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Construction of Enantioenriched [3.1.0] Bicycles via a Ruthenium-Catalyzed Asymmetric Redox Bicycloisomerization Reaction

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Supporting Information

ABSTRACT: Enantiomerically enriched [3.1.0] bicycles containing vicinal quaternary centers were synthesized from [1,6]-enynes using a cyclopentadienylruthenium catalyst containing a tethered chiral sulfoxide. The reaction was complicated by the fact that the substrates contained a racemic propargyl alcohol that could affect the selectivity of the process. Nonetheless, high levels of enantioinduction were observed, despite complications arising from the use of racemic substrates. Mechanistic studies showed that while the utilization of either enantiomer of the propargyl alcohol led to high product enantiomeric ratios when the reaction was conducted in acetone, a significant matched/mismatched effect was observed in tetrahydrofuran.

In recent years, transition-metal-catalyzed asymmetric cycloisomerization reactions[1] have become an important class of reactions for the construction of enantiomerically enriched complex molecules in an atom-,[2] step-,[3] and redox-economical[4] fashion. Examples of gold-,[5] platinum-,[6] palladium-,[7] and rhodium-catalyzed[8] simple asymmetric cycloisomerization reactions have been reported in the literature. While there has been progress in utilizing chiral ruthenium catalysts for asymmetric cycloaddition,[9] cyclopropanation,[10] and allylic alkylation reactions,[11] to the best of our knowledge there have been no reported examples of the use of a chiral ruthenium catalyst for cycloisomerization reactions. Ruthenium-catalyzed reactions have distinguished themselves as an important class of transformations that can construct complex organic molecules quickly and efficiently.[12] We previously reported the cyclopentadienylruthenium (CpRu)-catalyzed redox bicycloisomerization of [1,6]- and [1,7]-enynes to form structurally complex [3.1.0] and [4.1.0] bicycles that contain vicinal quaternary stereocenters (Figure 1a).[13] Intrigued by the possibility of making this process enantioselective, we hoped that an appropriate choice of ruthenium catalyst would deliver high levels of enantioinduction.

Chiral sulfoxides are a relatively unexplored ligand class for transition metals.[14] Very recently, we described the conveniently synthesized CpRu complex **1** (Figure 1b), which does not resort to a resolution of an intermediate CpRu complex,[15] and its application in asymmetric allylic substitution reactions.[16] It also has the added advantage of having its asymmetry-inducing element, the chiral sulfoxide, in close proximity to the metal center. This increases the possibility of asymmetric induction during the enantiodetermining step. Our hope was that the application of **1** would provide a means by which one could access enantioenriched [3.1.0] and [4.1.0] bicycles.

