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Asymmetric Intramolecular Diels-Alder Reactions of Trienals Catalyzed by Chiral Ruthenium Lewis Acids

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§SCS DSM Prize for best poster

Abstract: Chiral single-point binding ruthenium Lewis acid catalysts [Ru(acetone)((*S,S*)-BIPHOP-F)(Cp)][SbF_6] ((*S,S*)-**1a**) and [Ru(acetone)((*S,S*)-BIPHOP-F)(indenyl)][SbF_6] ((*S,S*)-**1b**) efficiently catalyze intramolecular Diels-Alder (IMDA) reactions of trienals under mild conditions to afford the *endo* cycloaddition products as the major products in good yields with high diastereo- and enantioselectivities.

Keywords: Asymmetric IMDA reaction · Chiral catalyst · Diels-Alder · Lewis acid · Ruthenium

Cycloaddition reactions with their potential for a high degree of stereo- and regiocontrol are arguably the most versatile processes for the construction of five- and six-membered rings. Spectacular asymmetric versions have been achieved by using chiral Lewis acid catalysts.[1] Our studies in this area focused on one-point binding chiral ruthenium Lewis acids (**1a** and **1b**) that are based on structurally well-defined monocationic half-sandwich complexes that incorporate a C_2-symmetric perfluoroaryl phosphinite ligand. This ligand enforces the appropriate chiral environment around the coordination site and it also offsets the donor properties of the cyclopentadienyl- and indenyl-ligands (Fig. 1). The chiral, electron-poor ligand contributes to the Lewis acidity of these complexes, and together with the aromatic arene, generate a chiral binding site that is ideal for the activation of α,β-unsaturated carbonyl compounds.

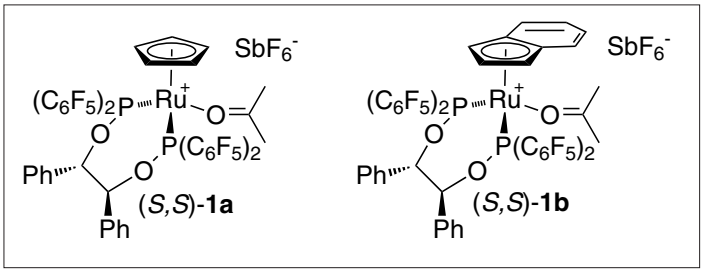
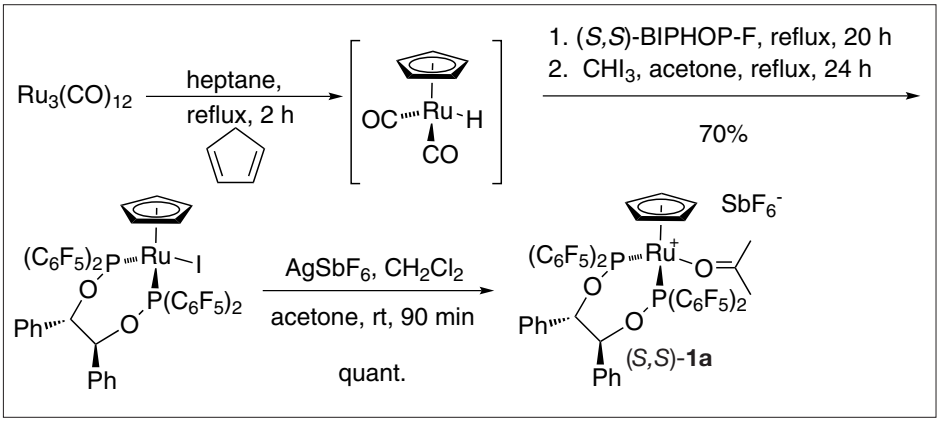


Fig. 1. Single-point binding chiral Ru Lewis acid catalysts.



Scheme 1. Synthesis of [Ru(acetone)((*S,S*)-BIPHOP-F)(Cp)][SbF_6] (**1a**).

The synthesis of the stable iodoruthenium complex was achieved in a 'one pot' procedure from [$Ru_3(CO)_{12}$]. Significant to the success was the hydride-labilizing effect, which enabled CO substitution in the *in situ* formed [$RuCp(CO)_2H$]. Heating at reflux in acetone in the presence of iodoform afforded the chiral Ru-iodo complex, and halide abstraction by $AgSbF_6$ generated Lewis acid **1a** as shown in Scheme 1.[2a]

Catalyst **1b** was synthesized *via* ligand exchange in [Ru(Cl)(indenyl)(PPh_3)$_2$] with BIPHOP-F to afford [Ru(BIPHOP-F)(Cl)(indenyl)]. Halide abstraction with $AgSbF_6$ furnished Lewis acid **1b** as shown in Scheme 2.[2b]

These mild chiral Lewis acids proved to be excellent catalysts for intermolecular Diels-Alder (DA) reactions of various dienes with enals[2] and enones,[3] 1,3-dipolar cycloadditions of enals with nitrones[4] and of enals with nitrile oxides[4b,5] as shown in Scheme 3. The 1,4-addition of thiophenols to enones could also be carried out using these catalysts.[6] Representative examples are shown in Scheme 4.

