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Chiral Ruthenium Lewis Acid Catalyzed Intramolecular Diels−Alder Reactions

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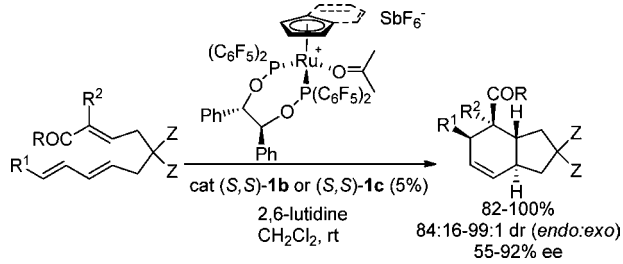
ABSTRACT



Single point binding ruthenium Lewis acid catalysts [Ru(acetone)(*S,S*)-BIPHOP-F)Cp][SbF_6] ((*S,S*)-1b) and [Ru(acetone)(*S,S*)-BIPHOP-F)-(indenyl)][SbF_6] ((*S,S*)-1c) efficiently catalyze intramolecular Diels−Alder (IMDA) reactions under mild conditions to afford the *endo* cycloaddition products as the major product in excellent yields with high diastereo- and enantioselectivities.

Cycloaddition reactions with their potential for a high degree of stereo- and regio-control are arguably the most versatile reactions 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 iron and ruthenium Lewis acids that are based on structurally well-defined monocationic half-sandwich complexes that incorporate a C_2-symmetric perfluoroaryl phosphinite ligand (Figure 1).

These mild chiral Lewis acids proved to be excellent catalysts for the conjugate addition of thiophenols to enones,[2] intermolecular Diels−Alder reactions of dienes with enals[3] and enones,[4] and 1,3-dipolar cycloadditions with nitrones[5] and nitrile oxides.[5a,6]

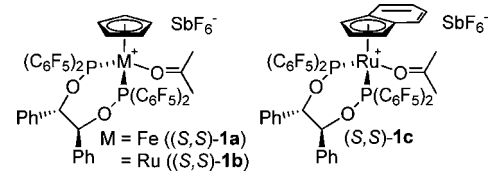


Figure 1. Single-point binding chiral Ru Lewis acid catalysts.

In this communication, we extend the application of catalysts (*S,S*)-**1b** and (*S,S*)-**1c** to the intramolecular

(1) (a) Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359. (b) Shen, J.; Tan, C.-H. *Org. Biomol. Chem.* **2007**, *6*, 3229. (c) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650. (d) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289. (e) Ishihara, K.; Yamamoto, H. *Advances in Catalytic Process*; Doyle, M., Ed.; JAI Press: London, United Kingdom, 1995; Vol. 1, pp 29. (f) Evans, D. A.; Johnson, J. S. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 3, Chapter 33.1.

(2) Kündig, E. P.; Bădoiu, A.; Bernardinelli, G.; Besnard, C. *Org. Biomol. Chem.* **2010**, *8*, 193.

(3) (a) Kündig, E. P.; Alezra, V.; Bernardinelli, G.; Corminboeuf, C.; Frey, U.; Merbach, A. E.; Saudan, C. M.; Viton, F.; Weber, J. *J. Am. Chem. Soc.* **2004**, *126*, 4843. (b) Kündig, E. P.; Anil Kumar, P. G.; Pregosin, P. S.; Vallet, M.; Bernardinelli, G.; Jazzar, R. F.; Viton, F. *Organometallics* **2004**, *23*, 5410. (c) Kündig, E. P.; Saudan, C. M.; Alezra, V.; Viton, F.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4481. (d) Kündig, E. P.; Saudan, C. M.; Viton, F. *Adv. Synth. Catal.* **2001**, *343*, 51. (e) Kündig, E. P.; Saudan, C. M.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1220. (f) Kündig, E. P.; Bruin, M. E. *Chem. Commun.* **1998**, 2635. (g) Kündig, E. P.; Bourdin, B.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **1994**, *33*, 1856.

(4) Kündig, E. P.; Rickerby, J.; Vallet, M.; Bernardinelli, G.; Viton, F. *Chem.—Eur. J.* **2007**, *13*, 3354.