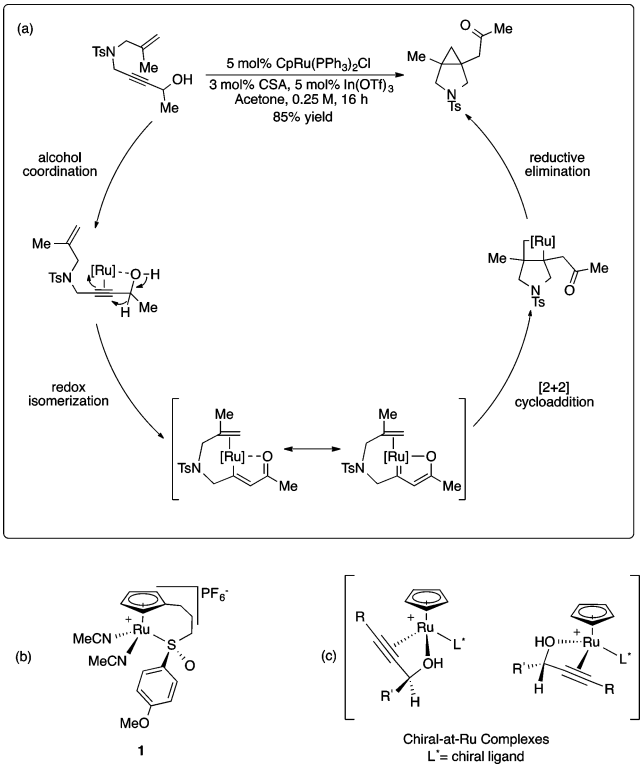

Figure 1. (a) Ruthenium-catalyzed redox bicycloisomerization reaction reported by Trost.[13] (b) Ruthenium catalyst **1** containing a tethered chiral sulfoxide. (c) Possible diastereomeric complexes formed by propargyl alcohol coordination.

However, the fact that substrates of this type contain a chiral, racemic stereocenter presents a complicating aspect to this reaction. One can envision that coordination of the propargyl alcohol to the metal center can occur with either one of two possible diastereochemical outcomes, thus creating a stereocenter at ruthenium (Figure 1c). While the aforementioned stereocenter is destroyed concomitant with redox isomerization, it is unclear whether this transfer of stereochemical information to the metal would have an adventitious, detrimental, or inconsequential impact on the selectivity.

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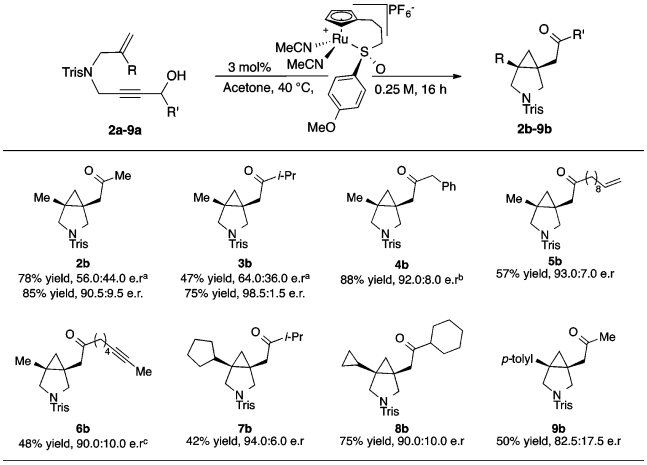
Initial optimization efforts were made on [1,7]-enynes containing racemic propargyl alcohols because of their products' similarity to triple-uptake inhibitors developed by GlaxoSmithKline.[17] From these initial studies, the use of a 2,4,6-triisopropylbenzenesulfonyl (Tris) group and tetrahydrofuran (THF) as the solvent were determined to be optimal for the enantioinduction and yield (see the Supporting Information).[18] However, when these conditions were applied to [1,6]-enynes, only low levels of enantioinduction were observed for substrates **2a** and **3a** (Table 1). Switching to acetone, a more

Table 1. Asymmetric Redox Bicycloisomerization with Tris-Substituted Nitrogen



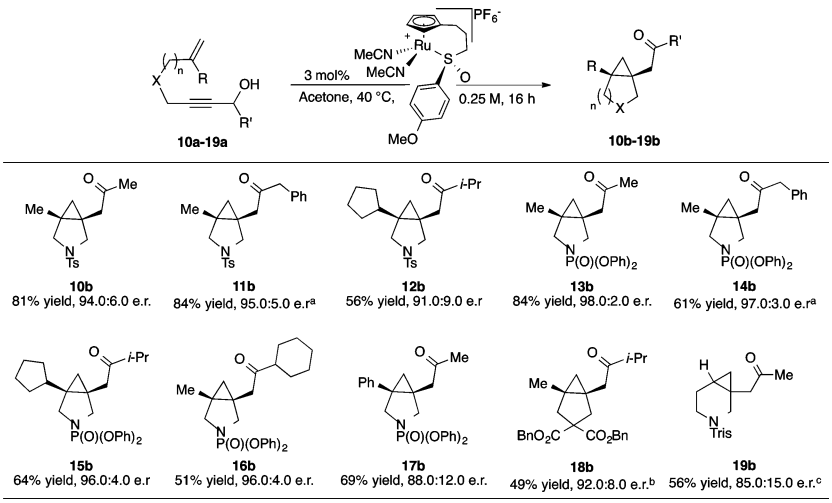
[a]Reaction conducted in THF. [b]5 mol % catalyst used. [c]8.5 mol % catalyst used.

