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Design of Ru(II)-NHC-Diamine Precatalysts Directed by Ligand Cooperation: Applications and Mechanistic Investigations for Asymmetric Hydrogenation

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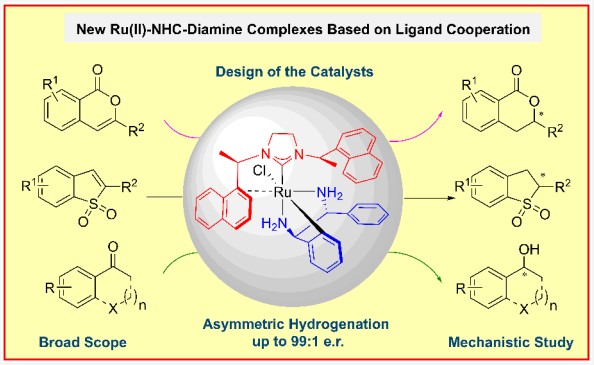
ABSTRACT: A modular synthesis of Ru(II)-NHC-diamine complexes from readily available chiral N-heterocyclic carbenes (NHCs) and chiral diamines is disclosed for the first time. The well-defined Ru(II)-NHC-diamine complexes show unique structure and coordination chemistry including an unusual tridentate coordination effect of 1,2-diphenylethylenediamine. The isolated air- and moisture-stable Ru(II)-NHC-diamine complexes act as versatile precatalysts for the asymmetric hydrogenation of isocoumarines, benzothiophene 1,1-dioxides, and ketones. Moreover, on the basis of the identification of reaction intermediates by stoichiometric reactions and NMR experiments, together with the DFT calculations, a possible catalytic cycle was proposed.

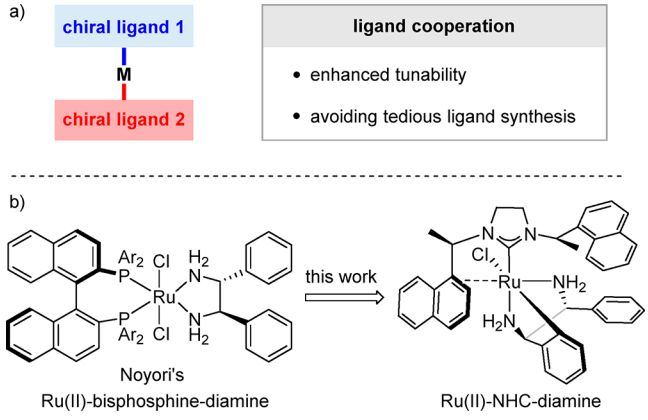


1. INTRODUCTION

The development of new chiral catalysts is key to improving efficiency and selectivity in asymmetric catalysis, even to discovering new modes of catalysis and new reactions.[1] Conventionally, the chiral environment of a transition-metal catalyst is optimized by the modification of the structure of a single chiral ligand. However, this strategy is limited to ligand structures that can be readily accessed. Even though much endeavor and time are spent on the ligand optimization, satisfactory results are often out of reach. The utilization of ligand cooperation is an alternative strategy, which has the potential to accelerate the optimization process through a simple mix of two different chiral ligands (Scheme 1a). Remarkably, the introduction of a second, readily available ligand not only adds a new tunable site but also offers a practical way to avoid the tedious synthetic problems caused by the modification of a complicated ligand.[2]

Noyori's elegant Ru(II)-bisphosphine-diamine catalyst is a representative example utilizing the ligand cooperation concept (Scheme 1b).[3] Since then, the cooperation of chiral phosphines and chiral diamines was applied widely in asymmetric catalysis. Nevertheless, novel cooperative systems beyond phosphine-type ligands have been rarely investigated for late transition metals.[2,4] Inspired by Noyori's catalyst and our ongoing interest in N-heterocyclic carbenes (NHCs),[5,6] we recently reported a new combination of chiral NHC and chiral diamine ligands for the Ru(II)-catalyzed enantioselective hydrogenation of isocoumarins.[7] However, the proposed

Scheme 1. Ligand Cooperation Strategy for the Design of New Chiral Catalysts



Ru(II)-NHC-diamine species was only supported by control experiments. Undoubtedly, the isolation and characterization of the Ru(II)-NHC-diamine complexes would not only

