Advances in Organic Catalysis: The Design of a Novel Asymmetric, Organocatalytic Intramolecular Diels Alder Reaction.

A thesis presented

by

Rebecca Mary Wilson

to

The Department of Chemistry

in partial fulfillment of the requirements

for the degree of

Masters of Science

in the subject of

Chemistry

California Institute of Technology

Pasadena, California

March, 2002

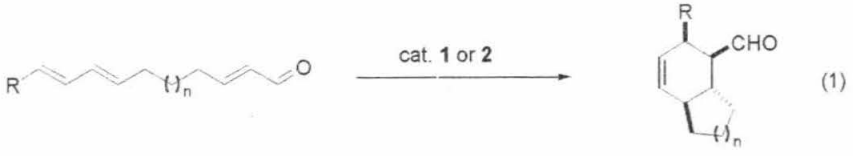
I. Introduction

The Diels-Alder reaction is one of the most powerful and widely exploited methods available for generating six-membered rings. Similarly, the intramolecular Diels-Alder (IMDA), in which the diene and dienophile reacting partners are tethered, has received a great deal of attention from synthetic chemists in recent years.[1] The IMDA usually proceeds with excellent levels of regio- and stereocontrol to generate complex bicyclic systems with up to four contiguous stereocenters from relatively simple precursors. There have been a number of efforts to develop diastereoselective variants of the IMDA, but there are considerably fewer examples of catalytic, asymmetric IMDA variants.

One area of focus in the MacMillan group is the development of asymmetric reactions catalyzed by purely organic molecules, and it is in this context that we sought to develop a novel enantioselective, organocatalytic intramolecular Diels-Alder reaction. We report herein the successful development of an amine-catalyzed asymmetric IMDA (eq. 1). The reaction can be extended to a diverse range of substrates, including a Type II and an ether-containing substrate, neither of which have been shown to work with existing enantioselective methods.

1

2



(1)

Background. The intramolecular Diels-Alder reaction is a concerted [4+2] cycloaddition involving an interaction between a diene and a dienophile. A myriad of

---

[1] For reviews, see: (a) Roush, W.R. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I, Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 4.4.; (b) Craig, D. *Chem. Soc. Rev.* **1987,** *16,* 187-238. (c) Fallis, A.G. *Can. J. Chem.* **1983,** *62,* 183-234 (d) Brieger, G.; Bennett, J.N. *Chem. Rev.* **1980,** *80,* 63-97.

variants of the IMDA are known, and the scope of the reaction is impressive. Because of its utility and versatility, the IMDA is frequently employed in natural product synthesis.[2] There have been reports of intramolecular Diels-Alder reactions utilizing heteroatoms in the tether,[3] the diene,[4] and the dienophile.[5] Though tethers in the Type I IMDA are typically 3-4 atoms in length, the reaction has been used to synthesize medium rings[6] and macrocycles.[7] The IMDA offers enhanced levels of stereo- and regiocontrol over its bimolecular counterpart, and as a result a number of variants have been developed that use removable tethers as a way to access Diels-Alder products through highly ordered intramolecular transition states.[8]

---

[2] For recent examples, see: (a) Nicolaou, K.C.; Gray, D.; Tae, J. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 3679-3683. (b) Munakata, R.; Ueki, T.; Katakai, H.; Takao, K.; Tadano, K. *Org. Lett.* **2001,** *3*, 3029-3032. (c) Njardarson, J.T.; McDonald, I.M.; Spiegel, D.A.; Inoue, M.; Wood, J.L. *Org. Lett.* **2001**, *3*, 2435-2438. (d) Chakalamannil, S.; Davies, R *Org. Lett.* **2001**, *3*, 1427-1429. (e) Miyaoka, H.; Yasuhiro, K.; Yamada, Y. *J. Org. Chem.* **2001**, *66*, 1429-1435. (g) Stocking, E.M.; Sanz-Cervera, J.F.; Williams, R.M. **2000**, *122*, 1675-1683. (h) Brosius, A.D.; Overman, L.E.; Schwink, L. **1999**, *121*, 700-709.

[3] For representative examples see: (ether) Ainsworth, P.J.; Craig, D.; Reader, J.C.; Slawin, A.M.Z.; White, A.J.P.; Williams, D.J. *Tetrahedron*, **1996**, *52*, 695-724. (amine) Wattanasin, S.; Kathawala, F.G.; Boeckman, R.K. *J. Org. Chem.* **1985**, *50*, 3810. (ester) Tantillo, D.J.; Houk, K.N.; Jung, M.E. *J. Org. Chem.* **2001**, *66*, 1938-1940. (amide) Handa, S.; Jones, K.; Newton, C.G., Williams, D.J. *J. Chem. Soc. Chem. Commun.* **1985**, *19*, 1362-1363.

[4] For examples see: (carbonyl) Jung, M.E.; Light, L.A.; *J. Org. Chem.* **1982**, *47*, 1084-1090. (oxazole) Jacobi, P.A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295-4303. (furan) Brickwood, A.C.; Drew, M.G.B.; Harwood, L.M.; Ishikawa, T.; Marais, P.; Morrison, V. *J. Chem. Soc. Perkin Trans. 1* **1999**, *8*, 913-921.

[5] For examples see: (imino) Grieco, P.A.; Kaufman, M.D. *J. Org. Chem.* **1999**, *64*, 6041-6048. (acylnitroso) Ozawa, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 2955-2958.

[6] (a) Sakan, K.; Smith, D.A. *Tetrahedron Lett.* **1984**, *25*, 2081-2084. (b) Craig, D.; Ford, M.J.; Gordon, R.S.; Stones, J.A.; White, A.J.P.; Williams, D.J. *Tetrahedron*, **1999**, *55*, 15045-15066.

[7] McCauley, J.A.; Nagasawa, K.; Lander, P.A.; Mischke, S.G.; Semones, M.A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647-7648.

[8] For examples of removable tethers, see: (boron) Batey, R.A.; Thadani, A.N.; Lought, A.J. *J. Am. Chem. Soc.* **1999**, *121*, 450-451. (magnesium and aluminum) Stork, G.; Chan, T.Y. *J. Am. Chem. Soc.* **1995,** *117*, 6595-6596. (silicon) Stork, G.; Chan, T.Y.; Breault, G.A. *J. Am. Chem. Soc.* **1992,** *114*, 7578-7579.

The origins of stereocontrol in the IMDA are based on a complex blend of steric and electronic factors. Unlike the bimolecular Diels-Alder, the Alder *endo* rule of secondary orbital overlap cannot necessarily be used to predict the product distribution of an IMDA. A full analysis of the intricacies of stereocontrol in the IMDA is outside the scope of this report, as each substrate class is subject to its own particular steric and electronic requirements. This discussion will focus on the basic principles governing stereocontrol in Type I IMDA reactions of terminally substituted nonatriene systems.

The IMDA is often divided into Type I and Type II variants. In the Type I IMDA, the tether linking the diene to the dienophile is attached at the 4-position of the diene and the fused products can be either *cis* or *trans* at the ring junction (figure 1). In the Type II IMDA, the tether is attached at the 3-position of the diene and cyclization always yields *syn* products.