We have established details of the mode of action of these catalysts, notably the role

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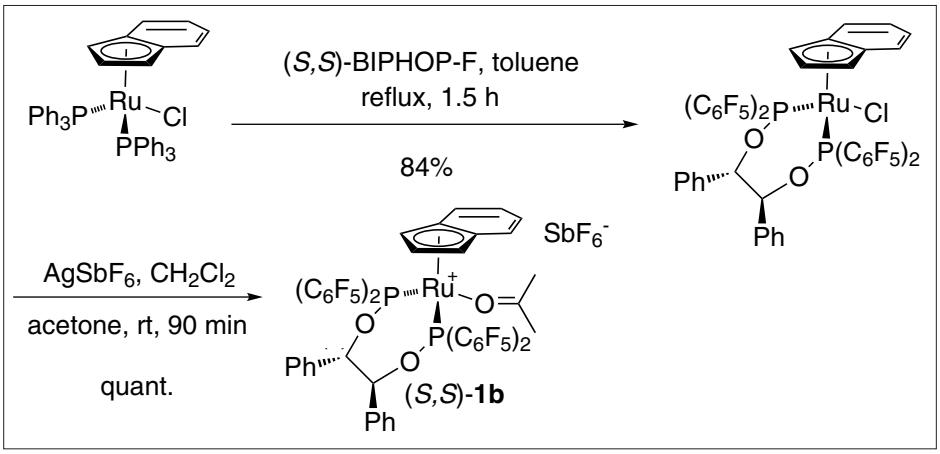
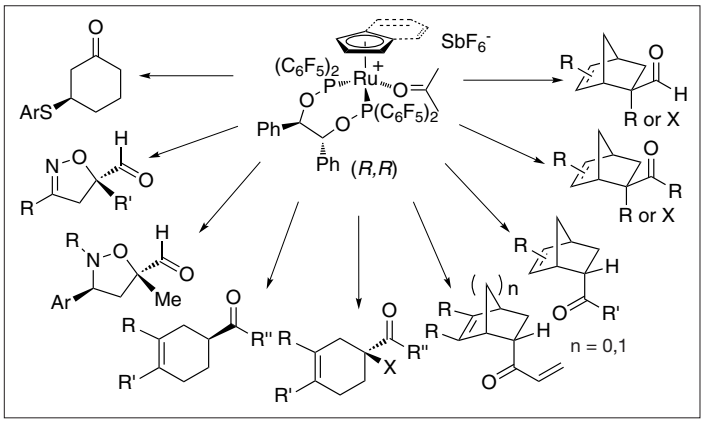
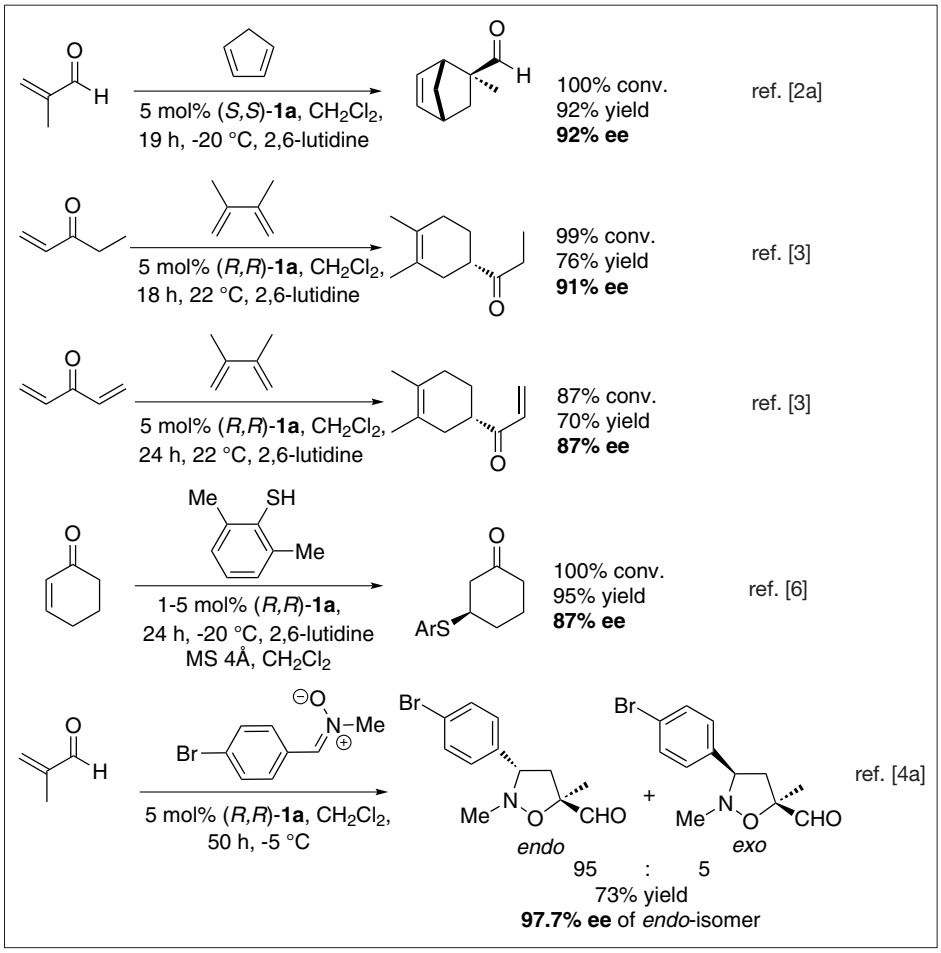


