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A Recyclable Chiral Ru Catalyst for Enantioselective Olefin Metathesis. Efficient Catalytic Asymmetric Ring-Opening/Cross Metathesis in Air

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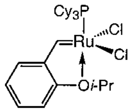
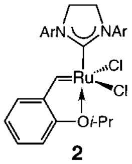
Various programs in these laboratories have focused on the development of efficient and practical olefin metathesis catalysts for stereoselective synthesis.[1] Through one initiative, we identified a class of potent Ru-based complexes that can be easily recycled (**1** and **2**).[2] These catalysts were later shown to exhibit reactivity and selectivity profiles that may not be observed with other Ru systems.[3,4] We have prepared and studied chiral Mo-based metathesis catalysts that can be used to synthesize a number of optically pure carbo- and heterocycles.[5−7] Related efforts in these laboratories have been in connection to the design, synthesis, and development of new *chiral Ru-based* catalysts for enantioselective olefin metathesis. The complementarity of Ru- and Mo-based complexes regarding reactivity and functional group compatibility, in addition to the stability and recyclability of systems represented by **1** and **2**, imparts considerable potential utility to chiral Ru catalysts.[8] Herein, we report the synthesis, structure, and reactivity of a new chiral Ru-based catalyst (**3**). Complex **3** bears a stereogenic Ru center,[9] can be prepared in >98% diastereo- and enantiomeric purity without resolution, and is air-stable and recyclable. Chiral Ru catalyst **3** efficiently promotes asymmetric ring-opening/cross metathesis (AROM/CM) in air, with undistilled solvents and with substrates that polymerize with chiral Mo catalysts.[7b]



1



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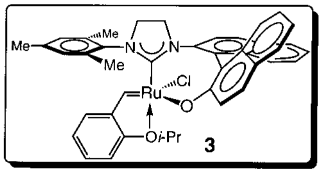


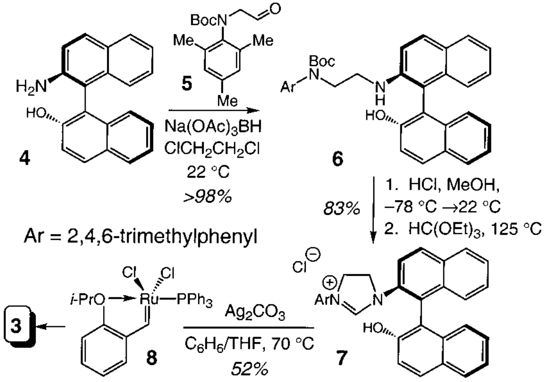
3

Ar = 2,4,6-trimethylphenyl

Preference for a bidentate chiral imidazolinylidene was based on the hypothesis that such a ligand would induce chirality more effectively (vs a monodentate ligand).[8] Although there was some concern regarding catalyst activity that could arise from substitution of a Cl with an aryloxide ligand (i.e., **2** vs **3**), we were encouraged by a report on active Ru catalysts that bear a bidentate phenolic Schiff base.[10]

The synthesis of optically and diastereomerically pure **3** was carried out as shown in Scheme 1; all reactions have been performed on gram scale. Reductive amination involving optically pure **4**[11] and aldehyde **5** in the presence of $NaBH(OAc)_3$ delivers amino alcohol **6** in >98% isolated yield. Conversion of **6** to imidazolinium salt **7** proceeds smoothly in two steps in 83% overall yield; optically pure **7** is obtained in analytically pure form after simple filtration. The pivotal step in the synthesis scheme proved to be the conversion of **7** to **3**. After extensive experimentation, we established that in the presence of silver carbonate and the catalytically inactive Ru complex **8**,[2a] the desired complex **3** is formed in 52% isolated yield after chromatography (light brown solid). Complex **3** *is air-stable, can be purified by silica gel chromatography with undistilled solvents* and its diastereo- and enantiomeric purity can be established by HPLC analysis (isolated in >98% de and ee). The chiral complex has been fully characterized and its ORTEP diagram is depicted in Figure 1 (details in the Supporting Information).

Scheme 1. Synthesis of Chiral Ru Complex **3**



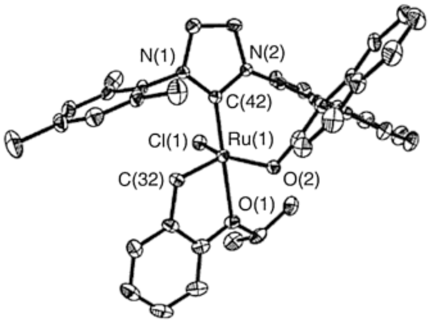


Figure 1. ORTEP diagram of complex **3**.