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confirm the previous proposal but also provide us a new platform to design NHC-based catalysts directed by the ligand cooperation concept. Herein, we report the synthesis and structure determination of the chiral ruthenium precatalysts and related complexes (Scheme 1b). Unprecedented procedures for the preparation of air- and moisture-stable Ru(II)-NHC-diamine precatalysts from commercial or other readily available materials were described in this endeavor. Furthermore, the newly established catalysts were successfully applied to asymmetric hydrogenations of several important substrate classes. In the end, detailed mechanistic studies of asymmetric hydrogenation catalyzed by the Ru(II)-NHC-diamine complexes were conducted.

2. RESULTS AND DISCUSSION

2.1. Synthesis and Structure of Ru(II)-NHC-Diamine Complexes. First, we developed a stepwise way to install a chiral NHC ligand and a chiral diamine ligand into one ruthenium complex (Figure 1). We hypothesized that silver

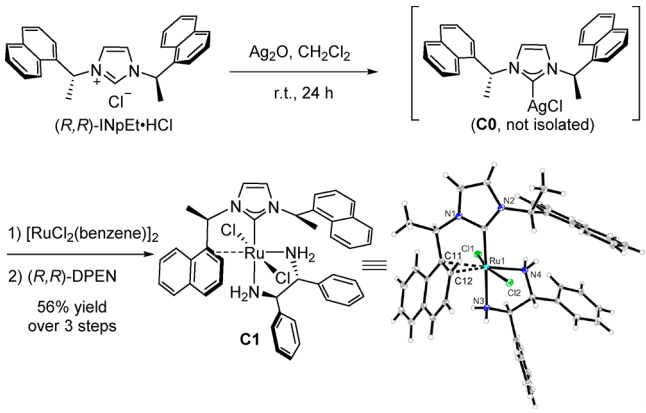

Figure 1. Synthesis and structure of *trans*-$RuCl_2$(INpEt)(DPEN) **C1**. Selected bond lengths (Å) and bond angles (deg) of **C1**: Ru1−C1, 1.986(6); Ru1−N4, 2.135(5); Ru1−N3, 2.187(5); Ru1−C12, 2.218(5); Ru1−C11, 2.239(6); Ru1−Cl2, 2.4265(16); Ru1−Cl1, 2.4266(16); C11−C12 1.418(8); C1−Ru1−N3, 177.6(3); N4−Ru1−N3, 78.46(18); Cl2−Ru1−Cl1, 62.53(5); C12−Ru1−C11, 37.1(2).

carbene complexes could serve as carbene transfer agents for the synthesis of the ruthenium complexes as this strategy had previously been used for the synthesis of palladium and gold complexes.[8] The NHC silver complex **C0** was prepared from imidazolinium chloride (*R*,*R*)-INpEt·HCl and Ag_2O according to the literature.[9] The desired heteroleptic complex **C1** was obtained in 56% overall yield following the transmetalation of the NHC from silver complex **C0** to the ruthenium precursor and subsequent replacement of benzene with (*R*,*R*)-1,2-diphenylethylenediamine (DPEN). The isolated complex **C1** is stable to air and moisture and can be stored in an ordinary vial for months. X-ray crystallographic analysis of **C1** indicated a distorted octahedral geometry of the ruthenium center with a *trans*-dichloro geometry. Interestingly, the NHC ligand is acting as a chelate ligand with a dative carbene bond and an additional η^2-coordination of the naphthyl ring to ruthenium. This was further verified by the distinct NMR signals at δ 4.99 (^{1}H NMR, *H*C12), δ 92.0 (^{13}C NMR, C11), and δ 72.7 (^{13}C NMR, C12). The NMR analysis of *trans*-$RuCl_2$(INpEt)(DPEN) **C1** shows that **C1** exists as a single conformer in solution (C_6D_6, $CDCl_3$, or THF-d_8).