Scheme 2. Synthesis of [Ru(acetone)((*S*,*S*)-BIPHOP-F)(indenyl)][SbF_6] (**1b**).



Scheme 3. Applications.



Scheme 4. Examples of reactions with CpRu **1a**.

of the counteranion,[2c,d] the pendulum motion in the Ru(BINOP-F) fragment,[2e] the competition of enals and nitrones for the Lewis acid site[4c] and the preference of coordination of enals and vinyl ketones to the Ru-center (*anti*-s-*trans* vs *syn*-s-*trans*).[3]

To extend the application, we probed the potential of (*S,S*)-**1a** and **1b** in the intramolecular Diels-Alder (IMDA) reaction. The study involved trienes **2** (Scheme 5) and **3**–**7** (Scheme 6) and the results of IMDA reactions of these substrates catalyzed by (*S,S*)-**1a** and **1b** were investigated.[3,7,8] Triene **2** containing a vinyl ketone dieneophile, provided the highly enantiomerically enriched bridgehead adduct **8** in good yield.[3] Reflecting the lower reactivity of β-substituted keto-dienophiles, triene **5** failed to react. Trienals **3**[9a,b] and **4**,[9c] which were previously used in asymmetric IMDA reaction by Yamamoto, furnished the cycloadducts **9** and **10**, respectively in good yields with high enantioselectivities. The Thorpe-Ingold effect from the dimethyl malonate group increased the reactivity of trienals **6** and **7** shortening reaction times, from days to hours. An X-ray structure of a derivative of **9** confirmed the tentative assignment made previously based on spectroscopic data.

The absolute configurations of products **10**, **12** and **13** were assigned by comparison of the CD spectra of the SAMP-hydrazones to that derived from **9** (Scheme 7).

X-ray structures of chiral Ru Lewis acid/substrate complexes have been instrumental for the interpretation of observed selectivities in cycloaddition reactions.[2–6] For the IMDA reaction involving triene **3** the diene approach leading to the observed *endo* product **9** was modeled as shown in Fig. 2. It is proposed that the enal dienophile (orange) coordinates to the Ru Lewis acid in an *anti-s-trans* conformation and the diene (blue) approaches the C_α-*Re*-face of the enal moiety in an *endo* mode. The pentafluorophenyl moiety of the (*S,S*)-BIPHOP-F ligand blocks the *Si*-face (Fig. 2). This results in the observed product stereochemistry of **9**.

Conclusion

We have developed efficient one-point binding Ru Lewis acid catalysts ((*S,S*)-**1a** and **1b**) capable to catalyze diastereo- and enantioselectively not only DA reactions, 1,3-dipolar cycloadditions and Michael additions but also IMDA reactions. This method gives access to highly enantiomerically enriched bicyclic products of potential use in organic synthesis.