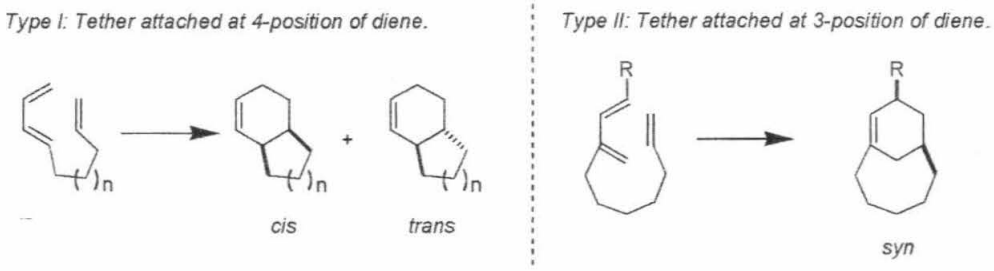


Figure 1. Type I vs. Type II Intramolecular Diels-Alder.

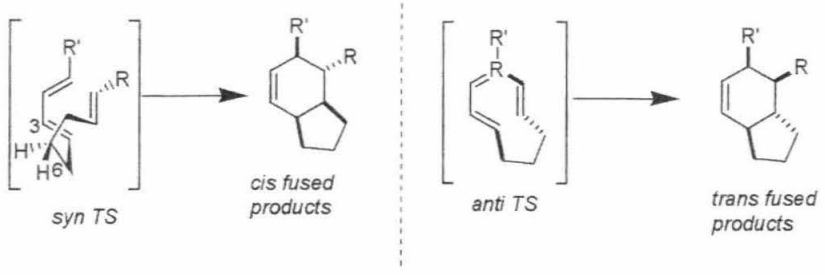
Because product stereochemistry is highly predictable in the Type II IMDA, the remainder of this discussion will focus on diastereoselectivity in the Type I IMDA.[9]

Type I intramolecular Diels-Alder reactions proceed through either *syn* or *anti* transition states. In the former, the tether linking the diene to the dienophile is pointed into the transition state (figure 2a). In the *anti* transition state, the tether is situated away from the reacting center. It is notable that the *syn* transition state is more sterically demanding due to interactions between the C_3 substituent of the diene and C_6 of the tether.

---

[9] For an excellent review of the Type II IMDA, see: Bear, B.R.; Sparks, S.M.; Shea, K.J. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 821-849.

(a) *Representative Transition States for E,E diene*



(b) *Representative Transition State for E,Z diene*

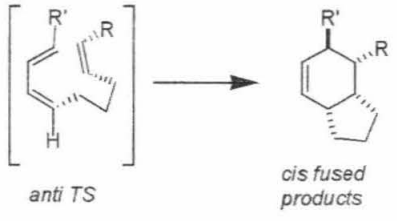


Figure 2. *Syn* vs. *anti* transition states in the Type I IMDA.

Both *E,E* and *E,Z* dienes will participate in the IMDA reaction. *E,Z* dienes react much more slowly than do *E,E* dienes, due to increased steric congestion in the transition state. Due to these unfavorable steric interactions, an *E,Z* - diene will always react through an *anti* transition state to afford *cis* fused bicyclic products (figure 2b). In the reaction of *E,E* dienes, product distribution is highly dependent on the nature of the substrate.

Unsubstituted nonatriene **3** cyclizes to form a 3:1 mixture of *cis* and *trans* product isomers (eq. 2).[10] Because the reaction is kinetically controlled, it appears that the more

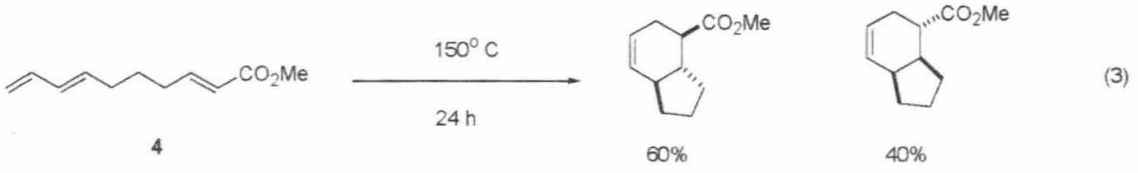
(2)

sterically demanding *syn* transition state is favored by about 1 kcal/ mol in the case of an unsubstituted triene.

When a dienophile activating group with *E* geometry, such as an ester, is introduced, the product distribution reverses so that the *trans* product, the result of an *anti*

[10] Lin, Y.-T.; Houk, K.N. *Tetrahedron Lett.* **1985**, *26*, 2269.

transition state, is slightly favored under thermal conditions (eq. 3).[11] This observation is



(3)

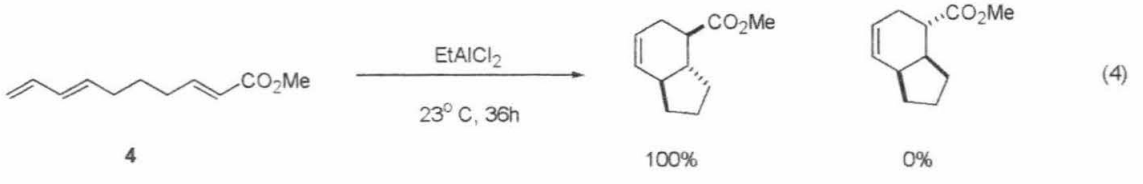
attributed to a shift from a symmetrical to an unsymmetrical transition state. Although the IMDA is a concerted reaction, bond formation can be asynchronous in the transition state.[12] In a synchronous transition state, both the internal and external bonds are formed to the same extent (figure 3a). However, in the case of **4**, the terminal activating group increases the size of the coefficient at the internal position of the dienophile (C_3 – figure 3b).

Synchronous vs. Asynchronous Transition States

Figure 3. Relative sizes of LUMO and HOMO orbitals in a synchronous (a) and an asynchronous (b) transition state.

As a result, the internal bond ($C_3 - C_7$) will be more fully formed in the transition state and the steric effects will be magnified. The sterically favored *anti* transition state becomes lower in energy than the *syn* transition state (~ 0.5 kcal/mol).

These effects of asynchronicity are exaggerated when Lewis acid, which further increases the LUMO coefficient at the internal carbon, is used to catalyze the reaction.[11] In the case of the nonatriene ester **4**, the *trans* fused bicycle is the only product observed when $EtAlCl_2$ is added to the catalyze the reaction (eq. 4).



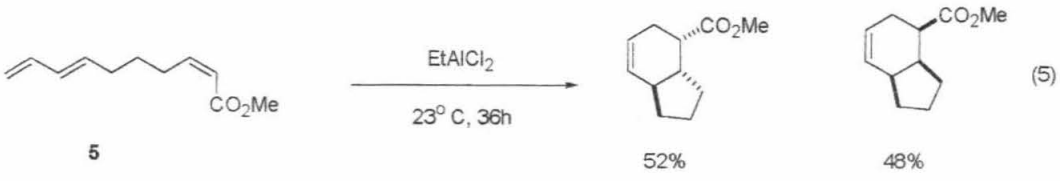
(4)

Alder *endo* rules would seem to explain these observations, as Lewis acid is known to increase the effects of secondary orbital overlap, and the observed product is

[11] Roush, W.R.; Gillis, H.R.; Ko, A.I. *J. Am. Chem. Soc.* **1982**, *104*, 2269.