Furthermore, we developed a one-pot procedure for the synthesis of Ru(II)-NHC-diamine complexes (Figure 2). The

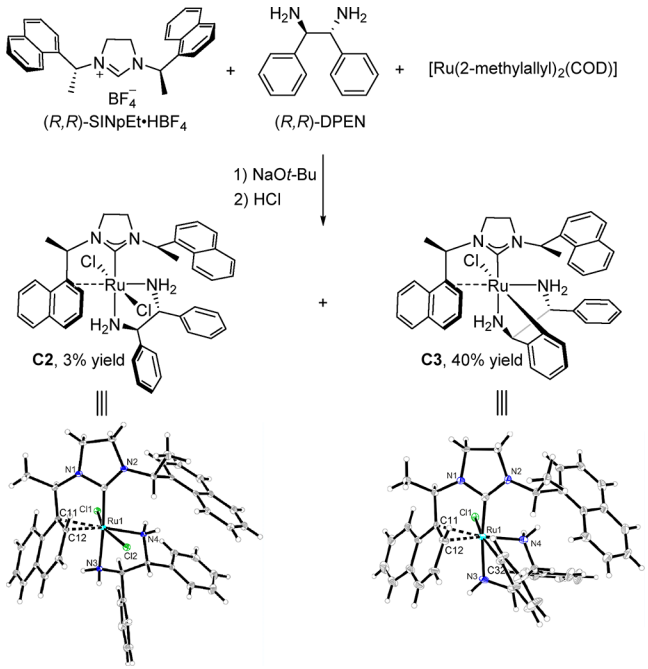

Figure 2. Synthesis and structure of *trans*-$RuCl_2$(SINpEt)(DPEN) **C2** and RuCl(SINpEt)(DPEN) **C3**. Selected bond lengths (Å) and bond angles (deg) of **C2**: Ru1−C1, 1.984(3); Ru1−N4, 2.146(3); Ru1−N3, 2.214(2); Ru1−C12, 2.222(3); Ru1−C11, 2.229(2); Ru1−Cl2, 2.4205(7); Ru1−Cl1, 2.4211(7); C11−C12, 1.423(5); C1−Ru1−N4, 103.22(11); C1−Ru1−N3, 172.73(11); N4−Ru1−N3, 78.58(9); C12−Ru1−C11, 37.30(12); Cl2−Ru1−Cl1, 160.63(2). Selected bond lengths (Å) and bond angles (deg) of **C3**: Ru1−C1, 1.953(9); Ru1−C32, 2.061(9); Ru1−N4, 2.153(7); Ru1−C12, 2.192(8); Ru1−N3, 2.203(7); Ru1−C11, 2.206(7); Ru1−Cl1, 2.549(2); C1−Ru1−C32, 99.3(3); C1−Ru1−N3, 173.8(3); N4−Ru1−N3, 75.5(3); C32−Ru1−Cl1, 160.0(3).

direct isolation of the Ru(II)-NHC-diamine species formed in situ by reacting [Ru(2-methylallyl)$_2$(COD)], NHC precursor (*R*,*R*)-SINpEt·HBF_4, diamine ligand (*R*,*R*)-DPEN, and NaO*t*-Bu in *n*-hexane was unsuccessful. We rationalized that the introduction of a chloride ligand might stabilize the ruthenium complex, thus simplifying the purification and isolation. After quenching the reaction with HCl solution (4.0 M in dioxane), ruthenium dichloride **C2** and ruthenium monochloride **C3** were isolated by flash chromatography on silica gel in 3% yield and 40% yield, respectively. In contrast, the combination of (*R*,*R*)-SINpEt·HBF_4 and (*S*,*S*)-DPEN gave only trace amounts of Ru(II)-NHC-diamine complexes, thus demonstrating a strong matched/mismatched effect. X-ray and NMR analyses revealed that ruthenium complex **C2** is structurally similar to complex **C1**. Unexpectedly, ruthenium monochloride **C3** contains an unusual tridentate binding of the diamine through an additional cyclometalation. This metal−carbon bond is formed through C−H activation at the 2-positon of the phenyl ring (^{13}C NMR shift: δ 176.5 in toluene-d_8).[10] Similar to **C1** and **C2**, the chelating NHC ligand in **C3** binds via carbene coordination and η^2-naphthyl coordination. Despite the polar carbon−metal bond, complex **C3** is not sensitive to air and moisture in the solid state. However, **C3** decomposes in solution over time. **C3** was also confirmed to remain a single conformer in solution by NMR spectroscopy (in C_6D_6,