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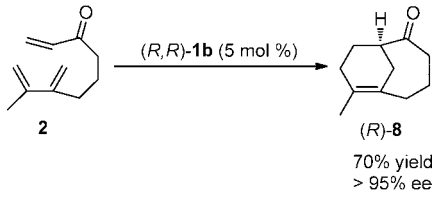
Scheme 1. Synthesis of Bridgehead Adduct **8**



Diels−Alder (IMDA) reaction. A first example was reported previously and involved trienone **2** and (*R*,*R*)-**1b** as catalyst to construct the bicyclic adduct (*R*)-**8** (Scheme 1).[4,7] This result encouraged us to explore the IMDA reaction of trienes **3**−**7** (Figure 2).

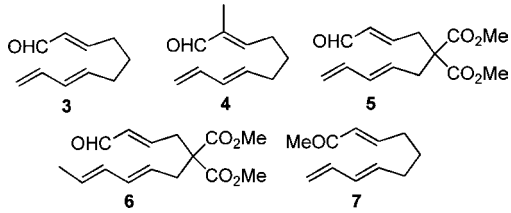
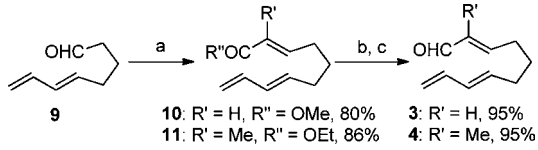


Figure 2. Trienes for the asymmetric IMDA reaction.

Horner−Wadsworth−Emmons reaction of aldehyde **9**[8a,b] with methyldiethylphosphonoacetate and triethylphosphonopropionate, respectively, afforded α,*β*-(*E*)-unsaturated esters **10**[8c] and **11** in good yield (Scheme 2). A reduction/oxidation sequence afforded trienes **3**[9a,b] and **4**[9c] in excellent yield.

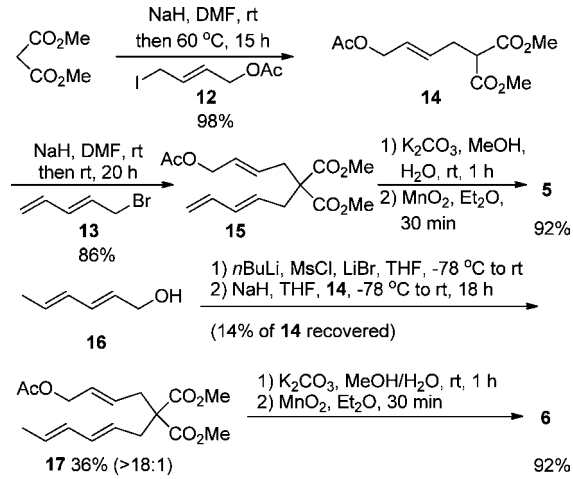
Scheme 2. Synthesis[a] of Trienes **3**[9a,b] and **4**[9c]



[a] Reagents and conditions: (a) NaH, THF, rt, then methyl diethylphosphonoacetate for **10** or triethylphosphono-propionate for **11**; (b) DIBALH, Et_2O, 0 °C, 2 h; (c) MnO_2, CH_2Cl_2, rt, 1 h.

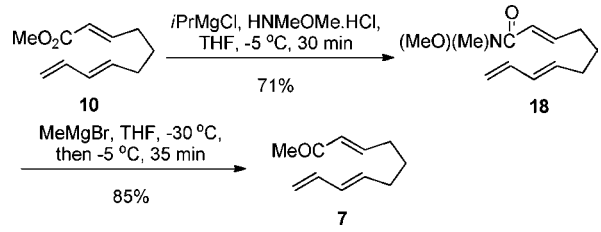
Trienes **5** and **6** were synthesized by using two sequential alkylations of dimethylmalonate followed by selective saponification and oxidation (Scheme 3).[10]

Scheme 3. Synthesis of Trienes **5** and **6**



The keto-triene **7** was prepared from ester **10** in high yield via the Weinreb amide **18** and reaction with MeMgBr (Scheme 4).