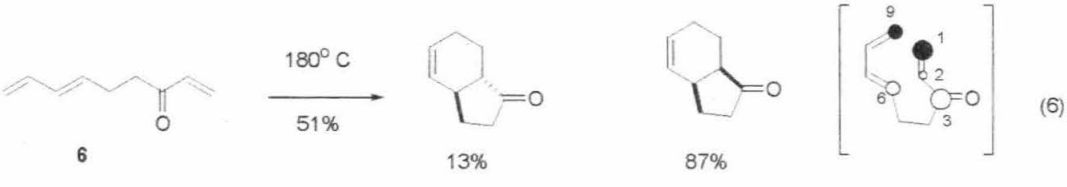
[12] Boeckman, R.K.; Ko, S.S. *J. Am. Chem. Soc.* **1982**, *104*, 1033.

the result of an *endo* transition state. Surely *endo/exo* considerations do play a role in the selectivity; however, the Alder *endo* rule is not sufficient, as evidenced by the reaction of the *Z* ester **5** with Lewis acid (eq. 5).



Triene **5** cyclizes to form a nearly equal mixture of *syn* and *anti* products.[11] Clearly, asynchronous bond formation (which would promote the formation of *trans* fused adduct via an *anti* transition state) and Alder *endo* rules (which would dictate the formation of *cis* fused adduct via the *syn*/ *endo* transition state) are in competition. In such a case, an undesirable mixture often results.

Substrate **6**, an internally activated triene further illustrates the concept of asynchronous bond formation (eq. 6). In this case, the external LUMO coefficient is increased with respect to the internal position of the dienophile.[13] In a synchronous transition state, the *syn* conformation is preferred, and in the case of internal



activation, the steric demands of the *syn* transition state are significantly reduced by asynchronous external bond formation. The result is the selective formation of *cis* fused IMDA adducts.

It bears mentioning that decatrienes behave in a similar manner to the nonatrienes, and are subject to the same principles of the asynchronous transition state and Alder *endo* rules. However, when the tether is four atoms long, the substrate adopts a chair

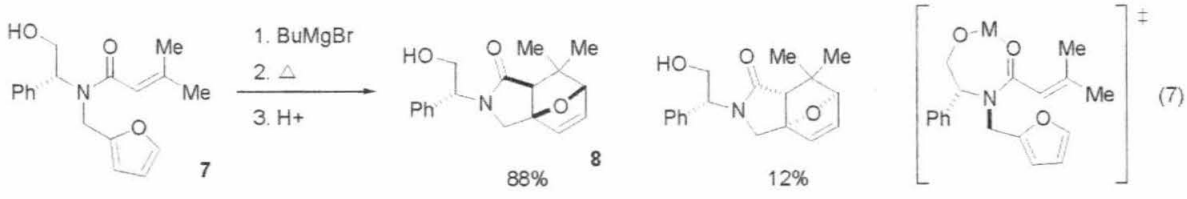
---

[13] Roush, W.R.; Peseckis, S.M. *J. Am. Chem. Soc.* **1981**, *103*, 6696.

conformation in the transition state. The chair is much less strained than the transition state for the nonatriene, and as a result all steric demands become less pronounced in the decatriene system.[14] As a result, secondary orbital overlap can become a more significant factor in determining the product distribution with decatriene systems. In addition, the exceptional levels of stereoselectivity that are often observed in the nonatriene IMDA adducts are usually harder to achieve in decatriene cyclizations.

Diastereoselective Intramolecular Diels-Alder Reactions. There are many instances in which stereochemical relay has been achieved through the use of chiral centers along the tether in both nonatriene and decatriene substrates.[15] In these cases, the stereocenter is usually adjacent to the diene or the dienophile and allylic strain in the transition state dictates the orientation of the tether and thus the product stereochemistry. While effective to varying degrees, these diastereoselective IMDA reactions which rely on stereochemical relay usually do not involve easily removable substituents and thus are only useful when the IMDA adduct contains substitution on the tether. Chiral auxiliary-controlled IMDA variants provide a much more general method for accessing IMDA adducts in enantioenriched forms.

Mukaiyama published the first diastereoselective IMDA that utilizes an easily cleaved chiral auxiliary.[16] The auxiliary, a phenylglycine derivative, is attached to an amide on the tether (eq. 7). It is proposed that, in the reaction of furan **7**, Mg chelates the amide carbonyl and the alkoxide of the auxiliary.



(7)

---

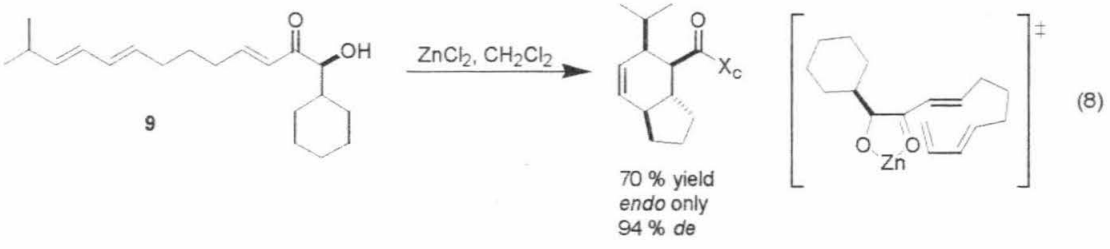
[14] Brown, F.K.; Houk, K.N. *Tetrahedron Lett.* **1985**, *26*, 2297.

[15] (a) Oppolzer, W.; Frostl, W. *Helv. Chim. Acta.* **1975**, *58*, 587. (b) Boeckman, R.K.; Barta, T.E. *J. Org. Chem.* **1985**, *50*, 3241.

[16] Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1981**, 29-32.

With the phenyl group locked into place pointed back, the furan moiety wraps around to the top face of the dienophile and undergoes a [4+2] with the internally activated dienophile to afford IMDA adduct **8**. The reaction proceeds with only moderate levels of diastereocontrol (76 % *de*) and the bicyclic system formed by the IMDA is broken up in the excision of the auxiliary, but Mukaiyama's internal chiral auxiliary laid the groundwork for further development of auxiliary-controlled variants of the IMDA.

External chiral auxiliaries, where the chiral component is linked to the end of the dienophile, are more prevalent and more generally useful than the internal auxiliary. Masamune's α- hydroxy ketone was an early example of an external chiral auxiliary (eq. 8).[17] The reaction of **9** is believed to proceed through a transition state where Zn is bidentate chelated to the α- hydroxy ketone, forcing



(8)

the cyclohexyl moiety of the auxiliary to point out. The tether then wraps around the back of the dienophile to avoid unfavorable steric interactions with the auxiliary. This reaction proceeds with quite high levels of stereocontrol (94 % *de*) and good yield. However, a useful chiral auxiliary should be easily cleaved under mild conditions and it is in this regard that the α- hydroxy ketone auxiliary falls short, as the conditions for auxiliary removal require sodium periodate, a harsh oxidizing reagent with limited functional group compatability.