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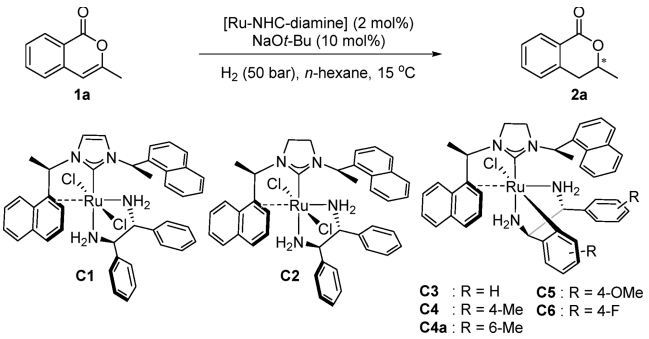
toluene-d_8, or THF-d_8). It is noteworthy that the addition of an excess of HCl (4.0 M in dioxane) to the **C3** solution (*n*-hexane, toluene, or THF) did not convert the monochloride complex to dichloride complex **C2**. Likewise, treatment of dichloride **C2** with a strong base like NaO*t*-Bu did not yield monochloride **C3**. According to the same one pot procedure, precatalysts **C4**, **C4a**, **C5**, and **C6** were prepared (Table 1).

Table 1. Catalyst Test for the Enantioselective Hydrogenation of Isocoumarins[a]



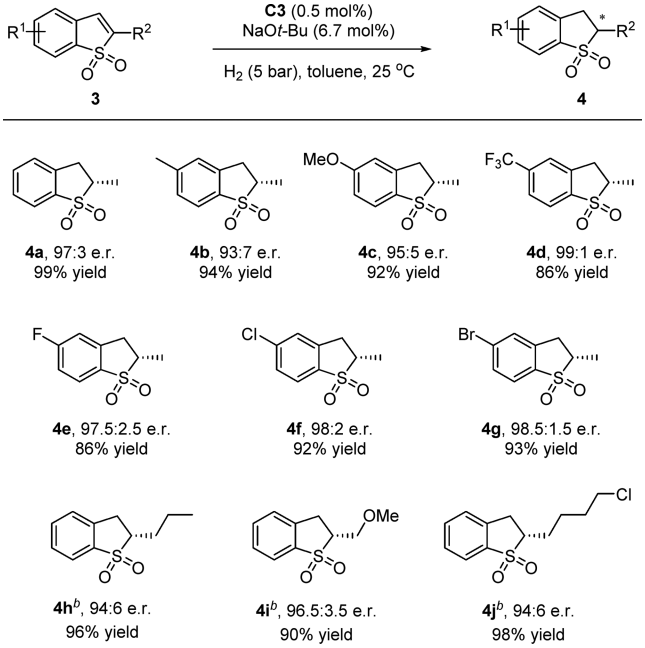
entry	precatalyst	time (h)	yield (%)[b]	e.r.[c]
1	**C1**	24	trace	ND
2	**C2**	24	trace	ND
3	**C3**	18	80	98:2
4	**C4**	18	83	98.5:1.5
5	**C5**	18	80	97:3
6	**C6**	18	78	96:4
7	**C4a**	18	65	72:28

[a]Reactions were carried out with **1a** (0.2 mmol), the indicated ruthenium complex (0.004 mmol, 2 mol %), and NaO*t*-Bu (0.02 mmol, 10 mol %) in *n*-hexane (4.0 mL) under 50 bar of H_2 at 15 °C for the indicated time. [b]Isolated yields. [c]Determined by HPLC analysis using a chiral stationary phase.

