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Catalytic Enantioselective Diels–Alder Reaction by Self-Assembly of the Components on a Lewis Acid Template

Dale E. Ward* and Michael Santos Souweha

Department of Chemistry, University of Saskatchewan, 110 Science Place, Saskatoon, SK, S7N 5C9 Canada

Dale.Ward@usask.ca

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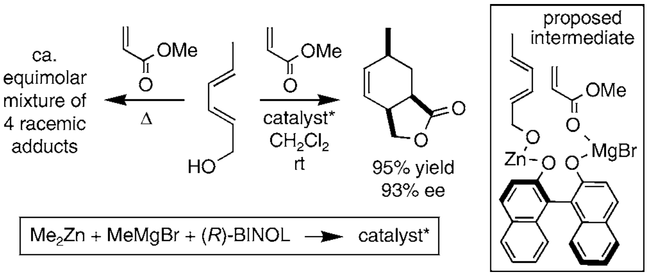
ABSTRACT



Thermal Diels–Alder reaction of 2,4-hexadienol with methyl acrylate is unselective. By simultaneous coordination of diene and dienophile to a chiral bimetallic Lewis acid catalyst, a LACASA-DA reaction occurs with complete control of regio-, diastereo-, and enantioselectivity to give a single adduct.

Despite its long history,[1] the Diels−Alder (DA) reaction continues to be of fundamental importance to the theory and practice of organic chemistry. A continuous evolution of strategies to improve the scope, reactivity, and selectivity of the process has made the DA reaction an extremely powerful and versatile synthetic tool.[2] Recently we reported a new strategy to control DA reactions based on a Lewis acid-catalyzed reaction of a “self-assembled” complex (LACASA-DA).[3] In this approach, enhanced reactivity, regioselectivity, and diastereoselectivity are achieved via “intramolecular” DA reaction of the activated intermediate produced by simultaneous coordination of the diene and dienophile to a Lewis acid template (Figure 1). The synthetic potential of this strategy was recently demonstrated by Barriault et al.[4] An obvious extension of this design was to establish an enantioselective version by providing an appropriate chiral ligand sphere for the Lewis acidic metal center.[5] In this paper we report highly enantioselective LACASA-DA reactions of **1** with **3** using a bimetallic complex of Mg(II) and Zn(II) with BINOL.

Thermal DA reaction of **1a** with **3** is unselective, giving all possible products (i.e., two pairs of diastereomeric regioisomers)[6] in nearly equimolar amounts. The adduct **5** (racemic) is obtained exclusively and in high yield by

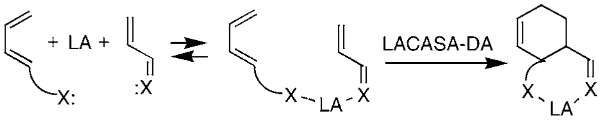


Figure 1. Diels−Alder reaction where a Lewis acid (LA) coordinates simultaneously to the diene and dienophile and induces an “intramolecular” reaction of the resulting complex.

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[1] Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98−122.

[2] (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667.

[3] Ward, D. E.; Abaee, M. S. *Org. Lett.* **2000**, *2*, 3937−3940.

[4] (a) Barriault, L.; Thomas, J. D. O.; Clement, R. *J. Org. Chem.* **2003**, *68*, 2317−2323. (b) Barriault, L.; Ang, P. J. A.; Lavigne, R. M. A. *Org. Lett.* **2004**, *6*, 1317−1319.

[5] Bienayme, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2670−2673.

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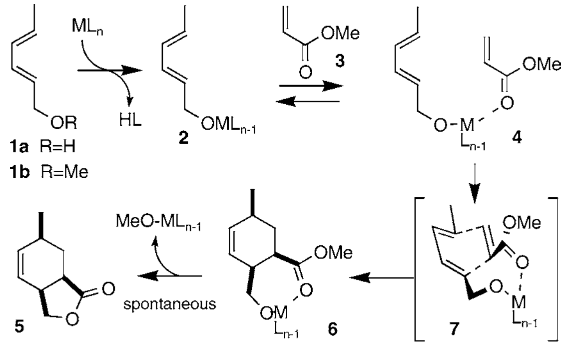
Scheme 1



