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Cp*Rh(III)/Chiral Disulfonate/CuOAc Catalyst System for the Enantioselective Intramolecular Oxyamination of Alkenes.

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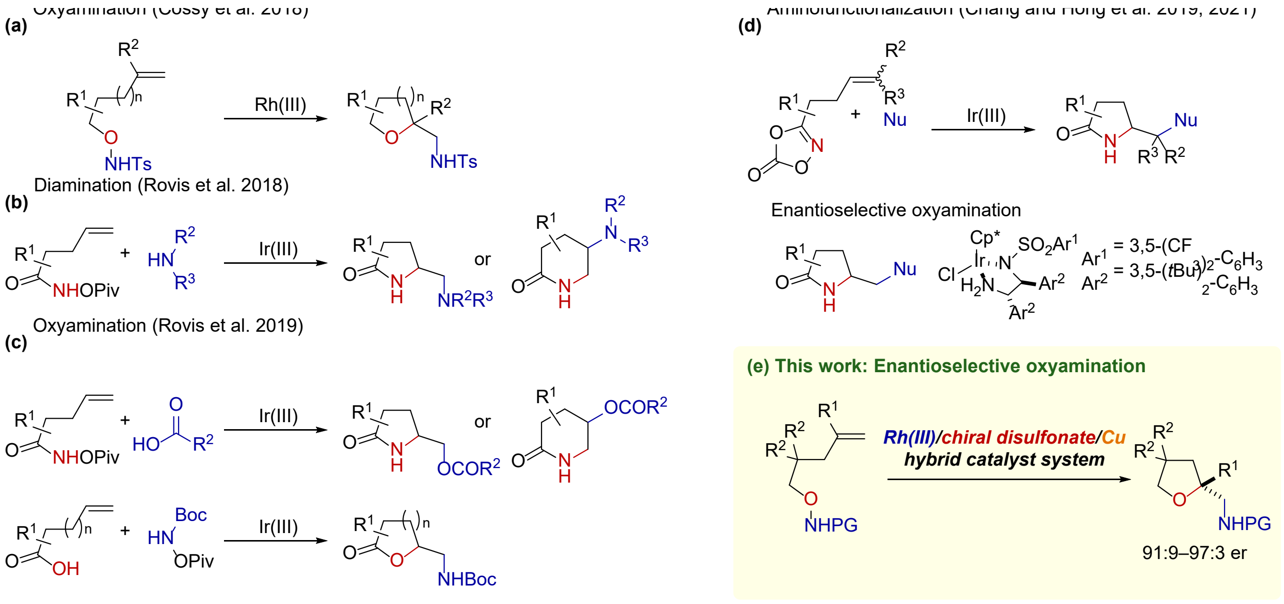
ABSTRACT: The enantioselective intramolecular oxyamination of unsaturated alkoxyamines using a hybrid catalytic system consisting of Cp*Rh(III)/chiral disulfonate/CuOAc is described. Tetrahydrofuran derivatives with a tetrasubstituted chiral center were obtained under the optimized conditions in 92:8–96:4 er. The use of a sterically hindered chiral disulfonate and a Cu additive was essential for the high enantioselectivity.

Trivalent group 9 metal complexes with a pentamethylcyclopentadienyl (Cp*) or other related ligands, Cp*M(III) (M = Co, Rh, Ir), have been widely exploited as robust and highly reactive catalysts for organic transformations.[1-6] Since the seminal work by Satoh, Miura, and co-workers in 2007,[1] C–H functionalization reactions using these catalysts have attracted much attention and thus, a large number of reactions of this type have been developed to date. In contrast, several recent studies have revealed a new direction for Cp*M(III) catalysis, i.e., the 1,2-hetero-difunctionalization of alkenes to regioselectively introduce two C–X bonds (X = hetero atom; Figure 1).[3-7] In 2018, Cossy and co-workers reported Cp*Rh(III)-catalyzed intramolecular oxyamination of unsaturated alkoxyamines to yield cyclic ethers (Scheme 1a).[3] Rovis and co-workers reported Ir(III)-catalyzed diamination using external amine nucleophiles to provide lactam products (Scheme 1b).[4] The same group later reported oxyamination reactions of unsaturated amides or carboxylic acids with external nucleophiles to give either lactams or lactones (Scheme 1c), where the regioselectivity was efficiently controlled by electronic tuning of the catalyst.[5] In 2019, Hong and Chang showed that Ir-nitrene species catalytically generated from dioxazolones could enable haloamination and