coordinating solvent, had a profound effect on the selectivity of the reaction, boosting the enantiomeric ratio (e.r.) to 90.5:9.5 and 98.5:1.5 for **2b** and **3b**, respectively. Encouraged by these results, we prepared substrates containing aromatic (**4a**), olefinic (**5a**), and alkynyl (**6a**) groups in an effort to probe steric and coordinative effects in the redox bicycloisomerization reaction. This series of substrates showcased the chemoselectivity of the redox bicycloisomerization reaction, which can tolerate both isolated alkenes and alkynes without significantly impacting the reactivity or enantioselectivity, a degree of chemoselectivity not reported for any previous metal-catalyzed asymmetric cycloisomerization to our knowledge.[19] Substrate **7a**, which contains a more bulky cyclopentyl group at the internal position of its alkene, also exhibits excellent enantioselectivity. Vinylcyclopropane **8a**, a type of substrate prone to metal-catalyzed reactions, is tolerated under these conditions, as the corresponding [3.1.0] bicycle **8b** can be obtained in 75% yield and 90:10 e.r. Finally, **9a**, which contains an aromatic moiety at the internal position of its olefin, was obtained in a slightly diminished e.r. (82.5:17.5).

During the course of our mechanistic studies (vide infra), it was observed that less bulky *p*-toluenesulfonamides **10a** and **11a** gave slightly improved e.r. compared with the analogous Tris-based substrates **2a** and **4a** (Table 2). A dependence of the nature of the nitrogen substituent was noted in comparing the two sulfonamides; we were intrigued by the notion that alternate groups on nitrogen may improve the enantioselectivity of the bicycloisomerization reaction. Indeed, we discovered that the diphenylphosphoramidate backbone gave even higher selectivities compared with the two sulfonamide backbones as well as improved yields in some cases. Thus, bicyclic products **13b**−**16b** were all obtained in good yield and greater than 96:4 e.r. Even the most challenging substrate among the sulfonamides, **9a**, displayed an improved selectivity of 88.0:12.0 when exchanged for a diphenylphosphoramidate backbone (**17a**). Furthermore, this chemistry can be extended beyond pyrrolidine products, as [3.1.0] carbocycle **18b** was isolated in 49% yield and 92.0:8.0 e.r. Finally, [4.1.0] bicyclic piperidine **19b** was obtained in 56% yield and 85.0:15.0 e.r. when the Tris functional group was utilized and the reaction was run in THF.

Intrigued by the high levels of asymmetry induced by chiral ruthenium catalyst **1**, we wondered whether the observed enantioselectivity is at all influenced by the stereochemistry of the starting alcohol even though the stereocenter is destroyed in the process. To test this, we synthesized tosyl-substituted [1,6]-enynes **10a** containing an enantiomerically enriched propargyl alcohol in both the *R* and *S* configurations, conveniently made utilizing the Zn-Prophenol catalyzed asymmetric alkynylation of acetaldehyde (see the Supporting

Table 2. Impact of the Enyne Backbone on the Enantioselectivity



[a]5 mol % catalyst used. [b]7.5 mol % catalyst used. [c]Reaction performed in THF.