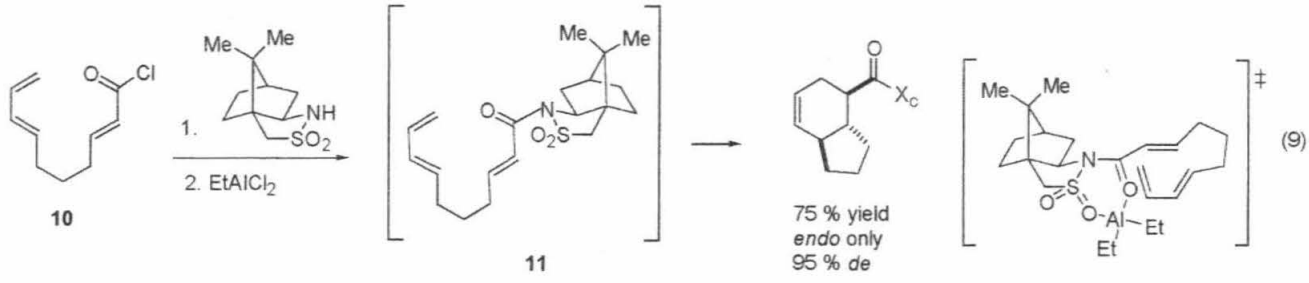
Oppolzer developed an easily cleaved acyl sultam auxiliary that affords IMDA adducts in good yields and diastereomeric excess (eq. 9).[18] In the Oppolzer IMDA, acyl sultam **11** is formed from acid chloride **10** *in situ* and $EtAlCl_2$ is subsequently added to catalyze the reaction. It is proposed that the metal center chelates the sulfonyl and

---

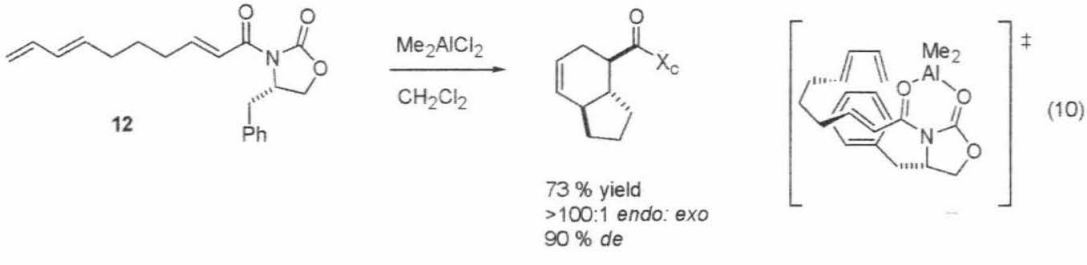
[17] Mukaiyama, M. *J. Org. Chem.* **1983,** *23*, 4441-4444.

[18] Oppolzer, W.; Dupuis, D. *Tetrahedron Lett.* **1985**, *26*, 5437-5440.

carbonyl, forcing the tether to wrap around to the bottom face of the dienophile to avoid steric interactions with the camphor moiety.



Similarly, Evans' chiral oxazolidinone **12** is chelated by Aluminum, and the phenyl group of the auxiliary is believed to engage in π - stacking interactions with the dienophile (eq. 10).[19] The diene tether then wraps around to the top face of the dienophile to react in the IMDA.



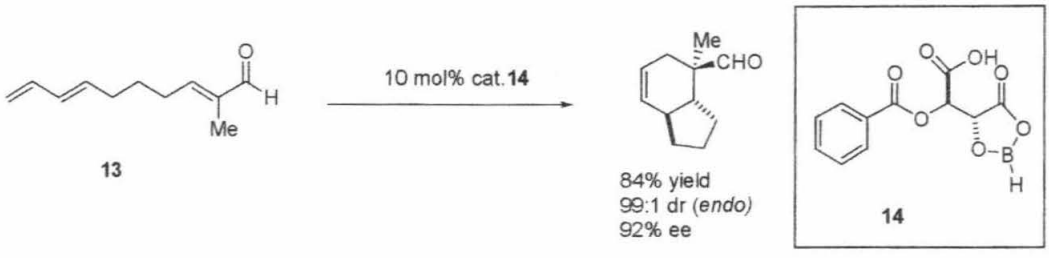
The development of a number of IMDA variants that employ chiral auxiliaries has been very valuable in allowing chemists to access enantioenriched IMDA adducts. However, catalytic asymmetric methods have the potential for far greater utility and practical benefit.

Enantioselective Intramolecular Diels-Alder Reactions. Despite the widespread interest in the development of asymmetric catalytic variants of the bimolecular Diels-Alder, there has been relatively little exploration into the development of asymmetric, catalytic IMDA reaction variants. In several cases, only one or two substrates have been examined, and often only in the context of an extension of bimolecular asymmetric versions.

---

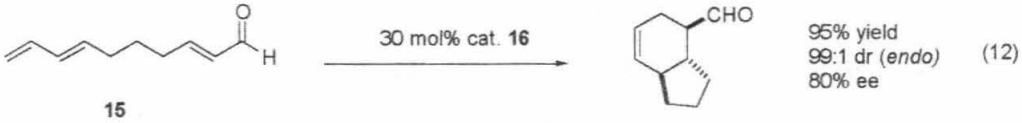
[19] (a) Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261-4263. (b) Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256.

Yamamoto's chiral acyloxyborane catalyst **14** was an early example of an asymmetric catalytic IMDA (eq. 11).[20] The reaction of **13** produces a Diels-Alder adduct with a quaternary carbon center in good *ee*. However, the limitation of the reaction is that only substrates with α - substituents appear to react with any significant levels of enantiomeric excess.

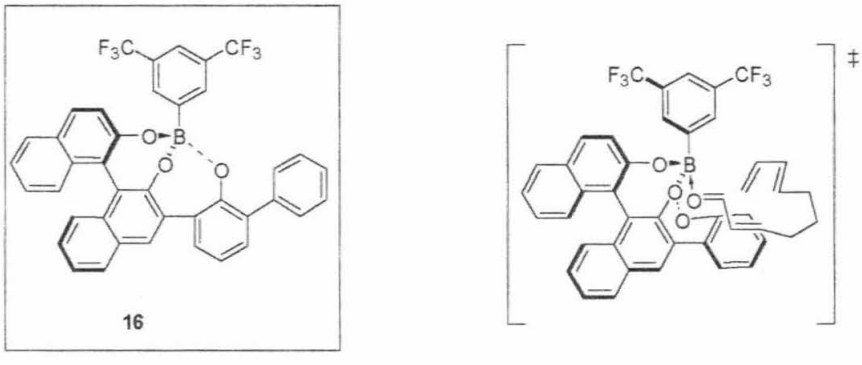


(11)

Yamamoto later improved upon his first catalyst with a second generation borane catalyst **16** that allows the cycloaddition of a non-substituted nonatrienal **15** in good yield and moderate *ee* (80%) (eq. 12).[21]



(12)



A Titanium TADDOL Catalyst **19** was shown by Narasaka to catalyze the IMDA of an oxazolidinone- activated substrate with moderate reactivity and variable *ee*.[22] Narasaka does not see any IMDA reaction in the unsubstituted decatriene substrate and