addition of CH_3MgBr or Et_2AlCl via LACASA-DA of the intermediate metal alkoxide **2** (Scheme 1; $-ML_{n-1} = -MgBr$ or $-AlEtCl$).[3] Control experiments verified the LACASA-DA mechanism and established that the selective formation of adduct **5** was a signature of this pathway.[3] Initially, the possibility of enantioselective LACASA-DA using one of the several known chiral Ti(IV) alkoxides[7] was contemplated; however, we were unable to induce a DA reaction of **1a** (or its Li alkoxide) with **3** using any of $TiCl_n(O^iPr)_{4-n}$ ($n = 0-4$).[8] In the previous study, addition of 1 equiv of pentanol increased both the yield and rate of the CH_3MgBr (1 equiv) promoted reaction of **1a** (1 equiv) with **3** (2 equiv).[3] These effects were presumed to result from beneficial changes in the ROMgBr speciation caused by the additional ROH ligand.[9] Consequently, the use of chiral nonracemic additives was attempted in hopes of promoting an enantioselective cycloaddition. Nonracemic **8**−**12** (0.5 equiv for **8a**, **9**, and **10**; 1 equiv for **11** and **12**) were screened as additives in the MeMgBr (1 equiv) promoted LACASA-DA reaction of **1a** with **3** (4 equiv). Although the yields of **5** were 50−90% with all additives except **10** (0%), the enantioselectivity was uniformly poor (<5% ee). Numerous chiral Al(III) Lewis acids have been prepared by reactions of Et_2AlCl with nonracemic alcohols and diols.[10] Accordingly, we investigated the Et_2AlCl-mediated reaction of **1a** with **3** in the presence of (*R*)-BINOL (**8a**).

Table 1. Et_2AlCl-Mediated LACASA-DA Reactions of **1a** with **3** in the Presence of (*R*)-BINOL (**8a**)[a]

entry	Et_2AlCl (equiv)	BINOL (equiv)	% yield of **5**[b]	ee of **5**[c] (%)
1	0.5	1	38	78
2	1	1	22	79
3[d]	1	1	37	75
4[e]	1	1	0	
5	1	**8b** (1)	35	20
6	1	**8c** (1)	35	15
7[f]	1	0.5	65	79
8[f]	1	1	70	81
9[f]	2	1	60	60
10[f]	3	1	62	64
11[g]	Me_3Al (1)	0	0	
12[g]	Me_3Al (1)	1	55	84
13[g]	Me_3Al (2)	1	55	79
14[g]	Me_3Al (3)	1	15	43

[a] Et_2AlCl added to a solution of **1a** and BINOL in CH_2Cl_2 ([**1a**] = 0.04 M) at 0 °C. After 5 min, **3** (15 equiv) was added; reaction at room temperature for 24 h. [b] **5** was the only DA adduct detected; yield determined by ^1H NMR of the crude reaction mixture using an internal standard. [c] Determined by ^1H NMR in the presence of (+)-Eu(hfc)$_3$; major enantiomer is (−)-**5** with absolute configuration as shown in Scheme 1. [d] Reaction in toluene. [e] Reaction in THF. [f] Reaction at −10 °C for 48 h. [g] Reaction at room temperature for 72 h.

The DA adduct **5** was produced with modest enantioselectivity under a variety of conditions (Table 1). Improved yields were obtained at reduced temperature (cf. entries 2 and 8) presumably due to the acid sensitivity of **1a**.[3] Because **5** was the only DA adduct detected, a LACASA-DA mechanism was implicated. However, the structure(s) of the species formed by reaction of **1a**, Et_2AlCl, and **8a** is uncertain. The much lower ee's obtained using **8b** or **8c** in place of **8a** and the absence of DA adducts from the reaction of **1b** under the optimal conditions for **1a** (entry 8) suggest positive roles for each of the −OH groups. Surprisingly, the enantioselectivity was relatively insensitive to the Et_2AlCl/**8a** ratio (cf. entries 1, 2, and 7).[11] The erosion of ee observed with a large excess of Et_2AlCl (entries 9 and 10) presumably results from a Et_2AlCl-mediated background reaction of **1a** with **3**.

We next investigated combinations of Me_3Al and **8a** as mediators for the DA reaction of **1a** with **3** (Table 1).[11] The background reaction was negligible using Me_3Al alone (entry 11); however, in the presence of **8a** a slow reaction ensued to give **5** in modest yield with an ee slightly higher than that obtained using Et_2AlCl (entry 12). Contrary to previous reports,[11] the use of higher ratios of Me_3Al to **8a** gave inferior catalysts (cf. entries 12−14).