2.2. Applications of Ru(II)-NHC-Diamine Complexes in the Catalytic Asymmetric Hydrogenation. The isolated ruthenium complexes were then tested as precatalysts for the enantioselective hydrogenation. Asymmetric hydrogenation of 3-substituted isocoumarins is a direct way to form chiral 3-substituted 3,4-dihydroisocoumarins which represent a key motif in a wide range of natural products and biological active molecules.[11,12] By use of the isolated precatalysts, the enantioselective hydrogenation of 3-substituted isocoumarines was probed (Table 1). A strong base like NaO*t*-Bu was determined to be necessary to activate the precatalysts. Only trace amounts of product were obtained in the presence of dichloride ruthenium complex **C1** or **C2** (Table 1, entries 1 and 2). Notably, RuCl(SINpEt)(DPEN) **C3** exhibited a good activity under basic conditions (entry 3), giving the desired product **2a** in 80% yield and 98:2 e.r.[13] Next, variations on the chiral diamine ligand were investigated. Complex **C4** with (1*R*,2*R*)-1,2-di-*p*-tolylethane-1,2-diamine gave slightly better results, delivering the product in 83% yield and 98.5:1.5 e.r. (entries 4). Further *para*-substituents on the diamine were tested and gave comparable results (entries 5 and 6). However, additional substituents in the *ortho* position turned out to be unfavorable for the enantioselective hydrogenation of **1a** (entry 7). Diamines containing *meta*-substituents were previously tested through the in situ system, giving lower enantioselectivities and yields.[7a] We then explored the substrate scope of the reaction using the optimized conditions (Table 1, entry 4) as shown in the Supporting Information (page S36). A broad scope of isocoumarin derivatives was hydrogenated while tolerating differential position and electronic nature of the substituents as well as functional groups like thiophenes or methyl ethers (see Supporting Information for further details).

Next, we explored the enantioselective hydrogenation of benzothiophene 1,1-dioxides. The chiral 2,3-dihydrobenzothiophene 1,1-dioxide framework is a versatile motif in pharmaceutical research and agrochemistry.[14] Recently, the Pfaltz group reported a novel way to prepare chiral 2,3-dihydrobenzothiophene 1,1-dioxides by the iridium-catalyzed asymmetric hydrogenation of substituted benzothiophene 1,1-dioxides.[15,16] Remarkably, high reactivity and enantioselectivity of the hydrogenation of substituted benzothiophene 1,1-dioxides were obtained with the ruthenium complex **C3** (Scheme 2). After optimization of the reaction conditions, 2-

Scheme 2. Ruthenium-Catalyzed Asymmetric Hydrogenation of Benzothiophene 1,1-Dioxides[a]



[a]Unless otherwise noted, reactions were conducted with **3** (0.3 mmol), **C3** (0.0015 mmol, 0.5 mol %), and NaO*t*-Bu (0.02 mmol 6.7 mol %) under 5 bar of H_2 in toluene (2.0 mL) at 25 °C for 24 h. Isolated yields after column chromatography are reported. The e.r. values were determined by HPLC analysis using a chiral stationary phase. [b]Using 30 bar of H_2 at 0 °C.

methylbenzo[*b*]thiophene 1,1-dioxide **3a** was smoothly reduced under mild conditions using 0.5 mol % of precatalyst **C3** and a low H_2 pressure (5 bar) furnishing the corresponding product **4a** in 99% yield and 97:3 e.r. The absolute configuration of **4a** was determined to be *S* by comparing its optical rotation data to the literature.[15] The effect of substituents on the phenyl ring was probed. Electron-poor substrate **3d** provided the corresponding product **4d** with excellent enantioselectivity and in a good yield, while the electron-rich substrates provided slightly lower e.r. values (**4b** and **4c**). Halogen substituents F, Cl, and Br were well-tolerated under the mild reaction conditions (**4e**–**g**). Substrates containing longer alkyl chains and functional groups were