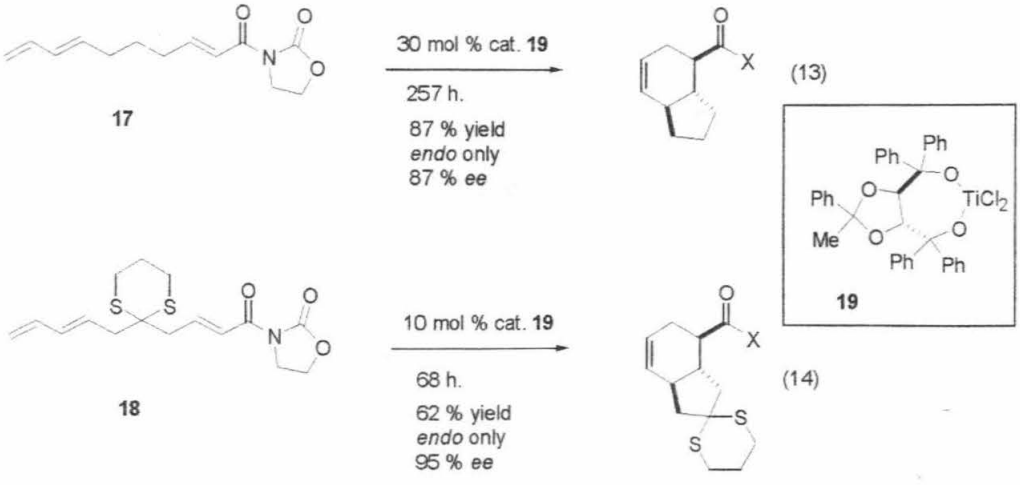
---

[20] Furuta, K.; Kanematsu, A.; Yamomoto, H.; Takaoka, S. *Tetrahedron Lett.* **1989**, *30*, 7231-7232.

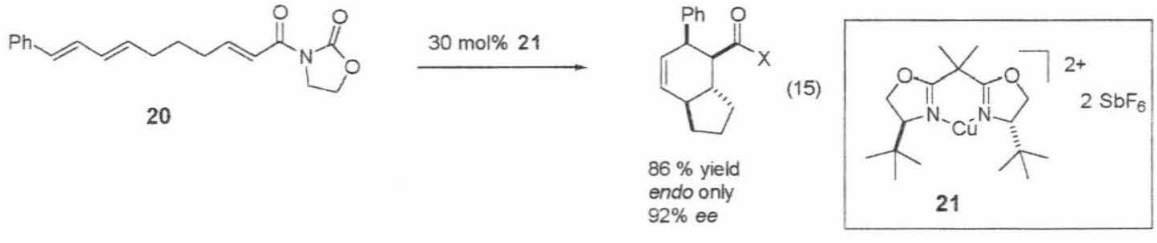
[21] (a) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049-3050. (b) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920-6930.

[22] (a) Iwasawa, N.; Sugimori, J.; Kawase, Y.; Narasaka, K. *Chem. Lett.* **1989**, 1947-1950. (b) Narasaka, K.; Saitou, M.; Iwasawa, N. *Tetrahedron: Asymmetry* **1991**, *2*, 1305-1318.

reports long reaction times in the nonatriene substrate **17** (eq. 13). Reactivity is greatly enhanced with the addition of a dithiane functionality on the tether, as in substrate **18**, presumably due to the Thorpe-Ingold effect (eq. 14).



The most extensive published study of the asymmetric, catalytic IMDA comes from the Evans laboratory.[23] Evans finds that the C_2- symmetric Cu(II) *tert*-butylbis(oxazoline) catalyst **21** affords enantioenriched IMDA adducts with good reactivity and selectivity (eq. 15). IMDA substrates, terminally activated with the bidentate chelating oxazolidone auxiliary will react to form [4.3.0] and [4.4.0] adducts (eq. 15).



While there has been some significant progress in the search for a general asymmetric catalytic IMDA, there are still improvements to be made on the existing methods. The most useful catalytic systems to date require the use of an achiral oxazolidone auxiliary and none of the examples explore a wide substrate scope. We felt that the organocatalysis program underway in the MacMillan lab could be applied towards the

[23] Evans, D.A.; Johnson, J.S. *J. Org. Chem.* **1997**, *62*, 786-787.

development of a broadly useful variant of the asymmetric, catalytic intramolecular Diels- Alder reaction.

Organocatalysis: Previous Studies.

The development of asymmetric catalytic methods is of utmost importance to organic chemists, industrial and academic alike. Most existing asymmetric methods utilize Lewis acid-bound chiral ligands, such as BINOL, bis(oxazoline), and stein. These catalyst systems are extremely versatile and are widely used in synthesis, but there are some serious drawbacks to Lewis acid catalysis. Chiral Lewis acids are often air- and water- sensitive and must be stored and handled under stringently anaerobic conditions. Many chiral Lewis acid catalysts must bidentate chelate their substrates in order to achieve the structural rigidity required for asymmetric induction. This means that achiral auxiliaries, such as oxazolidone, need to be installed on the substrate prior to reaction and subsequently cleaved to afford more useful functionalities. Finally, many Lewis acid catalysts are toxic and potential environmental hazards.

For these reasons and others, the MacMillan group became interested in developing a purely organic catalyst that would incorporate all of the positive qualities of a chiral Lewis acid catalyst – substrate and reaction generality as well as high levels of reactivity and enantioselectivity – while overcoming the aforementioned drawbacks plaguing Lewis acid catalysis. Importantly, organic catalysts also provide the potential to asymmetrically catalyze reactions that cannot be catalyzed by Lewis acids due to substrate-catalyst incompatibility.

Organocatalysis borrows the basic principles of Lewis acid (LA) catalysis. LA catalysis exploits the equilibrium that exists between an α, β - unsaturated carbonyl and a Lewis acid. When the LA is coordinated to the aldehyde, the substrate's LUMO is lowered, activating the substrate for reaction with an electron-rich reacting partner (figure 4). Similarly, in the presence of a secondary amine, there is an equilibrium that exists between an α, β - unsaturated aldehyde and an iminium ion. Formation of the iminium ion also lowers the LUMO energy and activates the substrate.

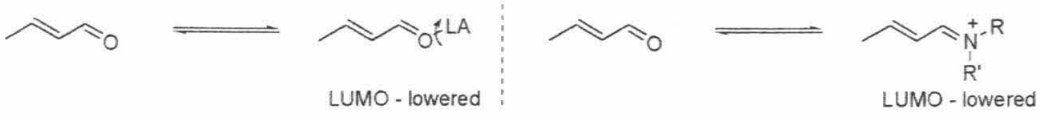


Figure 4. Useful equiibria for LUMO - lowering catalysis.

It should also be noted that in the case of the aldehyde, depicted in figure 4, the Lewis acid has free rotation about the O-LA bond. Most chiral Lewis acids do not work well with monodentate systems such as aldehydes because of the free rotation in the transition state. A chiral amine, however, is covalently bound to the substrate through a double bond, and this increased rigidity should allow for the transfer of enantioselectivity in the transition state. It was therefore postulated that a chiral secondary amine could be developed as a general asymmetric catalyst.

