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

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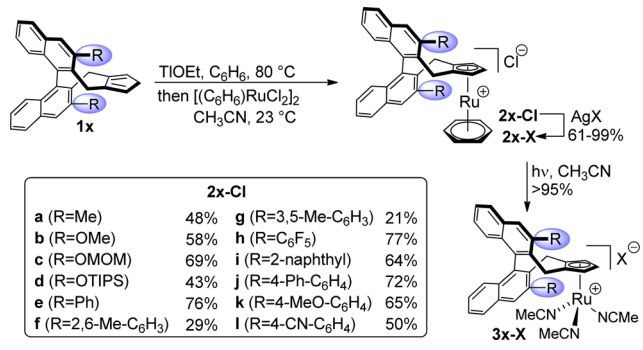
Supporting Information

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 yne-enone cyclizations via formal hetero-Diels–Alder reactions. The transformation proceeds in <1 h at −20 °C and provides pyrans in 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, 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 Ru 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 help 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 was to secure access to the corresponding complexes by a reliable preparative method. Most 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. After many attempts, Mann's protocol using CpTl,[10] which was also used for the syntheses of other chiral Cp-Ru(II) complexes,[3n] proved to be the best method (Scheme 1). Using [(C$_6$H$_6$)RuCl$_2$]$_2$ instead of the more common [(cymene)RuCl$_2$]$_2$ reduced the formation of undesired ruthenocene byproducts and provided moderate to good yields of **2a-Cl**–**2l-Cl**. 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 good shielding from the chiral Cp^x ligand (Figure 1).[11] Next, 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** in their solid state are 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$_6$H$_3$)	21%
b (R=OMe)	58%	**h** (R=C$_6$F$_5$)	77%
c (R=OMOM)	69%	**i** (R=2-naphthyl)	64%
d (R=OTIPS)	43%	**j** (R=4-Ph-C$_6$H$_4$)	72%
e (R=Ph)	76%	**k** (R=4-MeO-C$_6$H$_4$)	65%
f (R=2,6-Me-C$_6$H$_3$)	29%	**l** (R=4-CN-C$_6$H$_4$)	50%

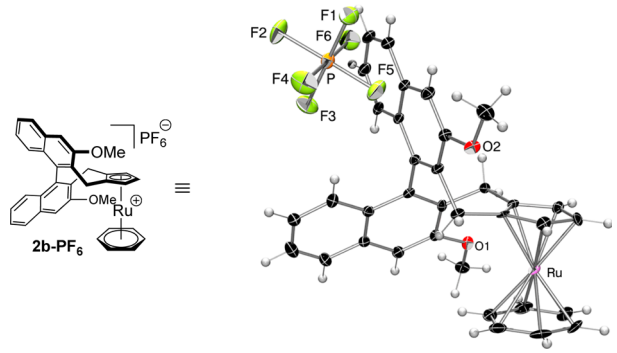


Figure 1. X-ray crystal structure of Cp^{x}Ru(C$_6$H$_6$)PF$_6$ (**2b-PF$_6$**).

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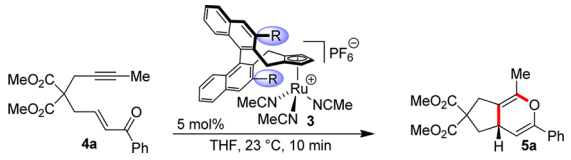
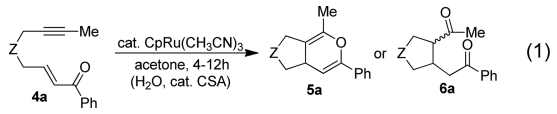
Table 1. Screening of Different Cp^{x}Ru Complexes 3[a]



entry	3-PF$_6$	R	conv (%)[b]	yield of **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$_6$H$_3$	24	16	45.5:54.5
7	**3g**	3,5-Me-C$_6$H$_3$	25	25	81.5:18.5
8	**3h**	C$_6$F$_5$	74	65	89.5:10.5
9	**3i**	2-naphthyl	24	22	87.5:12.5
10	**3j**	4-Ph-C$_6$H$_4$	35	27	55.5:44.5
11	**3k**	4-MeO-C$_6$H$_4$	30	29	45:55
12	**3l**	4-CN-C$_6$H$_4$	<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, we gauged the potential of these Cp^{x}Ru^{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$_2$Me)$_2$).[12] The transformation requires all three coordination sites of the Ru center, and adding 1 equiv of triphenylphosphine immediately inactivated the catalyst.