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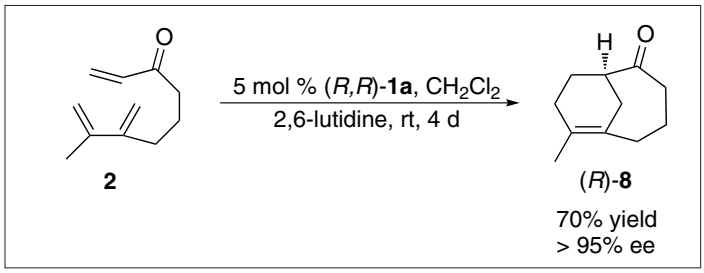
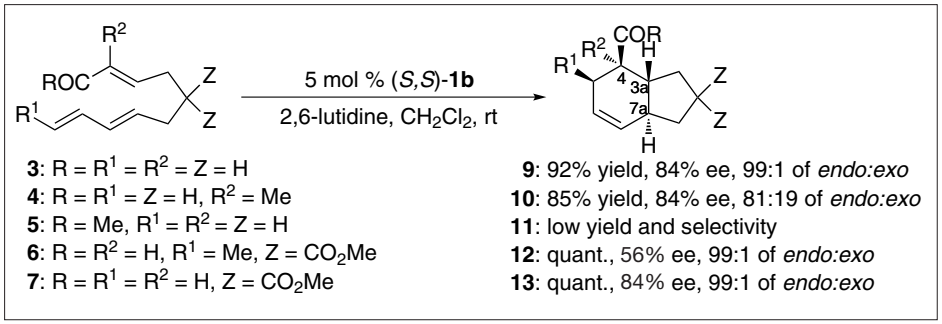


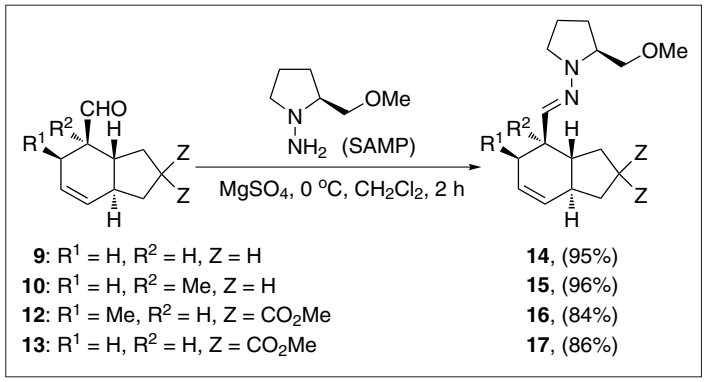
Scheme 5. IMDA reaction of triene **2** with Ru catalyst **1a**.



3: R = R^1 = R^2 = Z = H
4: R = R^1 = Z = H, R^2 = Me
5: R = Me, R^1 = R^2 = Z = H
6: R = R^2 = H, R^1 = Me, Z = CO_2Me
7: R = R^1 = R^2 = H, Z = CO_2Me

9: 92% yield, 84% ee, 99:1 of *endo:exo*
10: 85% yield, 84% ee, 81:19 of *endo:exo*
11: low yield and selectivity
12: quant., 56% ee, 99:1 of *endo:exo*
13: quant., 84% ee, 99:1 of *endo:exo*

Scheme 6. Asymmetric IMDA reactions catalyzed by (*S,S*)-**1b** (catalyst (*S,S*)-**1a** was less active, except in the case of triene **4**).[7]



9: R^1 = H, R^2 = H, Z = H
10: R^1 = H, R^2 = Me, Z = H
12: R^1 = Me, R^2 = H, Z = CO_2Me
13: R^1 = H, R^2 = H, Z = CO_2Me

14, (95%)
15, (96%)
16, (84%)
17, (86%)

Scheme 7. Synthesis of hydrazones **14–17**.

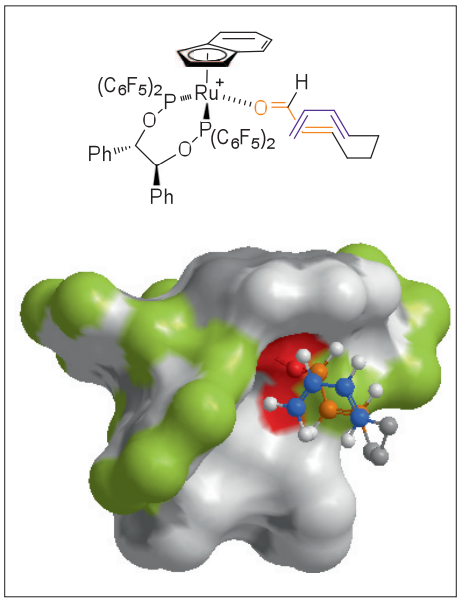


Fig. 2. Modelled approach of trienal **3** coordinated to Ru in (*S,S*)-**1b** in an *anti-s-trans* orientation (catalyst part taken from the X-ray structure of [Ru(acetone)((*S*,*S*)-BIPHOP-F)(indenyl)][SbF_6] ((*S*,*S*)-**1b**).[2b] This model rationalizes the product's (*3aR,4R,7aS*)-configuration.

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