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Development of a Coordinatively Unsaturated Chiral Indenylruthenium Catalyst

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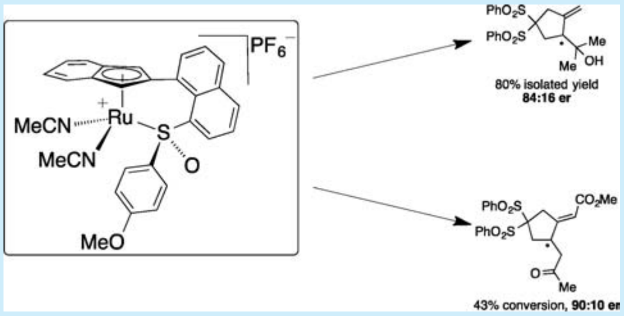
Supporting Information

ABSTRACT: An unprecedented coordinatively unsaturated chiral indenylruthenium complex **12** was designed and synthesized to provide additional coordination sites for Ru-catalyzed asymmetric transformations. In an attempt to catalyze an asymmetric enyne cycloisomerization reaction of 1,6-enyne, significant amounts of hydroxycyclization were observed. Up to 84:16 er of the hydroxycyclization product was obtained in 2-MeTHF. This chiral indenylruthenium catalyst could also perform an asymmetric redox isomerization/C−H insertion reaction in up to 90:10 er.



η^5-Indenylmetal complexes have been observed to be able to perform elementary organometallic reactions at an increased rate when compared to their η^5-cyclopentadienylmetal analogues.[1] The origin of this effect was attributed to the relative ease an indenyl ligand can slip between η^5 and η^3 coordination modes (Figure 1).[2] This ring slippage opens an additional coordination site on the metal. Additionally, the indenyl ligand offers a different steric profile than the Cp ligand, which could be beneficial for asymmetric catalysis. Chiral indenylmetal complexes that were used for enantioselective synthesis include indenylzirconium carboalumination catalysts[3] and indenylcobalt complexes for atroposelective [2 + 2 + 2] cycloaddition reactions.[4]

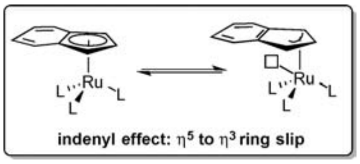
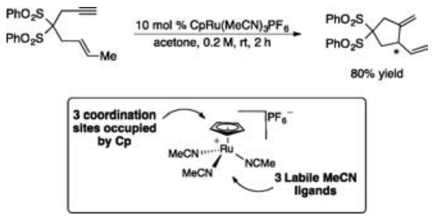


Figure 1. η^5 to η^3 ring slippage on an indenyl ligand.

Though less common than cyclopentadienylruthenium (CpRu) catalysis, there are a number of notable organic reactions catalyzed by indenylruthenium (IndRu) complexes.[5] While IndRu complexes containing chiral bidentate ligands are known and have been used for asymmetric Diels−Alder[6] and transfer hydrogenation[7] reactions, chiral indenylmetal complexes bearing 2−3 easily dissociable ligands like acetonitrile that have the potential to reach higher degrees of coordinative unsaturation have not been developed.

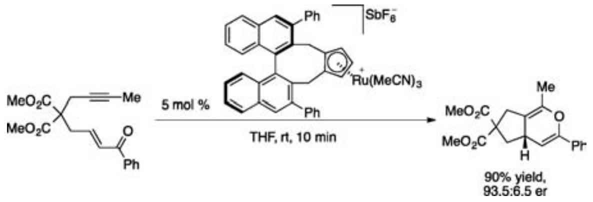
Scheme 1. Ru-Catalyzed Enyne Cycloisomerization and [5 + 2] Cycloaddition Reactions



Our group and others have shown that $CpRu(MeCN)_3PF_6$ is an excellent catalyst for atom-economical processes such as enyne cycloisomerization (Scheme 1).[8] However, rendering these processes asymmetric is challenging due to the fact that they require all three open coordination sites around the metal center. The monodentate and bidentate chiral ligands used for other asymmetric CpRu-catalyzed reactions[9] would only serve to impede catalysis.

To circumvent this issue, chemists have designed catalysts that have chiral information placed on either the counterion[10] or the Cp ring. Recently, the Cramer group successfully applied the latter strategy toward the enantioselective cyclization of yne-enones (Scheme 2).[11]

Scheme 2. Cramer's Asymmetric Yne-Enone Cyclization



Rather than synthesizing chiral Cp rings, we sought an alternative solution to the three coordination site requirement that would be compatible with using traditional chiral ligands.