Scheme 1. Rh(III)- and Ir(III)-Catalyzed Hetero Difunctionalization of Alkenes.



oxyamination reactions (Scheme 1d).[6a] The same group further expanded this catalytic system by introducing an *N*,*N*-chelating ancillary ligand and achieved a catalytic enantioselective oxyamination reaction that furnishes optically active γ-lactams.[6b]

Catalytic enantio-control under the Cp*M(III) catalysis has attracted significant attention over the past decade.[8-13] After the seminal studies by Cramer and co-workers on precisely designed chiral Cp^x ligands,[9] the development and applications of chiral Cp^x ligands have predominantly been focused on enantioselective C–H functionalization reactions.[10] Alternatively, approaches that use an artificial metalloenzyme have been presented by Ward, Rovis, and co-workers,[11] whilst chiral carboxylic acids have also been utilized to control the enantioselectivity.[12] In this context, our group has previously reported Cp*Rh(III)/chiral disulfonate hybrid catalysts for the enantioselective C–H alkylation of 2-phenylpyridine and 6-arylpurine derivatives.[13] However, none of these approaches that realize catalytic enantio-control has been applied to the above-mentioned diamination or oxyamination reactions of alkenes. Here we report that a combination of Cp*Rh(III), a chiral disulfonate, and CuOAc promotes the enantioselective intramolecular oxyamination[14,15] of unsaturated alkoxyamines to give chiral tetrahydrofurans adorned with an aminomethyl group (Scheme 1e).

Bi and co-workers reported a computational mechanistic study of the Rh(III)-catalyzed oxyamination that is shown in Scheme 1a.[16] Based on their results, a plausible catalytic cycle is shown in Figure 1. The deprotonation and coordination of the substrate (**I**), followed by a [3+2] cycloaddition (**II**) and a subsequent cleavage of the N–O bond furnishes Rh(V) nitrene **III**. Reductive elimination from **III** leads to the formation of **IV.** The final reductive elimination step has the highest barrier and is highly exergonic. Therefore, this step is thought to be irreversible and rate-determining. Because the formation of **III** from **I** would be endergonic and reversible, the reductive elimination (**III** to **IV**) would be an enantio-determining step of this reaction. Although Bi and co-workers performed calculations based on the assumption that an acetate ligand coordinates during the catalytic process (L = acetate), we hypothesized that the reaction could proceed with a non-coordinating chiral anion instead (L = none). This anion would recognize one of the enantiomers of **III** via contact-ion-pairing and induce the enantioselectivity of this reaction.[17]

To assess the plausibility of our hypothesis, we performed density functional theory (DFT) calculations for the reaction without an acetate ligand at the M06/def2TZVPP//M06L/def2SVP level of theory[18,19] with an SMD solvation model (DCE)[20] for both the geometry optimizations and single point energy calculations. The calculations were performed using GRRM17[21] and Gaussian 16 Rev. C.01[22] programs. As shown in Figure S1 (see Supporting Information), the transition-state structures for the [3+2] cycloaddition (**TS (I-II)**), the N–O bond cleavage step that affords a Rh-nitrene intermediate (**TS (II-III)**), and the C–N bond forming reductive elimination (**TS (III′-IV)**) were located. The energy diagram is similar to the one where an acetate ligand is included, as reported in the previous study. The final reductive elimination step of this reaction would be rate-determining and the sole irreversible step in the catalytic cycle with a reasonable activation barrier of 23.5 kcal/mol. These results indicate that a cationic mechanism without an acetate ligand where the enantiocontrol is mediated by a chiral anion should be possible.

