for the cyclization were conducted in wet THF (Scheme 4). Quenching the reaction directly after full conversion (5 min), a 1:1.23 mixture of pyran **5** and diketone **6** was observed. In the presence of acid, **5** hydrolyzed slowly to **6** within 24 h. An analysis of the optical purity *before* the hydrolysis revealed that **6** is formed in 91:9 er whereas **5** has a significantly lower value of 77:23 er. The optical purity of **6** after hydrolysis was 85:15 er, the expected averaged value.

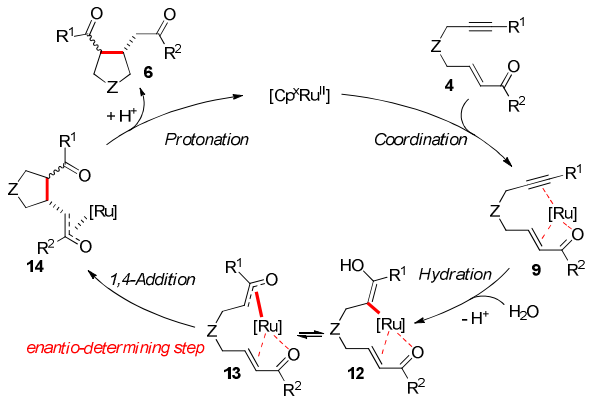
Scheme 4. Hydrative cyclization under wet conditions.



The initially detected amount of diketone **6** is formed directly without passing by pyran **5**, suggesting that two different catalytic cycles are simultaneously operative under wet conditions. The

first one described in scheme 3 accounts for pyran **5**. The lower selectivity compared to the dry reaction might be attributed to the coordination of water to the ruthenium center, changing the selectivity in analogy to the described counter ion effect seen in table 2. The proposed second cycle directly delivering diketone **6** is illustrated in scheme 5. Upon substrate coordination to the Ru-complex, addition of water leads to intermediate **12**. Related nucleophile additions were reported by Trost for the intermolecular reaction of alkynes and enones.[16] A subsequent 1,4-addition across the enone system (with possible prior tautomerization to enolate **13**) closes the cyclopentane ring as well as setting the stereogenic center of **14**. Protonation of enolate **14** releases diketone **6**. Given the high enantioselectivity for diketone **6** in this hydrative cycle, it would represent an attractive target transformation. However, the pyran pathway could not completely be suppressed.

Scheme 5. Suggested second mechanism for the hydrative cyclization.



In summary, we reported a new class of chiral Cp^xRu^{II} complexes. Using our atropchiral biaryl cyclopentadiene platform, the corresponding ruthenium complexes can be accessed in a straightforward manner. Their utility in asymmetric catalysis was demonstrated with a proof-of-concept application. Excellent levels of enantioselectivity were achieved for Trost's yne-enone cyclization. Given the vast diversity of transformations catalyzed by the cationic $CpRu^{II}$ complex, further work aims on expanding the application of the Cp^xRu^{II} complexes in synthetically valuable enantioselective transformations.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization data for all new compounds and HPLC traces of the chiral products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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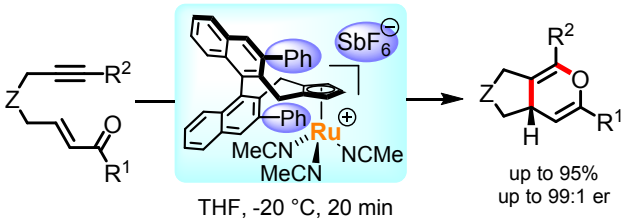
R2
Z
O
R1
Ph
SbF6
Ph
Ru
MeCN
MeCN
NCMe
THF, -20 °C, 20 min
R2
Z
O
R1
H
up to 95%
up to 99:1 er