

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

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Abstract: Chiral single-point binding ruthenium Lewis acid catalysts [Ru(acetone)((S,S)-BIPHOP-F)(Cp)][SbF₆] ((S,S)-**1a**) and [Ru(acetone)((S,S)-BIPHOP-F)(indenyl)][SbF₆] ((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 regio-control 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 C₂-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.

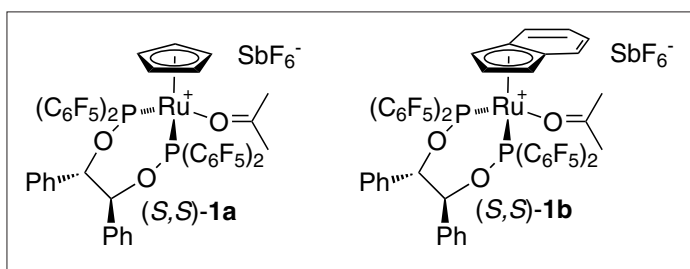
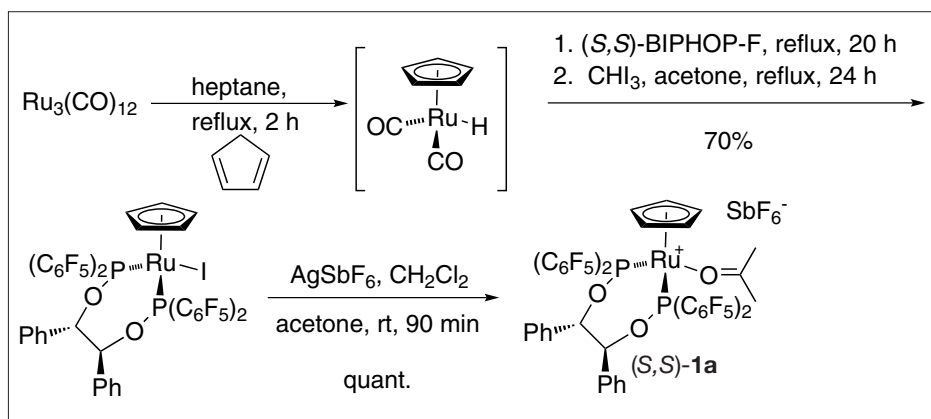


Fig. 1. Single-point binding chiral Ru Lewis acid catalysts.



Scheme 1. Synthesis of [Ru(acetone)((S,S)-BIPHOP-F)(Cp)][SbF₆] (**1a**).

The synthesis of the stable iodoruthenium complex was achieved in a ‘one pot’ procedure from [Ru₃(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 AgSbF₆ generated Lewis acid **1a** as shown in Scheme 1.^[2a]