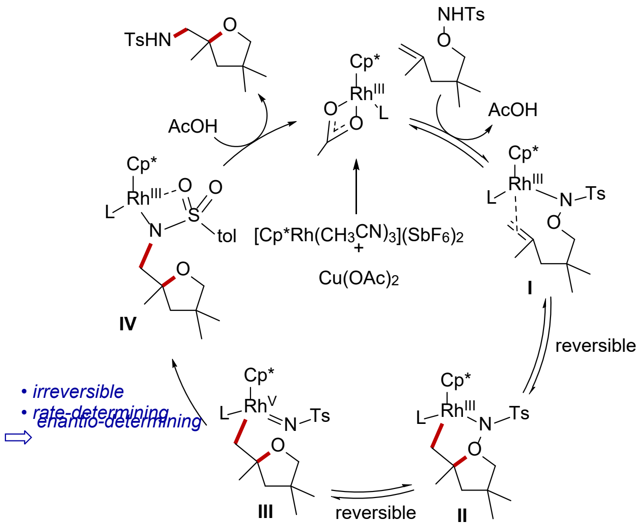


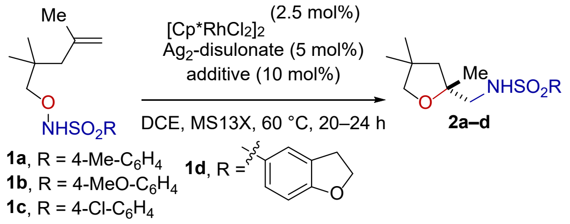
Figure 1. Catalytic cycle based on the computational study by Bi *et al* (L = OAc) and in this work (L = none; possibly with a non-coordinating chiral anion).

We started our experimental investigation by screening several chiral disulfonates[23] with **1a** as a model substrate (Table 1, entries 1–6). In this study, chiral disulfonic acids were converted to the corresponding Ag salts and mixed with [Cp*RhCl$_2$]$_2$ to generate the active chiral catalysts *in situ* via chloride abstraction to form AgCl. While a stoichiometric amount of Cu(OAc)$_2$ was used in the racemic reactions reported by Cossy et al., we used a catalytic amount of CuOAc to decrease the concentration of acetate anion present thus suppress a racemic reaction. Based on our previous report on a Cp*Rh(III)/chiral disulfonate catalytic system, we used 1,1′-binaphthyl-2,2′-disulfonate (**3a**; BINSate) and a spirocyclic disulfonate (**4**; SPISate). To our delight, a promising level of enantioselectivity was observed when **3a** was used (entry 1, 79:21 er), albeit that the yield was low. Further screening of chiral anions revealed that the substituents at the 3,3′-positions had a drastic effect on both the reactivity and enantioselectivity of the reaction (entries 3–6). The introduction of phenyl groups or 4-*t*Bu-C$_6$H$_4$ groups greatly enhanced the reactivity and selectivity (entries 3 and 5). However, the reaction barely proceeded when using a 3,5-(CF$_3$)$_2$-C$_6$H$_3$-substituted BINSate (**3c**; entry 4) or a 3,5-(*t*Bu)$_2$-C$_6$H$_3$-substituted BINSate (**3e**; entry 6). With the optimal catalyst (**3d**) selected, the effect of the protecting group on the substrate (**1**) was examined. We found that electron-rich sulfonyl groups slightly improved the yield (entries 7 and 9), while an electron-deficient sulfonyl group significantly diminished the yield (entry 8). The best result was obtained with substrate **1d** under the conditions in entry 9.

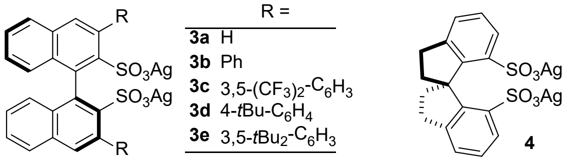
Changing CuOAc to other Cu sources or acetate sources gave rise to some striking results (entries 9–15). The use of copper(I) 2-thiophenecarboxylate (CuTC) led to the decreased reactivity and selectivity (entry 10). While

$Cu(OAc)_2$ exhibited a similar reactivity and selectivity to CuOAc, the use of CuO and CuCN afforded almost no product (entries 12 and 13), possibly because the deprotonation of the substrate is not viable without the acetate. As the Cu(I) and Cu(II) acetates afforded similar but slightly different results (entries 9 and 11), we speculated that the same Cu(I) active species might be generated from either Cu(I) or Cu(II). In contrast, when AgOAc or KOAc were used instead of CuOAc, the product was obtained as a racemic mixture (entries 14 and 15), indicating that a Cu ion is crucial for induction of the enantioselectivity. The desired reaction scarcely proceeded when using no acetate source (entry 16), using a disulfonic acid (BINSA) instead of its silver salt (entry 18), or omitting $[Cp^*RhCl_2]_2$ (entry 19). These control experiments suggest that a cationic Cp*Rh(III) species promotes the reaction and that the BINSate anion and Cu ion may cooperatively control the enantioselectivity. Omitting MS13X from the reaction resulted in a lower yield but similar enantioselectivity, although the reason is not clear at this point (entry 20).