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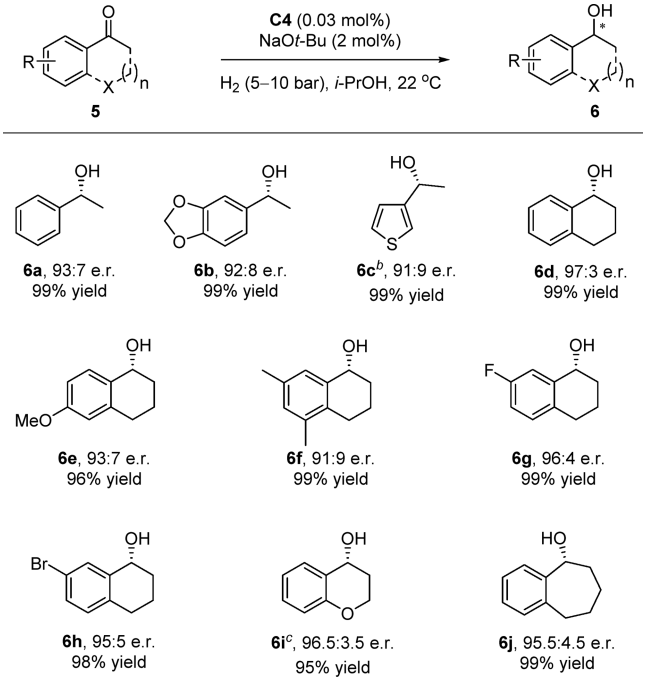
hydrogenated with good e.r. values and excellent yields (**4h–j**). Poor enantioselectivity was observed when 2-phenylbenzothiophene 1,1-dioxide was used, due to the deprotonation of the product's chiral center under basic conditions.

The enantioselective hydrogenation of ketones is among the most important asymmetric reactions, producing chiral alcohols that are common core structures in biologically active molecules and natural products.[3,17] To our delight, Ru(II)-NHC-diamine complexes can also be applied in this reaction (Scheme 3). Good enantioselectivities were obtained for

Scheme 3. Enantioselective Hydrogenation of Ketones Catalyzed by Ru(II)-NHC-Diamine Complexes[a]

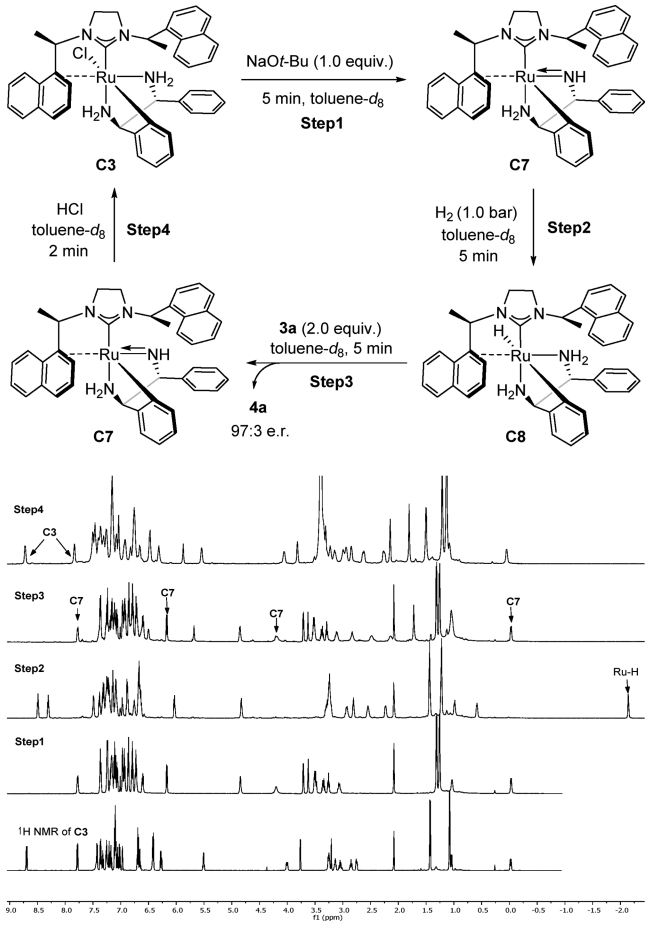


[a]Unless otherwise noted, reactions were carried out with **5** (1.0 mmol), **C4** (0.0003 mmol, 0.03 mol %), and NaO*t*-Bu (0.02 mmol, 2.0 mol %) under 5–10 bar of H_2 and in *i*-PrOH (1.0 mL) at 22 °C for 24 h. Isolated yields after column chromatography are reported. The e.r. values were determined by HPLC analysis using a chiral stationary phase. [b]Using 0.05 mol % of **C4**. [c]Using 0.5 mol % of **C4**.

acetophenones and 1-(thiophen-2-yl)ethan-1-one in the presence of ruthenium complex **C4** (**6a–c**). Moreover, various benzo-fused cyclic ketones underwent the hydrogenation smoothly in the current catalytic system, giving the corresponding chiral alcohols with high e.r. values (**6d–j**).[18]