A catalytic cycle is proposed for a bimolecular Diels-Alder reaction in which

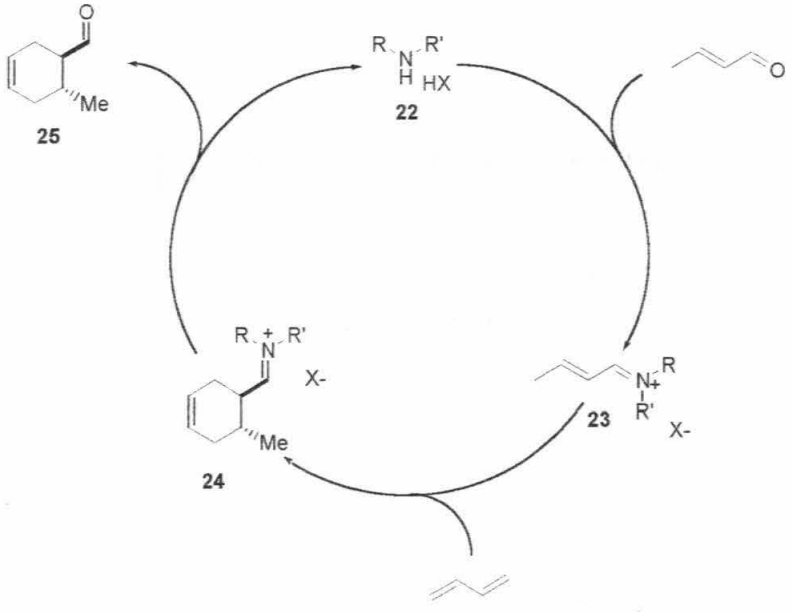


Figure 5. Proposed catalytic cycle for amine-catalyzed Diels-Alder.

the secondary amine salt **22** first reacts with crotonaldehyde to form an iminium ion (figure 5). This LUMO- lowered intermediate **23** undergoes a [4+2] cycloaddition with butadiene to afford the catalyst- bound product **24**. The product and catalyst disassociate to return the secondary amine to the catalytic cycle and release the aldehyde product **25**.

Imidazolidinone **1** was discovered in a screen of secondary chiral amine salts, and was shown to be an effective catalyst for an asymmetric bimolecular Diels-Alder reaction.[24]

Figure 6. First and second generation imidazolidinone catalysts.

It was soon discovered that the same amine effectively catalyzes an asymmetric nitrone [3+2] cyclization[25] and a pyrrole conjugate addition[26] with α, β– unsaturated aldehydes. Incidentally, chiral Lewis acids are ineffective in catalyzing both of these reactions.

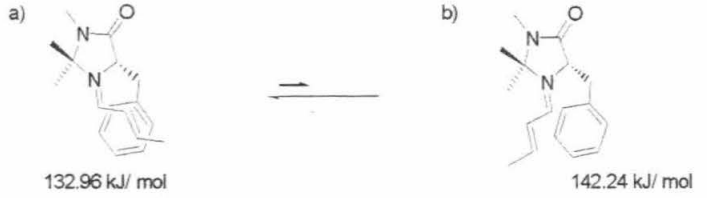


Figure 7. Possible conformations of iminium ion intermediate (a) dienophile *cis* to benzyl group (b) dienophile *trans* to benzyl group.

The origins of enantioselectivity can be explained by the preferred conformation of the catalyst- bound substrate. Studies of the iminium ion intermediate of imidazolidinone catalyst **1** indicate that there is a strong preference for the olefin of the α,β - unsaturated dienophile to exist in conformation (a) (figure 7), where the olefin is positioned over the benzyl group of the catalyst, and away from the dimethyl substituent. The preference for conformation (a) over (b) is about 9.2 kJ/mol. With the dienophile locked into position (a), the diene will approach from the top face of the catalyst-bound substrate.

Recently, a second generation imidazolidinone catalyst **2** was found to have increased reactivity and selectivity.[27]

---

[24] Ahrendt, K.A.; Borths, C.J.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.

[25] Jen, W.S.; Weiner, J.J.M.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2000**, *122*, 9874-9875.

[26] Paras, N.A.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2001**, *123*, 4370-4371.

[27] Austin, J.F.; MacMillan, D.W.C. *J. Am. Chem. Soc. (in press).*

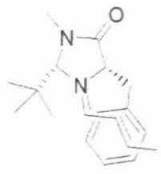


Figure 8. Preferred conformation of the substrate- catalyst intermediate of **2**.

The increase in reactivity is believed to derived from the fact that the amine lone pair is less shielded than in catalyst **1**. In **1**, the lone pair is eclipsed by one of the methyl groups, whereas in **2**, the lone pair is only eclipsed by a hydrogen, making it more basic and therefore more able to form iminium ion. The bulky *tert*- butyl substituent on the new catalyst is believed to be responsible for the increased selectivity. The first generation catalyst relies on the benzyl stereocenter to control the facial selectivity, but the second generation catalyst further reinforces the facial selectivity with the bulky *tert*- butyl substituent. I report herein my development of a novel, asymmetric organocatalytic intramolecular Diels-Alder reaction, involving a comparative study of the reactivity and selectivity of catalysts **1** and **2**.

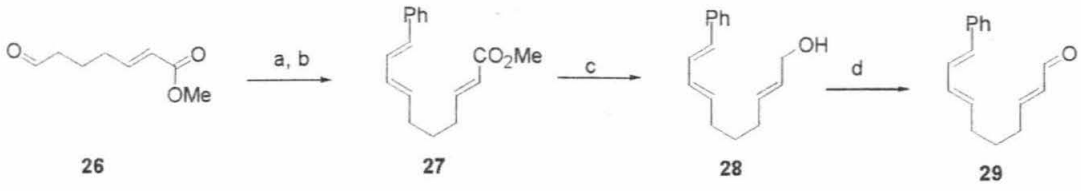
II. Results and Discussion

Subtrate Synthesis.

The phenyl-substituted nonatriene substrate **29** was prepared in three steps from the known ester **26**[28] (Scheme 1). **26,** which was prepared in one step from commercially available glutaric dialdehyde, was subjected to a Wittig reaction with cinnamyltriphenylphoshonium chloride to afford diene **27** as a mixture of diene isomers. The mixture was isomerized with catalytic I_2 to 5:1 dr. The resultant isomerically enriched **27** was then reduced and oxidized to afford IMDA substrate **29**.

[28] House, H.O.; Cronin, T.H. *J. Org. Chem.* **1965**, *30*, 1061-1070.

Scheme 1.

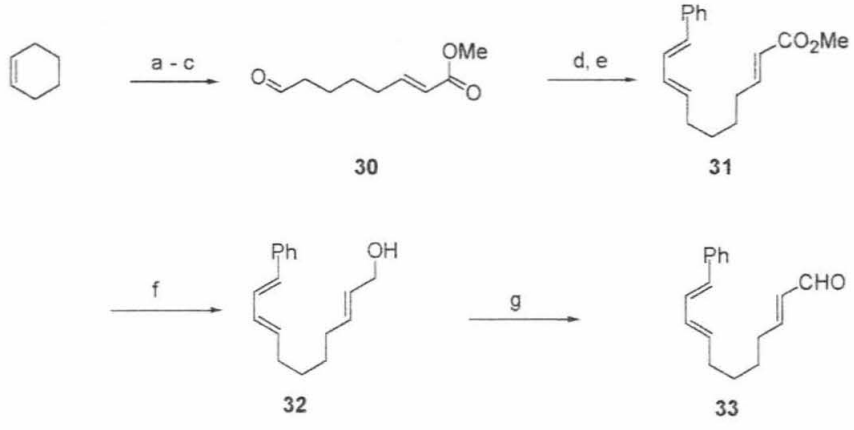


26 **27** **28** **29**

(a) cinnamyltriphenylphosphonium chloride, tBuOK, Et_2O, 25 °C, 63 %; (b) I_2 (5 mol%), CH_2Cl_2; (c) DIBAl-H, CH_2Cl_2, -78 °C, 95%; (d) TPAP, NMO, CH_2Cl_2, 25 °C, 50%.