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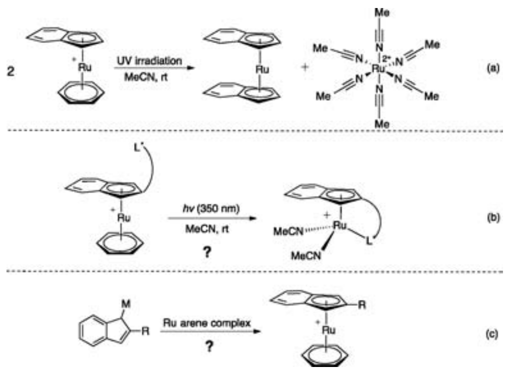
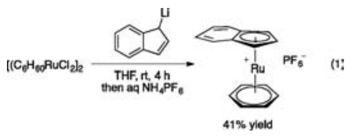
We believed that an IndRu complex would be able to catalyze the enyne cycloisomerization reaction by taking advantage of the η^5 to η^3 ring slippage of the indenyl ligand while maintaining the coordination of an exogenous or tethered chiral ligand. The other two coordination sites would be occupied by labile ligands, such as acetonitrile, that can be displaced by a substrate during the catalytic reaction. Because such a complex that meets all of these requirements has not been reported previously, we needed to design and execute a reasonable synthesis of these compounds. Indeed, evidence in the literature (vide infra) even questions whether such compounds can exist. Thus, if generated, would it spontaneously decompose?

Ideally, this catalyst would contain indenide, a chiral ligand, two labile acetonitrile ligands, and a PF_6 counterion, analogous in structure to the $CpRu(MeCN)_3PF_6$ catalyst used for racemic enyne cycloisomerization. The difficulty of creating such a catalyst became apparent to us once we considered the various synthetic challenges that would be facing us. First, one cannot simply add a chiral ligand to "$(Ind)Ru(MeCN)_3PF_6$" because this unsaturated indenyl complex cannot be isolated. Kudinov and co-workers showed that irradiating $(Ind)Ru(C_6H_6)PF_6$ in acetonitrile with UV light generates the intermediate $(Ind)Ru(MeCN)_3PF_6$, which disproportionates to $(Ind)_2Ru$ and $Ru(MeCN)_6(PF_6)_2$ (Scheme 3a).[12] Though it has not been previously demonstrated in the literature, it is possible that a ligand tethered to the indenide could trap the reactive intermediate and prevent disproportionation (Scheme 3b). Second, there is only one example of adding an indenylmetal fragment to a ruthenium arene complex (eq 1).[12]

Scheme 3. (a) Disproportionation of IndRu Mixed Sandwich Complex under UV Irradiation, (b) Proposed Trap of Reactive Intermediate with a Tethered Ligand, and (c) Indenylmetal Addition to a Ruthenium Arene Complex





Can the same reaction be performed with substituted indenes (Scheme 3c)?

For the chiral IndRu catalyst structure, we drew inspiration from the CpRu catalyst containing a tethered chiral sulfoxide ligand (Figure 2). This complex was proven to be an effective catalyst for the asymmetric allylic substitution[9f] and redox bicycloisomerization reactions.[9g] Chiral sulfoxides are air-stable, readily available compounds that can be synthesized via nucleophilic substitution of a sulfinate ester with a Grignard reagent.[13]

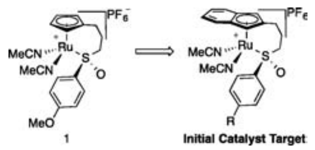
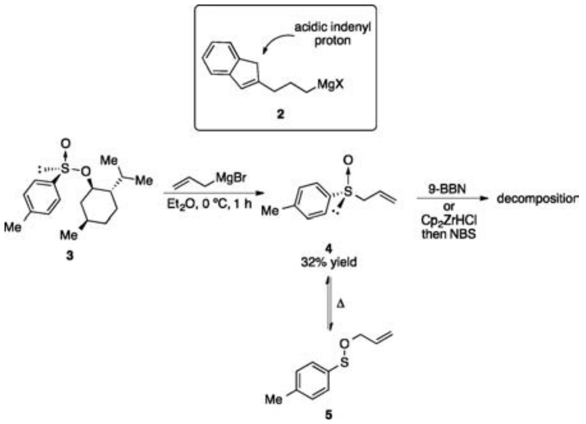


Figure 2. CpRu complex **1** as inspiration for IndRu complex design.

However, the construction of an indenyl sulfoxide ligand with a three-carbon tether is not a straightforward prospect.