Scheme 4. Synthesis of Triene **7**



The results of IMDA reactions catalyzed by Lewis acids (*S*,*S*)-**1b** and (*S*,*S*)-**1c** are detailed in Table 1. Trienes **3** and **4** gave the cycloadducts **19** and **20** (entries 1−4), in good yields with high enantioselectivities albeit long reaction times were required. Whereas **19** was obtained with excellent *endo*-diastereoselectivity, the *endo/exo* ratio was somewhat lower for **20** (entries 3−4). Both catalysts gave similar results though reaction times to completion were generally shorter for catalyst (*S*,*S*)-**1c**.

As expected, the IMDA reactions of trienes **5** and **6** were more efficient (Thorpe-Ingold effect[11]) (entries 5−8) and reaction times were reduced from days to hours. Trienes **3**

(5) (a) Kündig, E. P.; Bădoiu, A.; Brinkmann, Y.; Viton, F. *Pure. Appl. Chem.* **2008**, *80*, 1013. (b) Kündig, E. P.; Bădoiu, A.; Bernardinelli, G.; Mareda, J.; Viton, F. *Chem. Asian. J.* **2008**, *3*, 1298. (c) Kündig, E. P.; Viton, F.; Bernardinelli, G. *J. Am. Chem. Soc.* **2002**, *124*, 4969.

(6) Kündig, E. P.; Brinkmann, Y.; Madhushaw, R. J.; Jazzar, R.; Bernardinelli, G. *Tetrahedron* **2007**, *63*, 8413.

(7) *Rac*-**8** was a key intermediate in the synthesis of Ledol: (a) Gwaltney, S. L.; Sakata, S. T.; Shea, K. J. *J. Org. Chem.* **1996**, *61*, 7437. (b) Gwaltney, S. L.; Shea, K. J. *Tetrahedron Lett.* **1996**, *37*, 949.

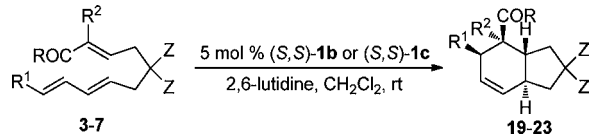
(8) (a) Spino, C.; Crawford, J.; Bishop, J. *J. Org. Chem.* **1995**, *60*, 844. (b) Spino, C.; Crawford, J. *Tetrahedron Lett.* **1994**, *35*, 5559. (c) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Chem. Am. Soc.* **1982**, *104*, 2269.

(9) (a) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920. (b) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049. (c) Furuta, K.; Kanematsu, A.; Yamamoto, H. *Tetrahedron Lett.* **1989**, *30*, 7231.

(10) Carrying out the synthesis of **17** analoguously to that of **15** afforded an inseparable mixture of S_N2, S_N2', and S_N2'' reaction products, hence the modification.

(11) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107*, 1080.

Table 1. Enantioselective IMDA Reaction with Chiral Ru Lewis Acids



3-7 19-23

entry	triene	catalyst	2,6-lutidine (mol %)	time[b]	product[c]	yield (%)[d]	*endo*/*exo*	ee (%)
1	**3**	(*S*,*S*)-**1b**	2	9 d	**19** R = R^1 = R^2 = Z = H	82	99/1	72[e]
2	**3**	(*S*,*S*)-**1c**	2	7 d	**19** R = R^1 = R^2 = Z = H	92	99/1	84[e]
3	**4**	(*S*,*S*)-**1b**	2	7 d	**20** R = R^1 = Z = H, R^2 = Me	82	84/16	92, 91[f]
4	**4**	(*S*,*S*)-**1c**	2	6 d	**20** R = R^1 = Z = H, R^2 = Me	85	81/19	84, 90[f]
5	**5**	(*S*,*S*)-**1b**	5	5 h	**21** R = R^1 = R^2 = H, Z = CO_2Me	quant	99/1	43[g]
6	**5**	(*S*,*S*)-**1c**	5	4 h	**21** R = R^1 = R^2 = H, Z = CO_2Me	quant	99/1	84[g]
7	**6**	(*S*,*S*)-**1b**	5	5 h	**22** R = R^2 = H, R^1 = Me, Z = CO_2Me	quant	99/1	55[h]
8	**6**	(*S*,*S*)-**1c**	5	4 h	**22** R = R^2 = H, R^1 = Me, Z = CO_2Me	quant	99/1	56[h]
9	**7**	(*S*,*S*)-**1b**	2	7 d	**23** R = Me, R^1 = R^2 = Z = H	10	99/1	0[i]
10	**7**	(*S*,*S*)-**1c**	2	7 d	**23** R = Me, R^1 = R^2 = Z = H	12	99/1	0[i]