Next, we examined the activity provided by **3** as a metathesis catalyst. As the representative examples in Scheme 2 indicate, Ru complex **3** promotes the RCM of diene and enyne substrates to deliver cyclic unsaturated products bearing di- or trisubstituted olefins (>98% conversion). However, **3** is less active than the achiral parent system **2**,[2b] since longer reaction times and elevated temperatures are required for complete conversion. This difference in potency is expected: replacement of a Cl with the less electronegative phenoxide of the chiral ligand and the increased steric bulk of the binaphthyl are likely responsible for the diminished

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Scheme 2. Activity and Recyclability of Chiral Ru Catalyst **3**

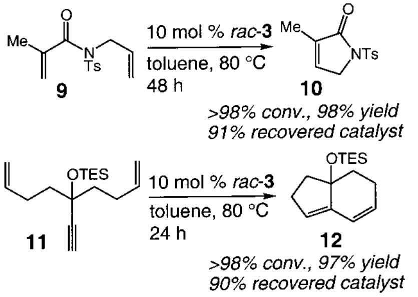
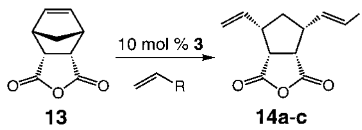


Table 1. Ru-Catalyzed AROM/CM of Tricyclic Norbornenes[a]



entry	R		temp (°C); time (h)	conv (%)[b]; yield (%)[c]	recov. cat. (%)[c]	trans:cis[b]	ee (%)[d]
1	Ph	**a**	50; 1.0	>98; 71	96	>98: 2	80
2	n-C_5H_{11}	**b**	50; 1.5	>98; 57	92	>98: 2	>98
3	Cy	**c**	50; 1.0	>98; 60	88	>98: 2	>98

[a] Conditions: 5 equiv of terminal olefin in entry 1 and 2 equiv in entries 2 and 3; THF, under N_2. [b] By 400 MHz ^1H NMR analysis. [c] Isolated yields after chromatography. [d] By chiral HPLC (see the Supporting Information).

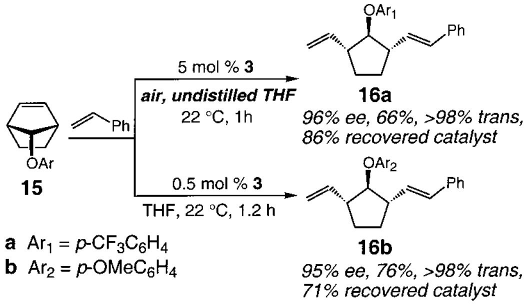
activity.[10,12] As illustrated in Scheme 2,[13] catalyst **3** can be recovered in high yield by silica gel chromatography. Upon isolation, **3** may be reused without significant loss of activity. For example, the catalyst recovered from the synthesis of **10** effects RCM of **9** again with equal facility (93% conversion, 48 h) and provides the desired product in 90% isolated yield (78% recovered catalyst). It should be noted that conversion of **11** to **12** cannot be promoted with Mo-based catalysts (<10% conversion).[14]

Initial studies indicate that **3** is an effective and practical chiral catalyst for enantioselective metathesis. Several examples of Ru-catalyzed AROM/CM are depicted in Table 1. As illustrated in entry 1, treatment of **13** with 5 equiv of styrene in the presence of 10 mol % **3** in THF (50 °C)[15] leads to the formation of **14a** in 80% ee and 71% isolated yield (>98% trans). Ru-catalyzed AROM/CM of **13** is exceptionally selective with aliphatic olefins. With 1-heptene and sterically bulky vinylcyclohexane (entries 2−3), **14b**,**c** are obtained in >98% ee, >98% trans, and 57−60% yield. Several additional issues regarding the reactions in Table 1 merit mention: (i) The chiral catalyst can be recovered after chromatography (88−96% yield). (ii) Byproducts from homodimerization of the terminal olefins or additional cross metathesis (CM) of **14a**,**c** to afford meso dienes are not observed (<5%, ^1H NMR).[7b] (iii) Recovered **3** can be reused without significant loss of enantioselectivity and with similar reactivity.[16] (iv) None of the transformations can be effected with chiral Mo-based catalysts, which would rapidly polymerize substrates such as **13** (no AROM/CM product even with >10 equiv terminal olefin).[7b]

The catalytic AROM/CM reactions in Scheme 3 further underline the significant potential of chiral Ru complex **3** in enantioselective synthesis. Transformation of **15a** is catalyzed by 5 mol % **3** at room temperature, in air, and with undistilled and nondegassed THF to deliver **16a**[17] in 96% ee and 66% isolated yield (>98% trans). Moreover, *with only 0.5 mol %* **3**, **15b** reacts in 75 min to afford **16b** in 95% ee and 76% yield (>98% trans). It should be noted that the reactions shown in Table 1, carried out at 50 °C, can also be run in air without significant change in reactivity or enantioselectivity.

Ongoing research involves the development of additional chiral Ru catalysts and their supported variants for use in enantioselective combinatorial synthesis.[4] Investigation of Ru-catalyzed asymmetric ring-closing metatheses and study of other metal complexes of the new chiral imidazolinium ligands are in progress.

Scheme 3. Ru-Catalyzed AROM/CM of 7-Oxonorbornenes



Acknowledgment. We dedicate this paper to our colleague, Professor T. Ross Kelly, on the occasion of his 60th birthday. Financial support from the NSF (CHE-9905806 and a predoctoral fellowship to J.S.K.) is gratefully acknowledged. We thank Dr. Richard Staples and Jarred Blank for assistance in determining the X-ray structure of **3**.

Supporting Information Available: Experimental procedures and spectral and analytical data for the chiral catalyst and reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Studies on catalytic enantioselective RCM of **11** and related substrates are in progress.
(14) Unpublished results of D. S. La and A. F. Kiely.
(15) Reduced enantioselectivity is observed in reactions of **13** at lower temperatures.
(16) For example, formation of **14b** is catalyzed with recycled **3** in >98% ee and 46% yield (86% recovered **3**).
(17) The identity of the major enantiomer of **16a** was established by comparison with authentic materials (see the Supporting Information); the remaining assignments are by inference.

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