Table 1. Optimization and Control Experiments for the Enantioselective Oxyamination of 1.[a]

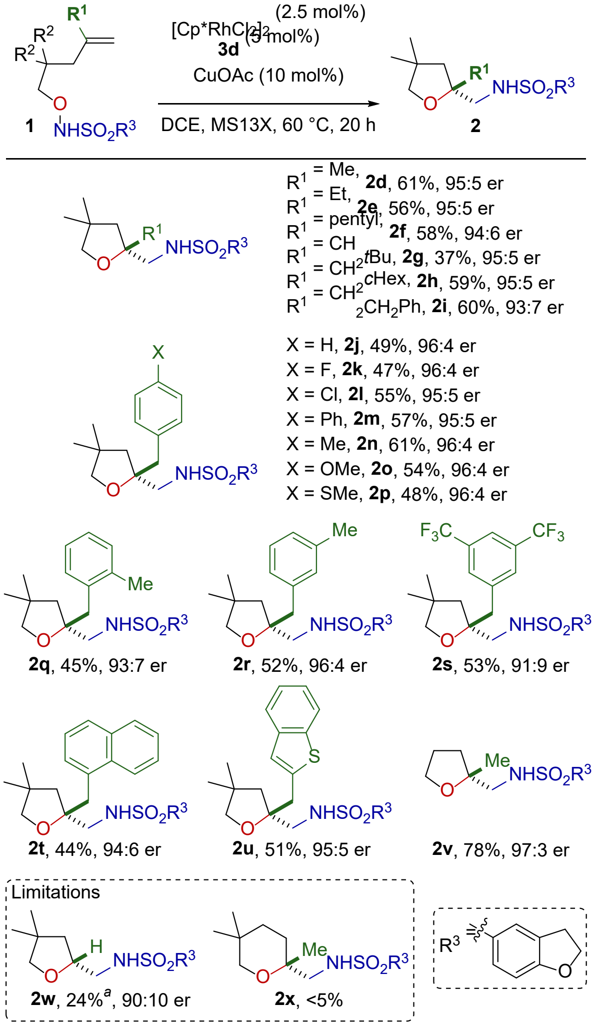


Entry	Substrate	Ag_2-disulfonate	Additive	Yield[b] [%]	Er[c]
1	**1a**	**3a**	CuOAc	15	79:21
2	**1a**	**4**	CuOAc	19	47:53
3	**1a**	**3b**	CuOAc	54	92:8
4	**1a**	**3c**	CuOAc	7	73:27
5	**1a**	**3d**	CuOAc	55	95:5
6	**1a**	**3e**	CuOAc	9	71:29
7	**1b**	**3d**	CuOAc	63	90:10
8	**1c**	**3d**	CuOAc	25	91:9
9	**1d**	**3d**	CuOAc	65	95:5
10	**1d**	**3d**	CuTC	30	91:9
11	**1d**	**3d**	$Cu(OAc)_2$	59	88:12
12	**1d**	**3d**	CuO	<5	ND
13	**1d**	**3d**	CuCN	<5	ND
14	**1d**	**3d**	AgOAc	17	50:50
15	**1d**	**3d**	KOAc	50	50:50
16	**1d**	**3d**	none	<5	ND
17	**1d**	none	CuOAc	11	ND
18	**1d**	[d]	CuOAc	<5	ND
19[e]	**1d**	**3d**	CuOAc	<5	ND
20[f]	**1d**	**3d**	CuOAc	34	94:6



[a] Reaction conditions: **1** (0.05 mmol), $[Cp^*RhCl_2]_2$ (1.25 μmol, 2.5 mol%) Ag_2-disulfonate (2.5 μmol, 5 mol%), additive (5 μmol, 10 mol%), and MS13X (3 mg) in DCE (2 mL) at 60 °C for 20–24 h unless otherwise noted. [b] Determined by ^1H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as the internal standard. [c] Determined by chiral HPLC analysis. [d] The parent disulfonic acid form of **3d** was added. [e] Without $[Cp^*RhCl_2]_2$. [f] Without MS13X.