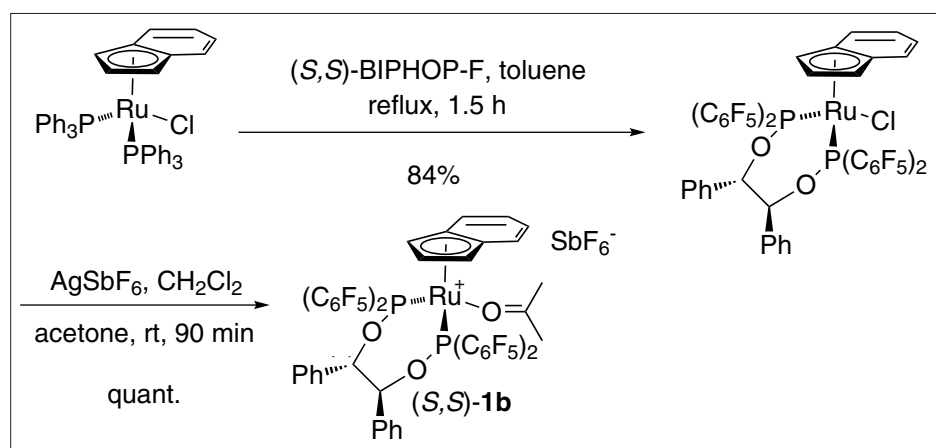
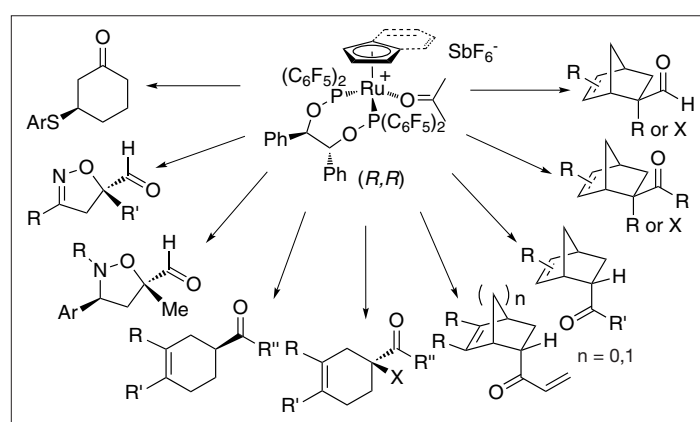
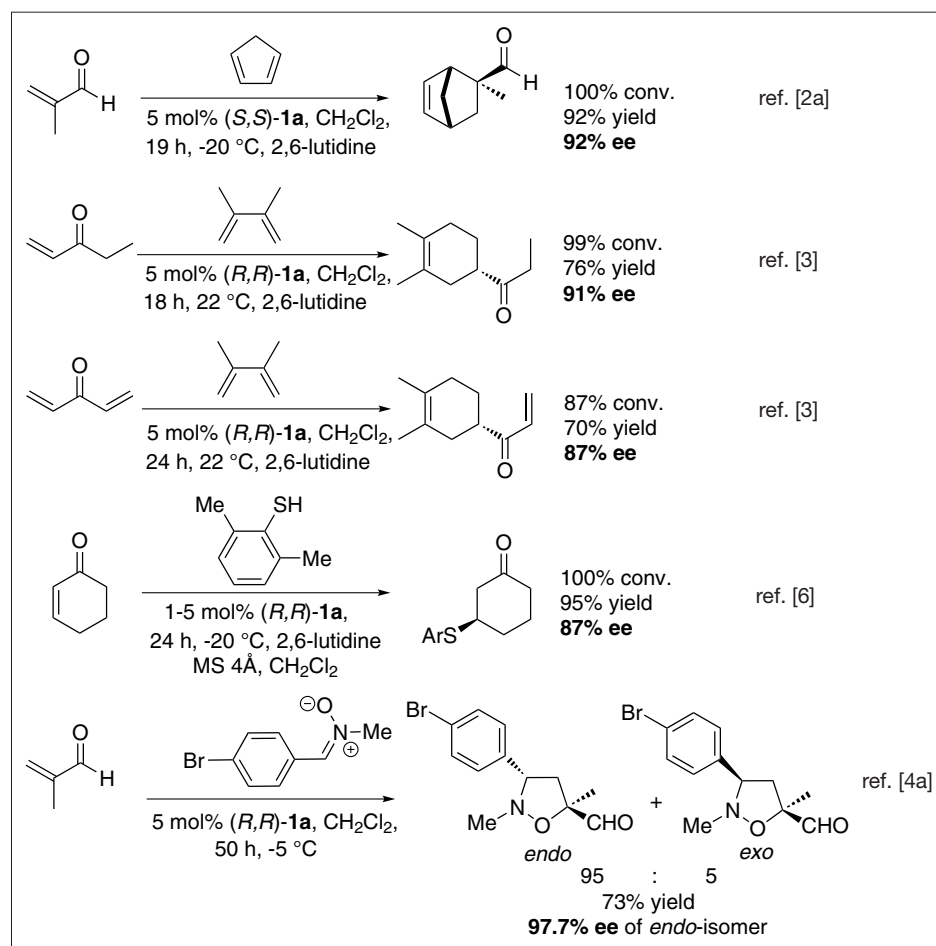
Catalyst **1b** was synthesized *via* ligand exchange in [Ru(Cl)(indenyl)(PPh₃)₂] with BIPHOP-F to afford [Ru(BIPHOP-F)(Cl)(indenyl)]. Halide abstraction with AgSbF₆

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))][SbF₆] (**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 dienophile, 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-hydrazone 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 $_{\alpha}$ -*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**.