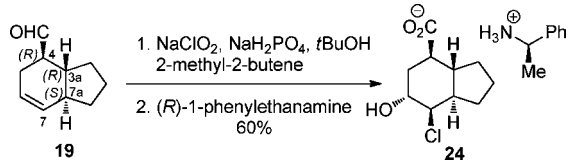
[a] All reactions were carried out in 0.15−0.30 M concentration. 2,6-Lutidine (2−5 mol %) was added to scavenge acid impurities. Results shown are the average of a minimum of three experiments. [b] IMDA reactions of **3**, **4,** and **7** were followed by TLC and **5** and **6** by IR. [c] Racemic reactions of **3**, **4**, and **7** were performd with $AlEt_2Cl$ and **5** and **6** with SiO_2. [d] Isolated yield. [e] ee of *endo*-isomer, determined by GC analysis. [f] ee of *exo*-isomer, determined by GC analysis. [g] ee, determined by ^{1}H NMR of its chiral amine derivative (see Supporting Information); 4% conversion was observed for the background reaction in the absence of catalyst. [h] Twenty-six percent conversion was observed for the background reaction in the absence of catalyst. [i] Eight percent conversion was observed for the background reaction in the absence of catalyst.

and **5** provided adducts **19** and **21** with higher ee using (*S*,*S*)-**1c** than with (*S*,*S*)-**1b**. In the case of triene **6**, both Ru catalysts afforded adduct **22** with modest ee because of the high background reaction of this triene as mentioned in footnote h of Table 1.

IMDA reaction conditions of triene **7** (entries 9−10) were screened but under all conditions adduct **23** was obtained in racemic form. This presumably reflects the lower reactivity of keto-dienophiles compared to the aldehyde substrates.

Trienals **3** and **4** were used previously by Yamamoto and co-workers in the IMDA reaction with the chiral boron Lewis acids BLA[9a,b] and CAB.[9c] The absolute configuration of adduct **19** (with (*S*,*S*)-**1c**, 84% ee) was initially established by comparison with the literature data[9b] in which the *endo*-isomer was described as the major adduct.[12] But the aldehyde protons of *endo* and *exo*-isomers of **19** are extremely close (δ_{exo} 9.67 and δ_{endo} 9.69) and difficult to distinguish. Bicyclic aldehyde **19** was therefore submitted to Pinnick oxidation[13] (Scheme 5). In addition to oxidizing the aldehyde function,

Scheme 5. Synthesis of Carboxylate **24**



we observed concomitant chlorohydroxylation of the alkene. Crystals suitable for X-ray analysis of **24** were obtained using (*R*)-1-phenylethanamine as crystallization partner (Figure 3). The structure shows that the ring junction is trans-configured and consequently, **19** is the *endo*-isomer with (3a*R*,4*R*,7a*S*)-configuration.

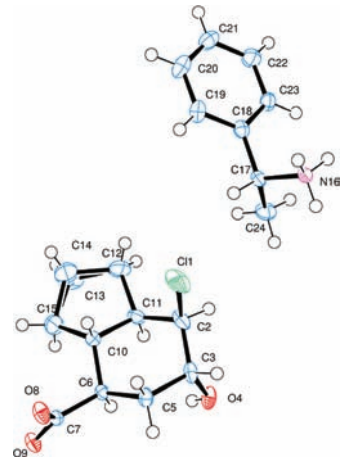
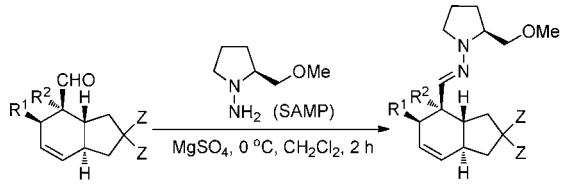


Figure 3. X-ray structure of carboxylate salt **24**.[14]

Adducts **19**−**22** were converted to their corresponding hydrazones **25**−**28** (Scheme 6) because their CD spectra could not be measured due to the overlap of the aldehyde peak with the solvent peak. The absolute configurations of **26**−**28** were assigned based on comparison of their the CD spectra with that of **25** (see Supporting Information).