Assuming that reaction of **1a** and **8a** with excess Me_3Al gives multinuclear Al species,[11] we reasoned that improved reactivity might result by using a "stronger" Lewis acid in combination with Me_3Al (Table 2). Thus our working hypothesis was based on "cartoon" structure **17** where LA_1 would tether the dienol to BINOL and LA_2 would tether the dienophile to BINOL (Scheme 2).[12] The development of bimetallic catalysts has been intensively studied in recent years.[13] In particular, asymmetric catalysts where two metals

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(6) One of these adducts cyclizes spontaneously to give **5**.

(7) Mikami, K.; Terada, M. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 2, Chapter 16, pp 799−847.

(8) Abaee, M. S. Ph.D. Thesis, University of Saskatchewan, Saskatoon, Saskatchewan, Canada, 1999.

(9) For examples of ROMgBr dimeric structures, see: (a) Coates, G. E.; Ridley, D. *J. Chem. Soc., Chem. Commun.* **1966**, 560−561. (b) Moseley, P. T.; Shearer, H. M. M. *J. Chem. Soc., Chem. Commun.* **1968**, 279−280.

(10) Wulff, W. D. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, Chapter 7, pp 283−354.

(11) Multinuclear Al(III)/BINOL complexes have been reported to be superior catalysts in DA reactions: (a) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1731−1733. (b) Ishihara, K.; Kobayashi, J.; Inanaga, K.; Yamamoto, H. *Synlett* **2001**, 394−396.

(12) We have no direct evidence for structures **16** or **17**. Thus far, we have been unable to obtain X-ray quality crystals of the putative **16** or **17** (with pentanol replacing **1a**).

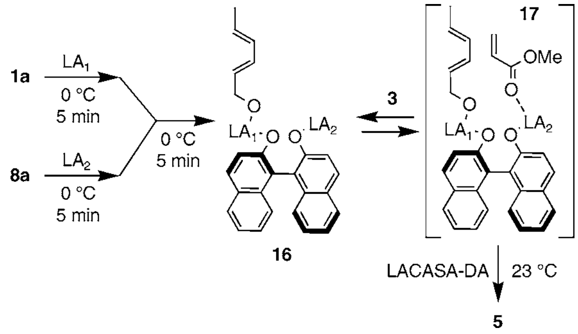
(13) *Multimetallic Catalysts in Organic Synthesis*; Shibasaki, M., Yamamoto, Y., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 295.

Table 2. LACASA-DA Reactions of **1a** with **3** Using Multinuclear Lewis Acid (*R*)-BINOL (**8a**) Catalysts[a]

entry	LA_1 (equiv)	LA_2 (equiv)	**8a** (equiv)	time (days)	% yield of **5**[b]	ee of **5**[c] (%)
1	Me_3Al (1)	Et_2AlCl (1)	1	1	60	90
2	Me_3Al (1)	MeMgBr (1)	1	3	54	50
3	Me_2Zn (1)		0	1	0	
4	Me_2Zn (1)	Et_2AlCl (1)	1	3	69	70
5	Me_2Zn (1)	MeMgBr (1)	1	1	95[d]	93
6	Me_2Zn (1)	Me_2Zn (1)	1	1	26	33
7	MeMgBr (1)	MeMgBr (1)	1	1	12	<5
8	MeMgBr (1)	Me_2Zn (1)	1	1	60	90
9	Me_2Zn (0.3)	MeMgBr (0.25)	0.25	14	95	96
10	Me_2Zn (1)	MeMgBr (1)	**8b** (1)	1	70	15
11	Me_2Zn (1)	MeMgBr (1)	**8c** (1)	1	50	<5
12	Me_3Al (1)	Et_2AlCl (1)	**13** (1)	7	10	<5
13	Me_3Al (1)	Et_2AlCl (1)	**14** (1)	7	20	80[e]
14	Me_3Al (1)	MeMgBr (1)	**14** (1)	3	20	0
15	Me_2Zn (1)	MeMgBr (1)	**14** (1)	7	10	88[e]
16	Me_3Al (1)	Et_2AlCl (1)	**15** (1)	1	50	88[e]

[a] Reactions conducted as summarized in Scheme 2. [b] **5** was the only DA adduct detected; yield determined by ^{1}H NMR of the crude reaction mixture using an internal standard. [c] Determined by ^{1}H NMR in the presence of (+)-Eu(hfc)$_3$; major enantiomer is (−)-**5** with absolute configuration as shown in Scheme 1. [d] Isolated yield of *ent*-**5** from an experiment conducted with (*S*)-BINOL. [e] Major enantiomer is *ent*-**5**.