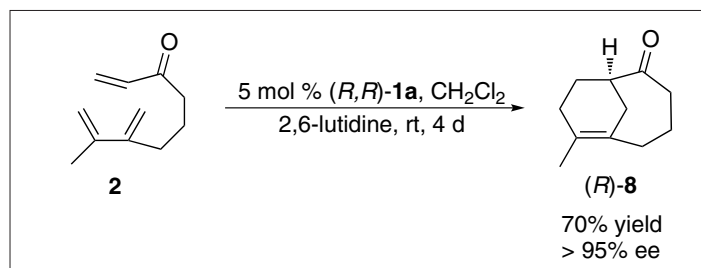
Conclusion

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.

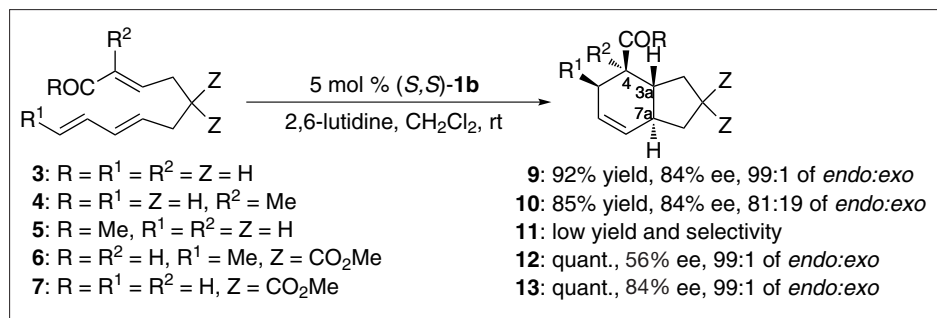
Acknowledgment

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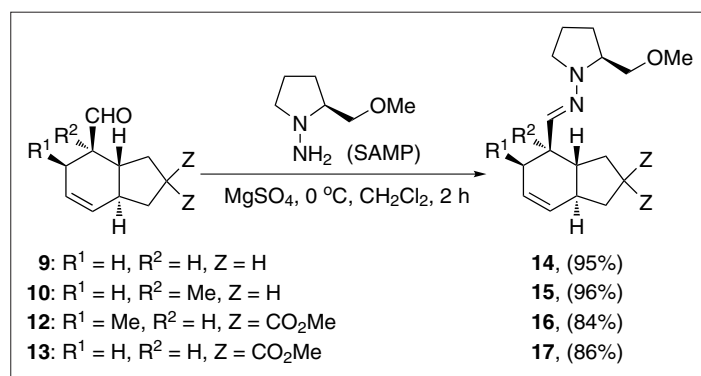
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Scheme 5. IMDA reaction of triene **2** with Ru catalyst **1a**.



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]



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

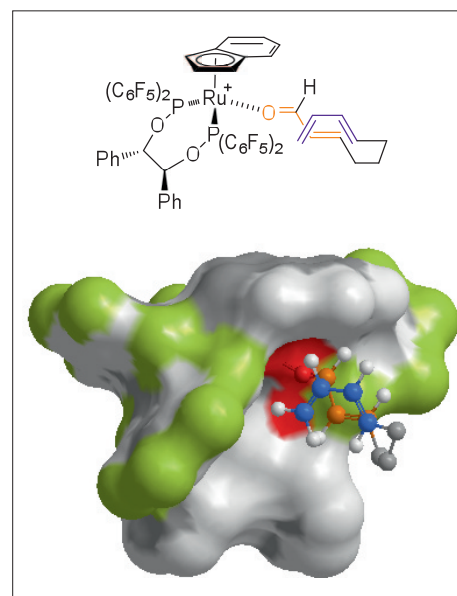


Fig. 2. Modelled approach of trienal **3** coordinated to Ru in (S,S)-**1b** in an *anti-s-trans* orientation (catalyst part taken from the X-ray structure of [Ru(acetone)((S,S)-BIPHOP-F)(indenyl)](SbF₆) ((S,S)-**1b**).^[2b] This model rationalizes the product's (3*aR*,4*R*,7*aS*)-configuration.