(12) Lit. correction: The structure and the name of the *endo* product in the Supporting Information of ref 9b was interchanged and the wrong structure was accidently drawn in ref 9a. E-mail correspondance with K. Ishihara.

Scheme 6. Synthesis of Hydrozones **25**−**28**



25: R^1 = H, R^2 = H, Z = H (95%)
26: R^1 = H, R^2 = Me, Z = H (96%)
27: R^1 = H, R^2 = H, Z = CO_2Me (86%)
28: R^1 = Me, R^2 = H, Z = CO_2Me (84%)

X-ray structures of chiral Ru Lewis acid/substrate complexes were 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 **19** was modeled using the X-ray structure of (*S*,*S*)-**1c**. It is proposed that the enal dienophile (orange) coordinates to the Ru in an *anti-s-trans* conformation and the diene (blue) approaches the *Re*-face of the enal moiety in an *endo* mode. The *Si*-face is shielded by the pentafluorophenyl moiety of the (*S*,*S*)-BIPHOP-F ligand (Figure 4). This results in the observed product stereochemistry of **19**.

Background reactions apart, we presume the product ee to reflect the competition between the two possible orientations of the coordinated dienophile (*anti-s-trans* or *syn-s-trans*). In intramolecular DA reactions of enals, the *anti-s-trans* conformation always dominates, though *syn-s-trans* coordination in the transition state is operative in conjugate addition of thiophenols to enones,[2] and in intermolecular DA reactions of some diene/enone reactions[4] with these catalysts. IMDA reaction of trienes **3** and **5** catalyzed by (*S*,*S*)-**1b** afford adducts **19** and **21**, respectively, in lower ee than the reactions catalyzed by (*S*,*S*)-**1c** (compare entries 1 and 2, respectively 5 and 6). It can be argued that this is because the indenyl roof of **1c** more strongly disfavors a reaction occurring *via* a *syn-s-trans* coordinated dienophile.

(13) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(14) CCDC-789209 contains the supplementary crytallographic data for **24**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) via http://www.ccdc.cam.ac.uk/data_reguest/cif.

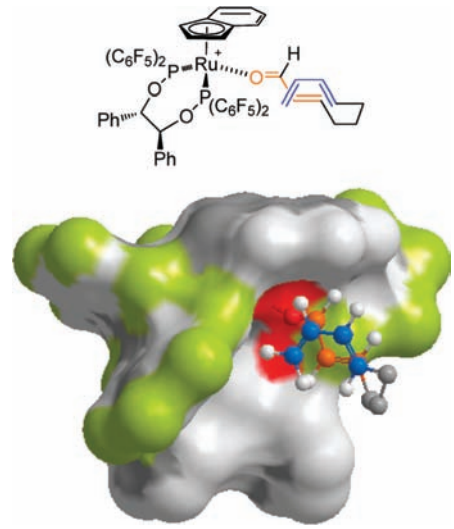


Figure 4. Modeled approach of trienal **3** coordinated to Ru in (*S*,*S*)-**1c** in an *anti-s-trans* orientation (catalyst part taken from the X-ray structure of [Ru(acetone)(*S*,*S*)-BIPHOP-F)Ind][SbF_6] ((*S*,*S*)-**1c**).[3c] Projection onto the C_α-*Re* face of the enal and showing the *endo* approach of diene. This model rationalizes the product's (3a*R*,4*R*,7a*S*)-configuration.

The favored *anti-s-trans* conformation then leads to a product in higher ee. For triene **4** (entries 3 and 4), the α-methyl substituent enforces the *anti-s-trans* conformation.

In conclusion, the chiral Ru Lewis acids (*S*,*S*)-**1b** and (*S*,*S*)-**1c** can satisfactorily catalyze diastereo- and enantioselective IMDA reactions of suitable trienes. This method allows the formation of highly enantiomerically enriched bicyclic products of potential use in synthesis.

Acknowledgment. We thank the Swiss National Science Foundation and the University of Geneva for financial support and Dr. Bettina Bressel for help with the manuscript.

Supporting Information Available: Details of experimental procedures and spectroscopic characterization (^1H and ^{13}C NMR, IR, and HRMS) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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