Trienal **33** was prepared in a similar manner from commercially available cyclohexene (Scheme 2). Ozonolysis of cyclohexene with reductive work-up, followed by Wittig reaction afforded ester **30** which was subjected to a second Wittig reaction to install the diene. I_2 – catalyzed isomerization of the resulting diene yielded **31** as a 5:1 mixture of geometric isomers. Reduction followed by oxidation afforded IMDA substrate **33**.

Scheme 2.



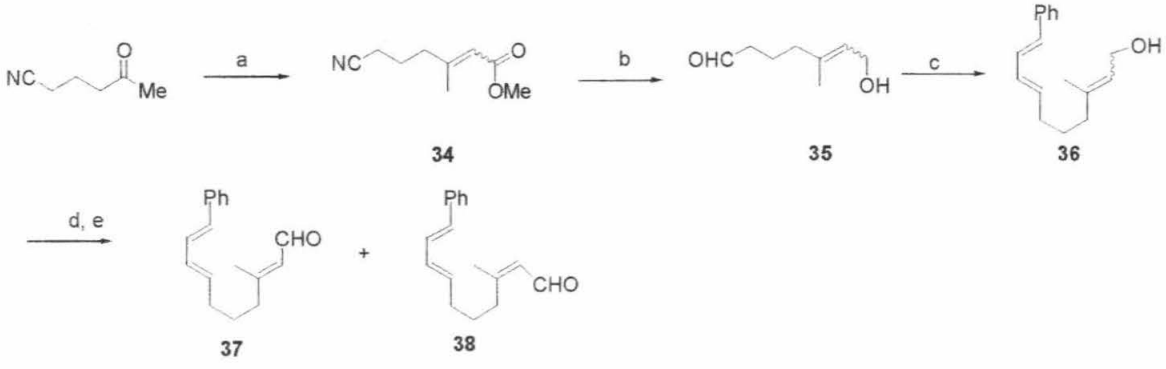
30 **31** **32** **33**

(a) O_3, CH_2Cl_2, -78°C ; (b) PPh_3, 25°C; (c) methyl (triphenylphosphoranylidene) acetate, 55%; (d) cinnamyltriphenylphosphonium chloride, *t*BuOK, Et_2O, 25°C; (e) I_2, CH_2Cl_2, 40%; (f) DIBAl-H, CH_2Cl_2, -78°C, 100%; (g) TPAP, NMO, CH_2Cl_2, 50%.

Trienals **37** and **38** were readily synthesized in five steps from commercially available materials (Scheme 3). Oxohexanenitrile was subjected to a Horner-Emmons reaction to afford **34** as a 1.4:1 mixture of olefin isomers. This mixture was carried through the remainder of the synthesis. **34** was reduced to the aldehyde **35**, and

subsequent Wittig homologation afforded diene **36** as a mixture of diene isomers which was carried to the next step. Oxidation of the allylic alcohol followed by iodine isomerization of the diene afforded the easily separable IMDA substrates **37** and **38**, both with a 5:1 (*E*, *E*) to (*E*, *Z*) ratio at the diene.

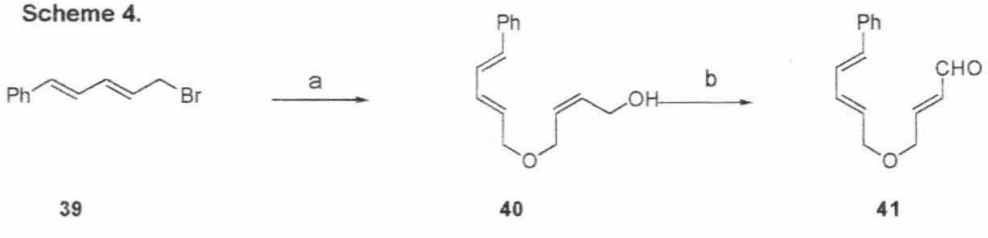
Scheme 3.



(a) methyl diethylphoshonoacetate, NaOMe, toluene, reflux, 79%; (b) DIBAl-H, CH_2Cl_2, -78 °C, 41%; (c) cinnamyltriphenylphoshonium chloride, *t*BuOk, THF, 25 °C; (d) TPAP, NMO, CH_2Cl_2, 25 °C; (e) I_2, CH_2Cl_2, 25 °C, 81%.

The ether IMDA substrate **41** was synthesized from the known dienyl bromide **39** (Scheme 4)[29]. Etherification of **39** with *cis* – butenediol produced **40**. Swern oxidation with concomitant aldehyde isomerization afforded the highly unstable IMDA substrate **41**.

Scheme 4.

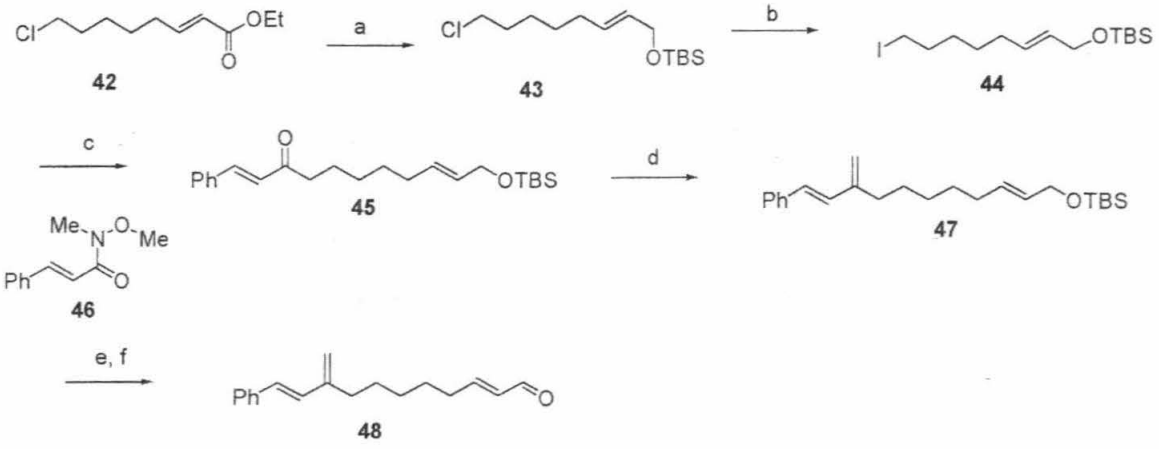


(a) 2-butene-1,4-diol, Bu_4NH_4Br, 50% NaOH (aq), CH_2Cl_2, 44%; (b) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, -78 °C, 38%.

[29] Drew, J.; Letellier, M.; Morand, P.; Szabo, A.G. *J. Org. Chem.* **1987**, *52*, 4047-4052.

Synthesis of Type II substrate **48** commenced with known ester **42**,[30] which was reduced and silyl protected to afford **43** (Scheme 5). Finkelstein reaction of the chloride **43** produced iodide **44** which was converted to an alkyllithium and added into known Weinreb's amide **46** to yield ketone **45**. Wittig homologation produced diene **47**, which was deprotected and oxidized to afford Type II substrate **48**.