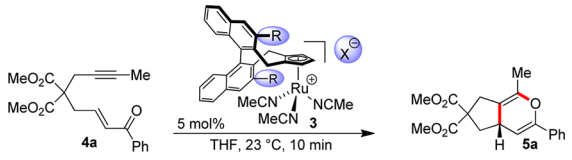


(1)

We initially evaluated several Cp^{x}Ru^{II} complexes with **4a** (Table 1). The reaction went to completion within 10 min 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), surpassed only by that of the 3,3′-phenyl congener **3e**, with 89.5:10.5 er (entry 5). Ligands with different substituted 3,3′-arenes were next 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 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). *p*-Cyanophenyl substitution totally inactivated the catalyst (entry 12). We speculate that the cyano group of **3l** coordinates to the Ru center, abolishing its catalytic performance. Although 2-naphthyl or pentafluorophenyl groups resulted in selectivities comparable to that obtained with **3e**, they render the complexes somewhat less reactive (entries 8 and 9).

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$_6^-$ (entries 1 and 2). Triflimide and the BARF$_{24}$ anion were less reactive and selective (entries 4 and 5). Surprisingly, the complex with a covalently bound chloride

Table 2. Effect of Counterion X on the Selectivity[a]



entry	R	X	conv (%)[b]	yield of **5a** (%)[b]	er[c]
1	OMe	PF$_6$	100	98	86:14
2	OMe	SbF$_6$	100	98	86.5:13.5
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***

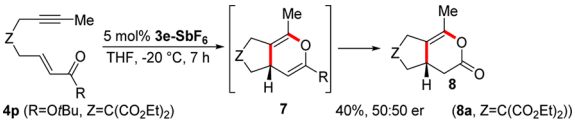
[a]Conditions: 25 μmol **4a**, 1.25 μmol **3**, 0.13 M in THF, 23 °C, 10 min. [b]Determined by ^{1}H NMR with an internal standard. [c]Determined by HPLC with a chiral stationary phase. [d]For 4 h. [e]0.1 mmol scale at −20 °C for 1 h. [f]Isolated yield.

gave the opposite enantiomer of **5a** in 28:72 er, although with significantly reduced reactivity (entry 6), requiring 4 h for the reaction to go to completion (entry 7). At present, the underlying effect of this reversed selectivity is not clear and is 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).

The scope for the enantioselective Ru-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 when R^1 is an alkyl group (entry 7). R^2 can be changed to longer or functionalized alkyl chains while keeping 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 thus hydrolyzed to diketone **6n** for isolation. A larger tether reduced the reaction performance with the current catalyst (entry 14).

Besides enones, *α*,*β*-unsaturated ester **4p** and amide **4q** were viable substrates (Scheme 2). The intermediate ketene acetal **7** could not be isolated and instead was directly hydrolyzed to 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 enantioinduction to give **8a** as a racemic mixture. In contrast, *α*,*β*-unsaturated Weinreb amides

Scheme 2. Dihydropyranones from Esters and Amides



4p (R=O*t*Bu, Z=C(CO$_2$Et)$_2$) 40%, 50:50 er (**8a**, Z=C(CO$_2$Et)$_2$))
4q (R=N(OMe)Me, Z=C(CO$_2$Et)$_2$) 68%, 94.5:5.5 er (**8a**, Z=C(CO$_2$Et)$_2$))
4r (R=N(OMe)Me, Z=NTs) 77%, 98:2 er (**8b**, Z=NTs)

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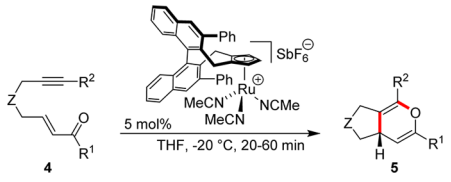
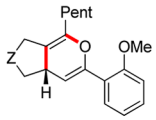
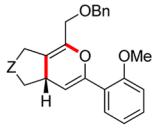
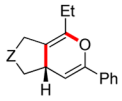
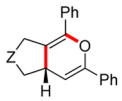
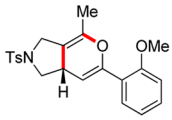
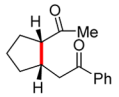
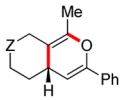
Table 3. Scope of the Synthesis of 4*H*-Pyrans 5[a]