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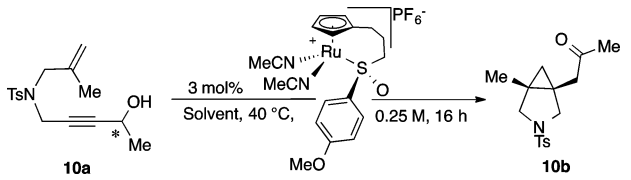
Information).[20] When these propargyl alcohols were applied to the standard reaction conditions in acetone, a very slight matched/mistmatched effect was observed (Table 3, entries 1–3). However, when the reaction was run in THF, a less coordinating solvent, a much more substantial effect was observed: a 92.0:8.0 e.r. was obtained with the (*R*)-propargyl alcohol, and a 68.0:32.0 e.r. obtained with the (*S*)-propargyl alcohol. The origin of this effect is currently unclear, but these mechanistic experiments suggest that acetone's ability to compete with the chiral alcohol to coordinate to the metal center during the course of the reaction is an important factor for obtaining high enantioselectivities.

Table 3. Effect of the Propargylic Stereocenter on the Enantioselectivity

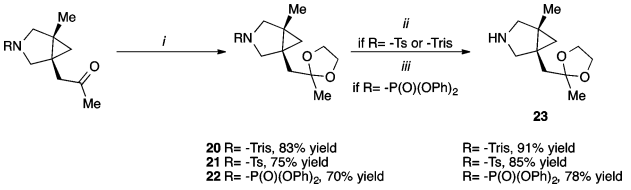


entry	solvent	alcohol configuration	yield (%)	e.r.
1	acetone	*rac*	81	94.0:6.0
2	acetone	*R*[a]	84	93.5:6.5
3	acetone	*S*[a]	81	96.5:3.5
4	THF	*rac*	52	80.0:20.0
5	THF	*R*[a]	61	92.0:8.0
6	THF	*S*[a]	52	68.0:32.0

[a]The starting alcohol had a 97:3 e.r.

Both sulfonamides can be deprotected to obtain the free pyrrolidine by using sodium naphthalide in THF after protection of the ketone as the ketal (Scheme 1). The diphenylphosphoramidate group can also be removed under reductive conditions with $LiAlH_4$ in ether. The direction of optical rotation of pyrrolidine **23** did not depend on the starting protected pyrrolidine, indicating that **20**–**22** have the same absolute configuration. The absolute configuration of ketal **20** was confirmed to be (*R,R*) on the basis of single-crystal X-ray crystallography (Figure 2).

Scheme 1. Reductive Removal of the Sulfonyl and Phosphoryl Groups on Nitrogen[a]



[a](*i*) $TsOH{\cdot}H_2O$, $(MeO)_3CH$, $(CH_2OH)_2$, r.t., 3 h; (*ii*) sodium naphthalide, THF, −78 °C to r.t., 5 min; (*iii*) $LiAlH_4$, Et_2O, r.t., 17 h.

In conclusion, we have developed the first asymmetric ruthenium-catalyzed redox cycloisomerization reaction known to date. This process exhibits a degree of chemoselectivity not reported for any other metal-catalyzed cycloisomerization. It is also important to note that this new chiral catalyst is effective for two very different types of processes, allylic alkylation and redox bicycloisomerization. Such a feature encourages examination of this new chiral catalyst for other ruthenium-catalyzed reactions. Ongoing studies are currently being performed to elucidate the mechanism of this transformation.

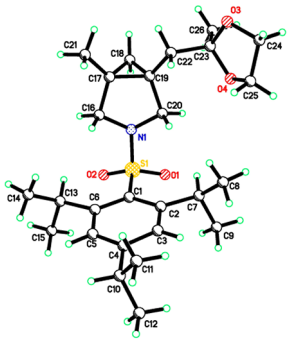


Figure 2. X-ray crystal structure of **20**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, crystallographic data (CIF), and characterization data. 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 interest.

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(18) Other catalyst systems were tried, but catalyst **1** proved to be the most reactive and enantioselective for the transformation. See the Supporting Information for details.

(19) All of the redox bicycloisomerization reactions presented here proceeded to full conversion. The remaining mass balance in each case was a mixture of acyclic redox isomerization and β-hydride elimination products. For more information, see ref 13.

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