Scheme 2



act synergistically (e.g., "two-center",[14] "bifunctional",[15] "dual activation",[16] multinucleating,[17] Lewis acid assisted Lewis acid[18]) have attracted significant attention. Noteworthy in this regard is the pioneering work of Shibasaki et al. on the development and application of BINOL-based bimetallic catalysts to effect a variety of asymmetric transformations.[19] Despite the extensive investigation of asymmetric bimetallic catalysts, very few applications to DA reactions have been reported.[11,20] The most relevant analogy to our hypothesis (i.e., **17**)[12] is provided by the work of Inomata et al.[17] who used Zn and/or Mg bisalkoxides of tartarate esters as asymmetric catalysts for a variety of reactions including cycloadditions of allyic alcohols with nitrile oxides and nitrones and one example[20b,21] of a hetero Diels−Alder reaction of cylohexadienylmethanol with PhNO. In the event, **1a** was treated with an equimolar amount of Me_3Al (LA_1) and **8a** was treated with an equimolar amount of Et_2AlCl (LA_2), and then the mixtures were combined and **3** was added (Table 2, entry 1).[22] Under these conditions, the DA reaction was faster than with Me_3Al alone and gave **5** with a much higher ee. We also investigated Me_2Zn as LA_1 as it did not promote a background reaction of **1a** with **3** (entry 3). Although the combination of Me_2Zn with Et_2AlCl gave an inferior catalyst (entry 4), the use of Me_2Zn (LA_1) and MeMgBr (LA_2) gave **5** with excellent enantioselectivity and in near quantitative yield (entry 5). Using Me_2Zn or MeMgBr alone (i.e., as both LA_1 and LA_2 in Scheme 2) gave ineffective catalysts (entries 6 and 7). Reversing the "roles" of the Me_2Zn and MeMgBr by changing the order of addition gave **5** with high ee but much less efficiently (entry 8). These results are consistent with a catalyst structure where Zn acts as the "linker" between **1a** and **8a** and Mg acts as the Lewis acid coordinating to (and activating) **3** and suggest that formation of the active catalyst is thermodynamically favored from among the many possible species that might result from reaction of **1a**, **8a**, Me_2Zn, and MeMgBr.[23] The reaction works equally well in a catalytic format (entry 9); however, the turnover is very slow.[24] The use of **8b** or **8c** in place of **8a** gave much lower ee's (entries 10 and 11), and reaction of **1b** under the optimized conditions for **1a** did not give DA adducts. All of these results are consistent with the mechanistic hypothesis outlined in Scheme 2.[23]

To further confirm that these reactions proceed via a LACASA-DA mechanism and to provide evidence for a discreet "self-assembled" intermediate (e.g., **17**),[23] we examined the concentration dependence of the DA chemoselectivity between **1a** and cyclopentadiene competing for **3** (Scheme 3).[3] Otherwise identical experiments conducted with a 10-fold difference in concentration showed a ca. 8-fold difference in chemoselectivity (i.e., in the ratio of **18**:**5**) but with little change in the absolute amount of **5** formed.[25] This

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(14) (a) Steinhagen, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2339−2342. (b) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511−524. (c) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989−1999.

(15) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865−1882.

(16) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566−4583.

(17) Ukaji, Y.; Inomata, K. *Synlett* **2003**, 1075−1087.

(18) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924−1942.

(19) Reviews: (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1237−1256. (b) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3−15. Also see refs 13−18.

(20) (a) Morita, T.; Arai, T.; Sasai, H.; Shibasaki, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1445−1450. (b) Ding, X.; Ukaji, Y.; Fujinami, S.; Inomata, K. *Chem. Lett.* **2003**, *32*, 582−583.

(21) The intermediacy of a "self-assembled" complex is questionable in this system because a similar reaction of **1a** with PhNO gave poor regioselectivity (ref 20b).

(22) This protocol was adopted to promote the formaton of the putative **16** and to minimize the potential for a LA_2-mediated background reaction via **2** (i.e., with ML_{n-1} derived from LA_2).

(23) That is, structure **16** (or **17**) with LA_1 = −Zn− and LA_2 = −MgBr (however, see ref 12). Thus far, we have been unable to obtain X-ray quality crystals of the putative **16** or **17** (with pentanol replacing **1a**).

(24) This presumably is the consequence of a slow reaction of MeO−ZnO−BINOL−OMgBr with **1a** to give **16** and MeOH.

(25) These reactions were conducted as indicated for Table 2 (entry 5) using **3** (3 equiv) and adding cyclopentadiene (0.6 equiv) to **1a** prior to adding the Me_2Zn.