Scheme 2. Scope and Limitations for the Enantioselective Oxyamination of 1 using the Cp*Rh(III)/3d/CuOAc Catalyst.



Reaction conditions: **1** (0.10 mmol), $[Cp^*RhCl_2]_2$ (2.5 μmol, 2.5 mol%) Ag_2-disulfonate (5 μmol, 5 mol%), CuOAc (10 μmol, 10 mol%), and MS13X (6 mg) in DCE (4 mL) at 60 °C for 20 h. Isolated yields are shown. [a] Determined by ^1H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as the internal standard.

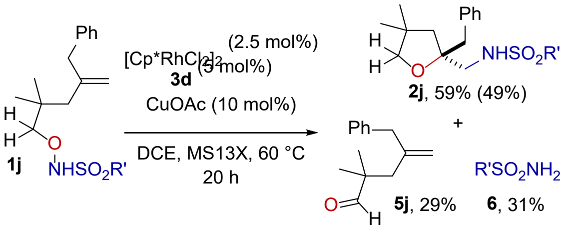
The optimized catalyst and reaction conditions (Table 1, entry 8) were applied to various unsaturated alkoxyamines

1, and the results are summarized in Scheme 2. Regardless of the substituent at the alkene moiety, moderate yields and high enantioselectivities (91:9–96:4 er) were obtained. Although both aliphatic and aromatic substituents were tolerated, a sterically hindered substituent led to a diminished yield (**2g**). Neither the presence of electron-withdrawing groups (**2k**, **2l**, **2s**) nor electron-donating groups (**2n–2p**) on the phenyl moiety resulted in a significant effect, and the products were afforded with high enantioselectivities. A 2-naphthyl-substituted substrate (**1t**) and a 2-benzothienyl-substutited substrate (**1u**) also gave products in moderate yields with high enantioselectivities. Furthermore, the geminal dimethyl substituents of the substrates were not essential, and a simple linear substrate afforded the corresponding product (**2v**) in 78% yield and 97:3 er. The absolute configuration of **2m** was determined by the single crystal X-ray diffraction analysis (for details, see Supporting Information).

The limitations of the current catalytic system are shown at the bottom of Scheme 2. A mono-substituted terminal alkene exhibited much lower reactivity and slightly diminished selectivity (**2w**). We also investigated the synthesis of a chiral tetrahydropyran **2x**, but the desired six-membered ring formation scarcely proceeded.

Even under the optimized conditions, the yield of **2** was moderate in most cases, which was attributed predominantly to the decomposition pathway of the alkoxyamines **1**. As shown in Scheme 3, we observed the formation of aldehyde **5j** and sulfonamide **6** when using **1j** as the substrate. Although the mechanism for this decomposition is not clear at this point, we speculate that the oxidative addition of a Rh species to the N–O bond and a subsequent β-hydride elimination might afford **5i** and **6**.

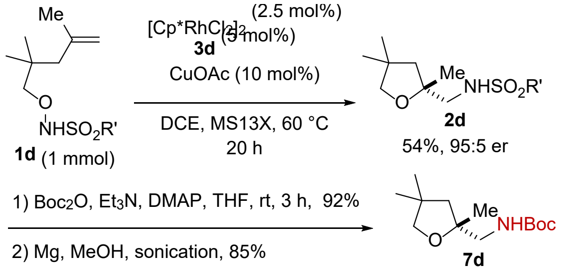
Scheme 3. Observed Byproducts When Using 1i as the Substrate.[a]



[a]The indicated yields were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as the internal standard. The isolated yield is shown in parentheses. R' = 2,3-dihydrobenzofuran-5-yl.

A preparative-scale reaction using **1d** (1 mmol) as the substrate proceeded smoothly to provide **2d** in 54% yield with 95:5 er (Scheme 4), which is comparable to the result of the small-scale reaction (Scheme 2, 61% yield, 95:5 er). The sulfonyl protecting group of the amino moiety of **2d** was successfully removed by Mg reduction after Boc protection,[24] thus demonstrating the synthetic utility of product **2**.