Grignard reagent **2** cannot be synthesized because the basic alkylmangesium would react with its own acidic indenyl proton (Scheme 4). Instead, we decided to try introducing functionality onto the chiral sulfoxide, which could then subsequently be appended with the reactive indenyl fragment. Chiral allyl *p*-tolyl sulfoxide **4** can be constructed from allylmagnesium bromide and chiral sulfinate ester **3**. Chiral allyl sulfoxides are difficult compounds to handle, as they tend to racemize at elevated temperatures due to sigmatropic rearrangement to **5**.[14]

Scheme 4. Attempted Synthesis of a Chiral Sulfoxide with an Alkyl-Tethered Indene



Attempts at functionalizing sulfoxide **4** with 9-BBN for a subsequent Suzuki coupling reaction only resulted in decomposition, as did a hydrozirconation/bromination sequence. The reason for this failure is most likely due to the Lewis basicity of the sulfoxide, which could interfere with the addition of Lewis acidic moieties to the pendant double bond.

At this point, we decided to revise our synthetic strategy. Construction of an indenyl sulfoxide ligand would be greatly simplified if the tether were sp^2-hybridized, as this would open up more straightforward cross-coupling strategies for the incorporation of the indenyl ligand. However, such a tether would still need to contain three carbon atoms between the indene and the sulfoxide. Therefore, this requirement precludes the use of an *ortho*-substituted arene as a ligand tether as in **6**, as this only contains a two-carbon spacer (Figure 3). On the other hand, the *peri*-substituted naphthalene in **7** would have the right number of carbons for our IndRu complex. In addition, since a

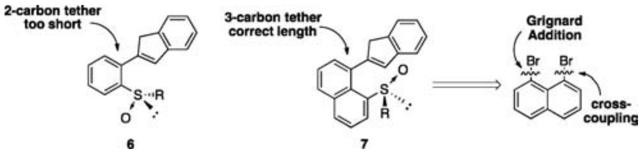


Figure 3. sp^2-Hybridized tethers and retrosynthesis.

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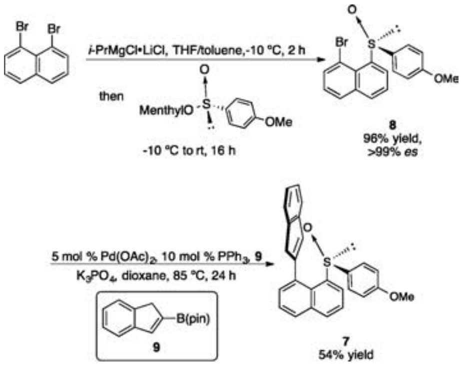
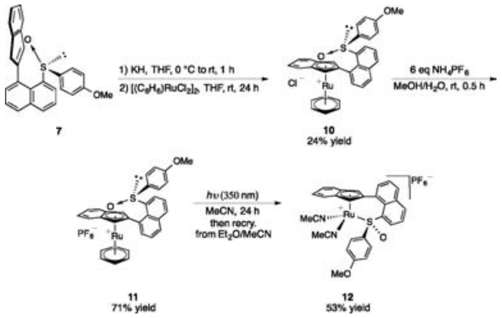
peri-substituted naphthalene is conformationally fixed, unlike an alkyl tether, it may bind the sulfoxide to the metal more tightly, increasing the chances of enantioinduction for a given asymmetric transformation. We envisioned that sulfoxide **7** can be synthesized from 1,8-dibromonaphthalene by Grignard addition into a sulfinate ester followed by a Pd-catalyzed Suzuki cross-coupling of an indenyl fragment.

The forward synthesis of these indenyl sulfoxide ligands is presented in Scheme 5. Magnesium/halogen exchange of 1,8-dibromonaphthalene and addition into a menthyl sulfinate ester furnishes sulfoxide **8** in good yield with >99% stereoinversion at sulfur. *p*-Anisyl **7** was constructed via Pd-catalyzed Suzuki cross-coupling of **8** with **9**.[15] Sulfoxide **7** exhibits broad peaks for some of their indenyl and sulfoxide protons in their ^{1}H spectrum, consistent with the expected hindered rotation of these bulky moieties on the *peri*-position of the naphthalene ring. Deprotonation of **7** with potassium hydride and addition to a ruthenium dimer $[(C_6H_6)RuCl_2]_2$ gave the desired half-sandwich complex **10** in modest yield (Scheme 6). Ion exchange to **11** with ammonium hexafluorophosphate and photolysis provided **12** cleanly as a single complex by ^{1}H NMR. Complex **12** is a bench-stable bright yellow solid that shows no signs of decomposition after 3 years of storage.