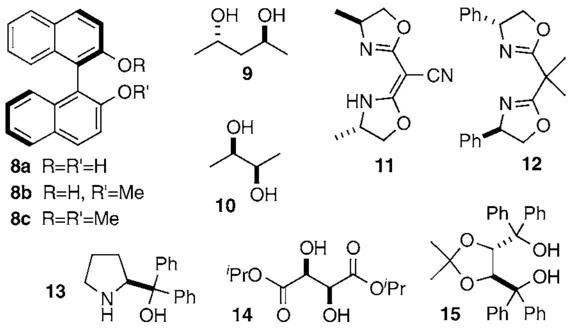
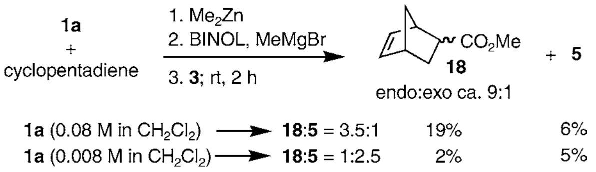


Figure 2. Chiral ligands used in this study.

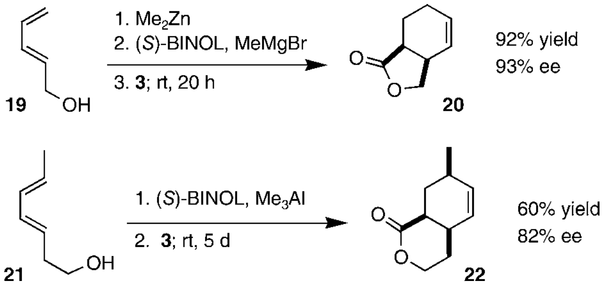
result is most easily accommodated by assuming that **18**[26] is formed via an intermolecular reaction and **5** is formed via an "intramolecular" reaction (e.g., **17**[23] or a related species).[3,27]

Scheme 3



In a preliminary survey, use of ligands **13**−**15** in place of BINOL gave inferior results (Table 2, entries 12−16). In particular, although good enantioselectivity was obtained with catalysts prepared from **14**,[17] the reactivities of these species were very low (entries 13−15).[28] DA reaction of dienol **19** with **3** under the optimized conditions gave **20** in good yield and with high ee (Scheme 4).[29] By contrast, reaction of **21** under these conditions gave **22** in modest yield (55%) with poor ee (33%). Athough this substrate performed better with the putative mononuclear catalyst prepared from BINOL and Me_3Al (1 equiv), further optimization in this series is clearly necessary for synthetic utility.

Scheme 4



In conclusion, we have demonstated the first examples of Diels−Alder reactions where the regio-, diastereo-, and enantioselectivity are controlled by simultaneous coordination of the components to a novel binuclear Lewis acid template. Using this approach, we exploited the benefits of intramolecularity and Lewis acid catalysis to transform a virtually unselective DA reaction into one that produces a single adduct with high enantiopurity. We expect that this strategy will be applicable to other systems and will report on our efforts in this context in due course.

Acknowledgment. Financial support from the Natural Sciences and Engineering Research Council (Canada) and the University of Saskatchewan is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Kobuke, Y.; Fueno, T.; Furukawa, Y. *J. Am. Chem. Soc.* **1970**, *92*, 6548−6553.

(27) That **18** was a 9:1 ratio of endo:exo diastereomers suggests a Lewis acid-mediated DA process; for example, reaction of cyclopentadiene with **17**. For a discussion, see ref 3.

(28) This could result from lower Lewis acidity of catalysts derived from **14** due to the additional coordination of the metals with the adjacent carbonyl groups; for examples of such proposed structures, see ref 17.

(29) For the use of (±)-**5** in synthesis see: (a) Rath, J.-P.; Kinast, S.; Maier, M. E. *Org. Lett.* **2005**, *7*, 3089−3092. For the use of (±)-**20** in synthesis, see: (b) Jiao, X. Z.; Xie, P.; Zu, L. S.; Liang, X. T. *Chin. Chem. Lett.* **2003**, *14*, 127−129. The saturated analogue of **20** has numerous synthetic applications. For example, see: (c) Baxendale, I. R.; Ernst, M.; Krahnert, W.-R.; Ley, S. V. *Synlett* **2002**, 1641−1644. (d) Hamilton, G. S.; Huang, Z.; Yang, X. J.; Patch, R. J.; Narayanan, B. A.; Ferkany, J. W. *J. Org. Chem.* **1993**, *58*, 7263−7270. (e) Brion, F.; Marie, C.; Mackiewicz, P.; Roul, J. M.; Buendia, J. *Tetrahedron Lett.* **1992**, *33*, 4889−4892.