2.3. Mechanistic Studies of the Ru(II)-NHC-Diamine Catalyzed Asymmetric Hydrogenation of Benzothiophene 1,1-Dioxides. To gain information on the mechanism of the catalytic process, several stoichiometric reactions were conducted followed by in situ NMR measurements (Scheme 4). First, precatalyst **C3** underwent a dehydrochlorination reaction upon treatment with NaO*t*-Bu (1.0 equiv) in toluene-d_8 giving the amido complex **C7** quantitively. This reaction was accompanied by a strong color change from yellow to dark red and took place in 5 min at room temperature. Removing *t*-BuOH under reduced pressure enabled the characterization of **C7** (Scheme 4, step 1; for detailed information, see Supporting Information). According to NMR analysis, the η^2-coordination of the naphthyl ring and the tridentate coordination of DPEN

Scheme 4. Stoichiometric Reactions and NMR Experiments



to the ruthenium center persisted at this stage. Complex **C7** then reacted instantaneously with H_2 (1 bar) in toluene-d_8 at room temperature to produce metal hydride species **C8** with a typical Ru–H hydride signal in the ^{1}H NMR spectrum (−2.14 ppm) (Scheme 4, step 2). NMR characterization of **C8** confirmed that no hydrogenolysis of the ruthenium–carbon occurred (for details, see Suppporting Information). Complex **C8** decomposes rapidly in solution (0.14 M in toluene-d_8) at room temperature but is stable for days at −78 °C. After release of H_2 from the NMR tube, an amount of 2 equiv of **3a** was added to **C8** in toluene-d_8 accompanied by a color change from brown to dark red. ^{1}H resonances associated with complex **C7** appeared while the signal corresponding to the Ru–H disappeared (Scheme 4, step 3). Meanwhile, **4a** was observed with 97:3 e.r. and roughly 50% NMR yield with respect to the amount of **3a**. If the mixture of step 3 was placed under H_2 atmosphere again, **C8** could be regenerated along with full conversion of **3a**. Finally, quenching of complex **C7** with an HCl solution (4 M in dioxane) regenerated the air-stable precatalyst **C3** (Scheme 4, step 4).

On the basis of the above experiments, previous mechanistic studies of Ru(II)-diphosphine-diamine catalyzed asymmetric hydrogenations of ketones,[19] and DFT calculations as described below (Scheme 6; see Supporting Information for details and unfavorable alternative pathways), we propose a mechanism for ruthenium-catalyzed asymmetric hydrogenation of benzothiophene 1,1-dioxides including the mode of enantioinduction (Scheme 5). The reaction between precatalyst **C3** and NaO*t*-Bu should give the active amido complex

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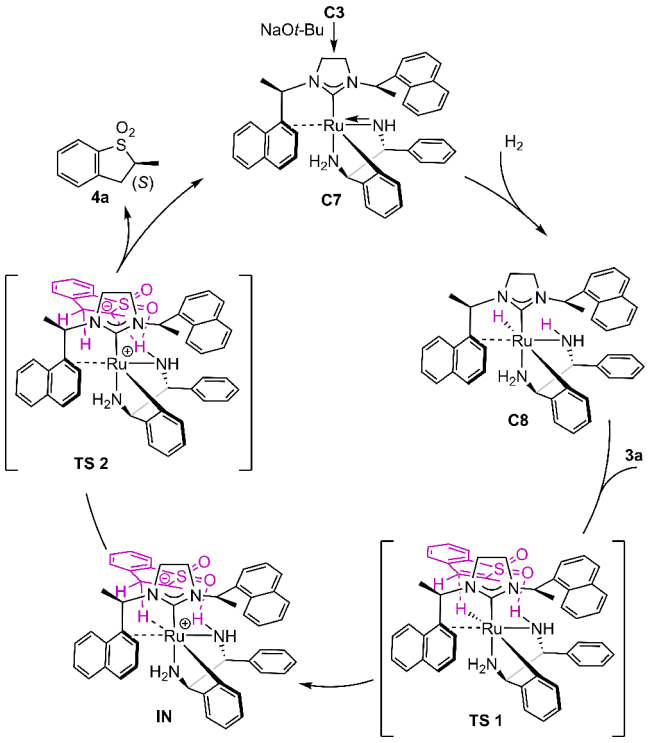
Scheme 5. Proposed Mechanism for Ruthenium-Catalyzed Asymmetric Hydrogenation of Benzothiophene 1,1-Dioxides