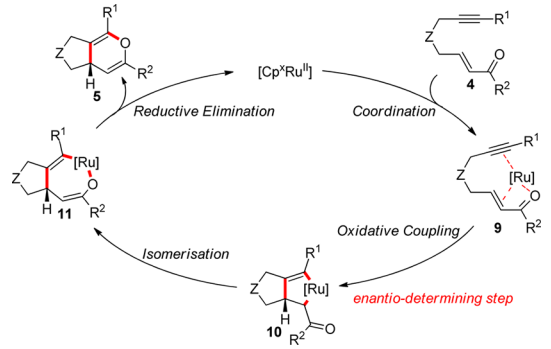
entry	4	5		yield (%)[b]	er[c]
1[e]	**4b**	**5b**	R^2=Me, R^1=2,4,6-Me-C_6H_2	71	97:3
2	**4c**	**5c**	R^2=Me, R^1=2-Me-C_6H_4	77	96.5:3.5
3	**4d**	**5d**	R^2=Me, R^1=2-MeO-C_6H_4	87	98.5:1.5
4	**4e**	**5e**	R^2=Me, R^1=4-MeO-C_6H_4	86	91:9
5	**4f**	**5f**	R^2=Me, R^1=2,4-MeO-C_6H_3	94	98.5:1.5
6	**4g**	**5g**	R^2=Me, R^1=4-NO_2-C_6H_4	95	89:11
7	**4h**	**5h**	R^2=Me, R^1=*i*Pr	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.

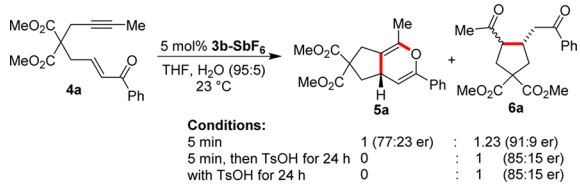
4q and **4r** were converted to **8a** and **8b** in a very good selectivity of 94.5:5.5 and 98:2 er, respectively. The absolute configuration of the cyclization was assigned by X-ray crystallography of **8b** to be (*S*).[11]

Based on the preceding reports,[14] the mechanism for pyran cyclization shown in Scheme 3 is likely. Initial coordination of the alkyne and olefin moiety of **4** to the cationic Cp^xRu^{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 pyran **5**, closing the catalytic cycle.

Scheme 3. Proposed Mechanism and Enantiodetermining Step in the Formation of Pyran 5

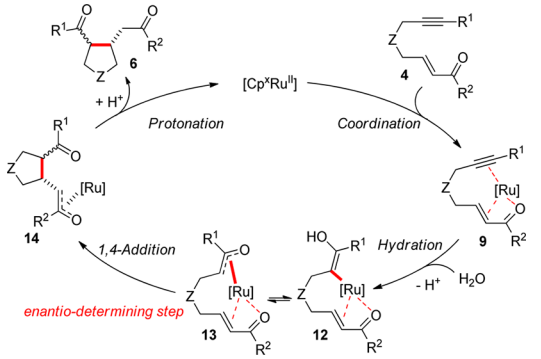


Scheme 4. Hydrative Cyclization under Wet Conditions



To gain further insights on the formation of diketone product **6**,[12] several cyclization experiments were conducted in wet THF (Scheme 4). On quenching the reaction directly after full conversion (5 min), a 1:1.23 mixture of **5** and **6** was observed. In the presence of acid, **5** hydrolyzed slowly to **6** within 24 h. 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 5. Suggested Second Mechanism for the Hydrative Cyclization



The initially detected amount of **6** is formed directly without passing by **5**, suggesting that two catalytic cycles are simultaneously operative under wet conditions. The first, shown in Scheme 3, accounts for **5**. The lower selectivity compared to the dry reaction might be attributed to the coordination of water to the Ru center, changing the selectivity in analogy to the counterion effect seen in Table 2. The proposed second cycle directly delivering **6** is shown in Scheme 5. Upon substrate coordination to the Ru complex, adding water leads to intermediate **12**. Related nucleophile additions were reported by Trost for the intermolecular reaction of alkynes and enones.[16]

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1,4-Addition across the enone system (with possible prior tautomerization to enolate **13**) closes the cyclopentane ring and sets the stereogenic center of **14**. Protonation of enolate **14** releases **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 be completely suppressed.

In summary, we have reported a new class of chiral Cp^xRu^{II} complexes. Using our atropchiral biaryl cyclopentadiene platform, the corresponding Ru 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 is aimed at expanding the application of the Cp^xRu^{II} complexes in synthetically valuable enantioselective transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08232.

Synthetic procedures, characterization data, and HPLC traces of the chiral products (PDF)

X-ray crystallographic data for **2b-PF$_6$** and **8b** (CIF)

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Notes

The authors declare no competing financial interest.

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