Scheme 4. Preparative-scale Reaction and Deprotection of the Sulfonyl Group.



Based on DFT calculations (Figure S1) and the observation that a Cu ion is essential for the induction of the enantioselectivity (Table 1, entries 8, 12–14), we would like to propose a mechanism for the control of the enantioselectivity (Figure 2). Intermediate **III** would be reversibly generated from substrate **1** and the Cp*Rh(III) catalyst. Reductive elimination from **III** would be the rate- and enantio-determining step, and hence this step is controlled by a chiral disulfonate. A Cu ion would also be involved in this step. Thus, we speculate that a Cu-disulfonate monoanionic complex might be the key species that controls the enantioselectivity of the reaction through interactions with **III** and the subsequent transition state of the reductive elimination step. Although the mode of the interaction between **III** and the chiral component remains unclear, ion-paring rather than coordination seems most plausible as the sterically hindered disulfonate anions exhibited, not only higher enantioselectivity, but also higher reactivity (Table 1, entries 1, 3, 5) than the less hindered anions.

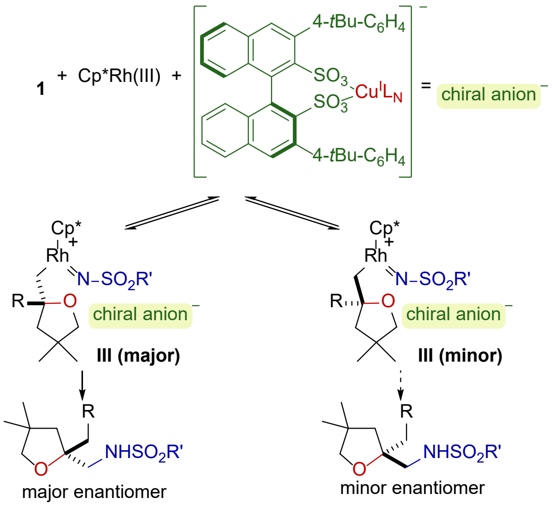


Figure 2. Proposed mechanism for the enantiocontrol of the oxyamination of **1** mediated by a chiral disulfonate.

In summary, we have developed a catalytic enantioselective intramolecular oxyamination of unsaturated alkoxyamines **1** using a combination of a Cp*Rh(III) catalyst, a chiral disulfonate, and CuOAc. Tetrahydrofuran derivatives with a tetrasubstituted chiral carbon centre adjacent to an aminomethyl moiety (**2**) were obtained in high enantioselectivities. The chiral disulfonate would likely control the rate- and enantio-determining reductive elimination step, in which a Cu ion would also be involved. The results not only represent a method for controlling enantioselectivity of Cp*Rh(III)-catalyzed oxyamination reactions but also suggest the possibility of using Cp*M(III)/chiral disulfonate/Cu hybrid catalysis for future applications.

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Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge at http://pubs.acs.org.

Details for DFT calculations, experimental procedures, characterization of the synthesized compounds, and NMR spectra (PDF). X-ray crystallographic data for the determination of the absolute configuration (CIF). Calculated structure data (xyz). These materials are available free of charge via the Internet at http://pubs.acs.org.

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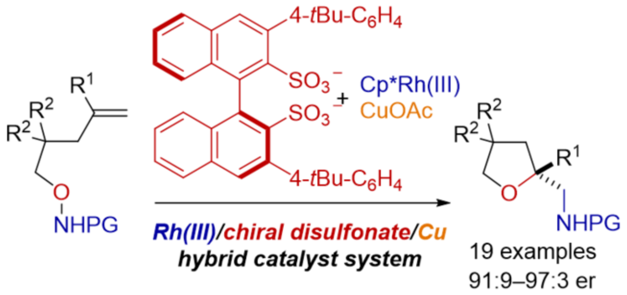
4-tBu-C6H4
SO3−
SO3−
4-tBu-C6H4
+
Cp*Rh(III)
CuOAc
R1
R2
R2
O
NHPG
Rh(III)/chiral disulfonate/Cu
hybrid catalyst system
R2
R2
R1
O
NHPG
19 examples
91:9–97:3 er