C7. We postulate that an unobserved dihydrogen intermediate might be generated when placing complex **C7** under an H_2 atmosphere. Then, an intramolecular heterolytic splitting of dihydrogen would provide hydride complex **C8**. When substrate **3a** is added to **C8**, a hydrogen-bond interaction between the amine proton and the oxygen atom of the sulfone group occurs. The resulting intermediate is stabilized by 0.8 kcal/mol relative to the reactants **3a** and **C8** for the pathway leading to the (*S*)-product according to our DFT (PBE0/def2-SVP) results (Scheme 6). A possible transition state **TS1** is proposed based on the outer-sphere bifunctional catalysis mechanism by Noyori and other groups.[19] The nucleophilic Ru−H hydride should attack the β position of the sulfone ring according to the reaction nature of benzothiophene 1,1-dioxide compounds.[20] Our calculations confirm the existence of a transition state in which the Ru−H hydride is transferred to the β position of the sulfone ring in the presence of the above-mentioned hydrogen bond (Scheme 6, **TS1**), resulting in a destabilization of 3.7 kcal/mol. An intrinsic reaction coordinate (IRC) analysis shows, however, that hydrogen and proton transfers proceed in a stepwise manner. The IRC analysis leads to intermediate **IN** (Scheme 6, **IN**), in which the proton still resides on the amine group. This intermediate is stabilized by 12.5 kcal/mol compared to **TS1**. The product complex is reached via a second transition state (Scheme 6, **TS2**, destabilized by 2.8 kcal/mol compared to **IN**) in which the proton is transferred. In this second step, the proton of the amine group in the intermediate **IN** should transfer to the α position of the sulfone group from the *Re* face of the prochiral center, thus giving rise to the product **4a** with *S* configuration and regenerating amido complex **C7**, resulting in a final stabilization of 14.2 kcal/mol.

3. CONCLUSIONS

We introduced a practical and general procedure for the synthesis of chiral Ru(II)-NHC-diamine complexes based on the concept of ligand cooperation. The characterized ruthenium dichloride and monochloride complexes show a unique structure with unusual binding of the ligands. The ruthenium monochloride complexes serve as versatile catalysts for the enantioselective hydrogenation of isocoumarines, benzothiophene 1,1-dioxides, and ketones. A possible mechanism was proposed based on the identification of reaction intermediates via stoichiometric experiments, NMR analyses, and a computational study.

■ ASSOCIATED CONTENT

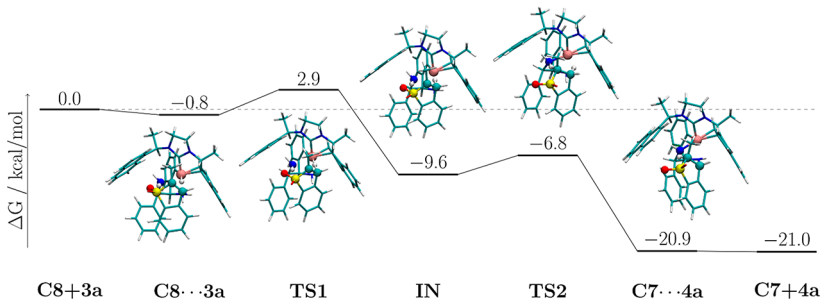
Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c00985.

Experimental details for data acquisition, full quantum chemical study concerning the reaction mechanism, and additional discussion (PDF)

CCDC-1879259 (C1), -1879260 (C2) and -1879261 (C3) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 6. Calculated Relative Gibbs Free Energies for the Ruthenium-Catalyzed Asymmetric Hydrogenation of Benzothiophene 1,1-Dioxides Leading to the (*S*)-Product[a]



[a]All values in kcal/mol.

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Notes

The authors declare no competing financial interest.

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