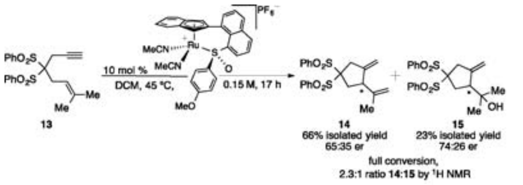
Scheme 5. Forward Synthesis of Sulfoxide 7



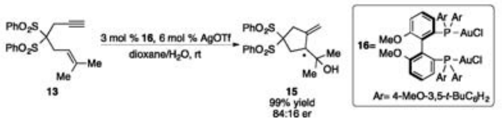
Scheme 6. Synthesis of IndRu Catalyst 12



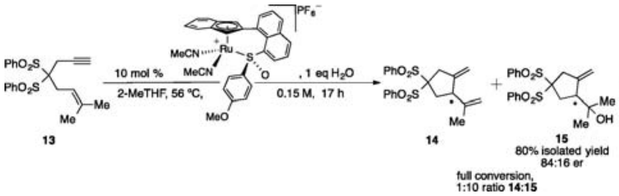
When enyne substrate **13** was subjected to 10 mol % of **12** in DCM, full conversion was observed in an unexpected 2.3:1 ratio of diene to hydrate (eq 2). The hydrate byproduct, formed from the addition of adventitious water to **13**, had never been observed with any previously developed chiral CpRu catalysts and was isolated in an encouraging 74:26 er. The η^5 to η^3 slippage of the indenyl ring in **12** seems to be facilitating the formation of this product. The Echavarren group reported the racemic synthesis of **15** from **13** under Pt(II) catalysis.[16] Michelet was able to obtain tertiary alcohol **15** in 84:16 er with cocatalytic Au(I)/Ag(I) (eq 3).[17] Using 10 mol % of **12** in 2-MeTHF with 1 equiv of water at 56 °C, full conversion of enyne **13** and a 1:10 ratio of diene **14** to hydrate **15** was observed by ^{1}H NMR (eq 4). Hydrate **15** could be isolated in an 80% yield and 84:16 er, comparable to the er observed by Michelet.



(2)



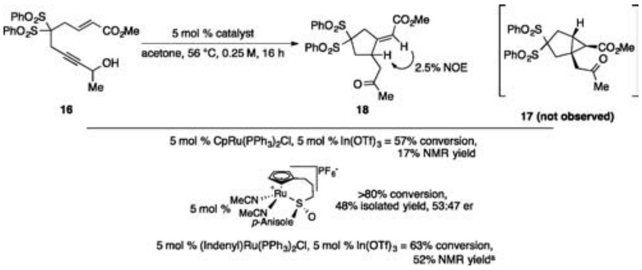
(3)



(4)

When subjecting (*E*)-acrylate 1,6-enyne **16** to redox bicycloisomerization conditions, rather than obtaining cyclopropane **17**, one observes a formal insertion reaction into a vinylic C−H bond (Scheme 7). Carbocycle **18** was observed to be one geometric olefin isomer, as determined by 1D NOE. Better conversion and a 48% isolated yield of **18** was obtained with Cp-sulfoxide catalyst **1**, though the product obtained was nearly racemic. Although (indenyl)Ru$(PPh_3)_2$Cl catalyzed this reaction to 63% conversion, the reaction was clean, as a 52% NMR yield was obtained. We reasoned that by switching to the more coordinatively unsaturated complex **12** would both improve the conversion and enantioselectivity of this reaction and minimize byproduct formation.

Scheme 7. Redox Isomerization/C−H Insertion of Enyne 17



[a]Performed in cyclopentanone at 100 °C.

When **16** was treated with 5 mol % of **12** in acetone at 56 °C, a 42% conversion to carbocycle **18** was observed, with the remaining mass balance being starting material (eq 5). However, this product was obtained in 87:13 er, indicating good chiral induction. Switching to THF with 10 mol % of catalyst loading increased the enantioselectivity to 90:10 er. Using DCE as a solvent improved reaction conversion but at the expense of enantioselectivity. It is not clear to the extent in which indenyl ring slippage factors into this reaction; however, it is clear that

(5)

Acetone= 42% conversion, 87:13 er (5 mol % catalyst)
THF= 43% conversion, 90:10 er
DCE= 65% conversion, 80:20 er

IndRu catalyst **12** is differential with respect to enantioselectivity when compared to catalyst **1**.

In conclusion, we designed and executed the synthesis of chiral IndRu sulfoxide catalyst **12**. This complex is the first of its kind in the literature and shows promise as a catalyst for the asymmetric enyne hydroxycyclization and redox isomerization/C−H insertion reactions in which our previous Ru catalysts performed poorly. Future studies will focus on exploring the substrate scope of these interesting reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01375.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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