- [1] a) 'Chiral Lewis Acid: Lewis Acids and Bases, Asymmetric Synthesis, Enantiomer, Asymmetric Induction, Lithium, Zinc, Aluminium, Boron, Diol, Racemic Mixture, Diels-Alder Reaction, Hydrocyanation, Ene Reaction', Eds. F. P. Miller, A. F. Vandome, J. McBrewster, Alphascript Publishing, **2010**; b) S. Raymond, J. Cossy, *Chem. Rev.* **2008**, *108*, 5359; c) J. Shen, C.-H. Tan, *Org. Biomol. Chem.* **2007**, *6*, 3229; d) E. J. Corey, *Angew. Chem. Int. Ed.* **2002**, *41*, 1650; e) 'Lewis acids in Organic synthesis' Ed. H. Yamamoto, Wiley-VCH, Weinheim, **2000**, vol.1.
- [2] a) E. P. Kündig, C. M. Saudan, G. Bernardinelli, *Angew. Chem. Int. Ed.* **1999**, *38*, 1220; b) E. P. Kündig, C. M. Saudan, V. Alezra, F. Viton, G. Bernardinelli, *Angew. Chem. Int. Ed.* **2001**, *40*, 4481; c) P. G. A. Kumar, P. S. Pregosin, M. Vallet, G. Bernardinelli, R. F. Jazzar, F. Viton, E. P. Kündig, *Organometallics* **2004**, *23*, 5410; d) E. P. Kündig, C. M. Saudan, F. Viton, *Adv. Synth. Catal.* **2001**, *343*, 51; e) V. Alezra, G. Bernardinelli, C. Corminboeuf, U. Frey, E. P. Kündig, A. E. Merbach, C. M. Saudan, F. Viton, J. Weber, *J. Am. Chem. Soc.* **2004**, *126*, 4843; f) M. E. Bruin, E. P. Kündig, *Chem. Commun.* **1998**, 2635; g) E. P. Kündig, B. Bourdin, G. Bernardinelli, *Angew. Chem. Int. Ed.* **1994**, *33*, 1856.
- [3] J. Rickerby, M. Vallet, G. Bernardinelli, F. Viton, E. P. Kündig, *Chem. Eur. J.* **2007**, *13*, 3354.
- [4] a) A. Bădoiu, G. Bernardinelli, E. P. Kündig, *Synthesis*, **2010**, 2207; b) A. Bădoiu, Y. Brinkmann, F. Viton, E. P. Kündig, *Pure. Appl. Chem.* **2008**, *80*, 1013; c) A. Bădoiu, G. Bernardinelli, J. Mareda, E. P. Kündig, F. Viton, *Chem. Asian. J.* **2008**, *3*, 1298; d) F. Viton, G. Bernardinelli, E. P. Kündig, *J. Am. Chem. Soc.* **2002**, *124*, 4969.
- [5] Y. Brinkmann, R. J. Madhushaw, R. Jazzar, G. Bernardinelli, E. P. Kündig, *Tetrahedron* **2007**, *63*, 8413.
- [6] A. Bădoiu, G. Bernardinelli, C. Besnard, E. P. Kündig, *Org. Biomol. Chem.* **2010**, *8*, 193.
- [7] S. Thamapipol, G. Bernardinelli, C. Besnard, E. P. Kündig, *Org. Lett.* **2010**, *12*, 5604.
- [8] *Rac-8* was a key intermediate in the synthesis of Ledol: S. L. Gwaltney, S. T. Sakata, K. J. Shea, *J. Org. Chem.* **1996**, *61*, 7437.
- [9] a) K. Ishihara, H. Kurihara, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 6920; b) K. Ishihara, H. Kurihara, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 304; c) K. Furuta, A. Kanematsu, H. Yamamoto, *Tetrahedron Lett.* **1989**, *30*, 7231.