Scheme 5.



(a) DIBAl-H, CH_2Cl_2, -78 °C, 97%; Et_3N, DMAP, CH_2Cl_2, TBDMSCl, 0 °C, 99%; (b) NaI, acetone, reflux, 82%; (c) Et_2O, *t*BuLi (1.7 M in pentane), -78 °C, then **46**, 35%; (d) $MePPh_3Br$, *t*BuOK, 61%; (e) TBAF-H_2O, THF, 86%; (f) TPAP, NMO, CH_2Cl_2,96%.

IMDA Reactions.

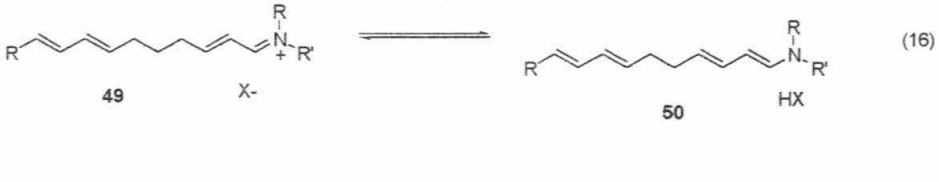
Each substrate that was examined in the course of this study was individually optimized for maximum yield and selectivity. Starting material polymerization and a dimerization side reaction (discussed shortly) both compete with the IMDA for starting material consumption, while background reaction and product epimerization must also be minimized in order to achieve high enantio- and diastereoselectivity. The extent to which each of these factors is an issue is dependent upon the stability and reactivity of the individual substrate, and it is thus difficult to present one optimal set of reaction conditions. Instead, this discussion will address some of the issues to consider when running organocatalyzed intramolecular Diels- Alder reactions.

---

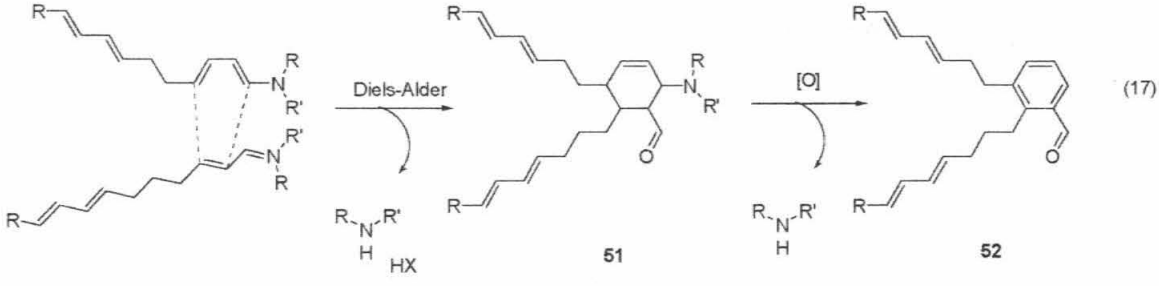
[30] Bunce, R.A.; Peeples, C.J.; Jones, P.B. *J. Org. Chem.* **1992**, *57*, 1727-1733.

The rates of epimerization, dimerization side reaction, and racemic background reaction can all be affected by the nature of the acid cocatalyst. It was found that more acidic cocatalysts, such as $HClO_4$, HCl, and TfOH, produce significantly less epimerization than less acidic cocatalysts, such as TFA and TCA. This is not unexpected, as the more basic counterions will be more likely to deprotonate the carbon adjacent to the aldehyde and facilitate epimerization.

In addition, when less acidic cocatalysts are used, a significant amount of side product **52** is often observed. When X- is a basic counterion, it can γ - deprotonate the iminium- bound substrate **49** to afford the enamine **50** (eq. 16). This enamine is a very reactive diene, and can react in a bimolecular sense with a separate molecule of catalyst-bound triene. The resultant product **51** is believed to eliminate the amine and further oxidize to form the fully aromatized side product **52** (eq. 17). This side route can be completely eliminated when the cocatalyst is a strong acid, such as HCl or $HClO_4$. It appears that substrates which are less reactive in the IMDA are more susceptible to this Diels- Alder dimerization- aromatization route.



(16)



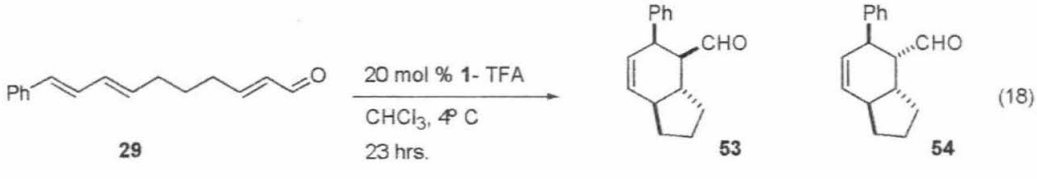
(17)

Although more acidic cocatalysts are often useful for decreasing epimerization and Diels-Alder dimerization- aromatization, it has also been found that highly acidic cocatalysts can decrease the enantioselectivity. This can probably be attributed to an increase in acid- catalyzed background reaction, especially when more reactive substrates are utilized.

In addition to the nature of the counterion, the reaction temperature was found to play an important role in the efficiency of the IMDA reaction. As expected, it was found that more reactive substrates could be run at temperatures as low as -20°C to afford IMDA adducts with high enantioselectivity, decreased epimerization, and good yield. When less reactive substrate- catalyst systems are run at low temperature, starting material polymerization becomes a major side product. In addition, the highly extended reaction times required for these less reactive substrates leads to significant product epimerization in many cases. In general, less reactive substrates can be run at room temperature to afford IMDA adducts with excellent enantioselectivities in a timely manner, while the more activated trienes should be run between 4 °C and -20°C.

Water and solvent play an important role in mediating the amount of polymerization, epimerization, and background reaction. Studies found that acetonitrile, chloroform, isopropanol, and butanol are the best solvents. Acetonitrile and chloroform are appropriate choices when substrate polymerization and solubility are of concern, while butanol and isopropanol can work well in combating epimerization. A ratio of about 98:2 solvent: water is usually used in order to facilitate catalyst turnover.

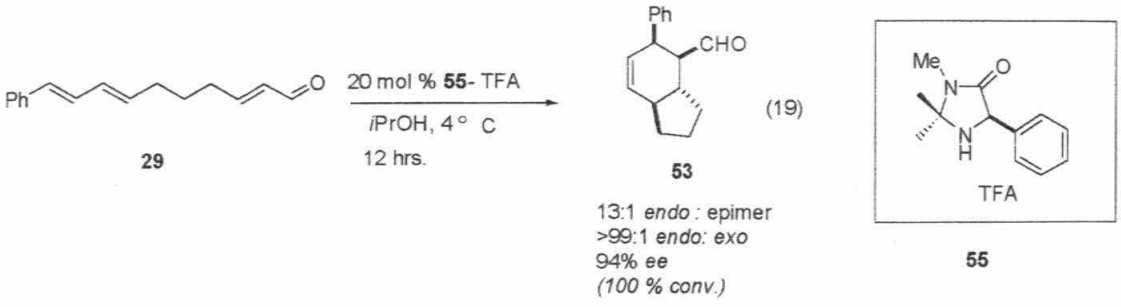
Initial studies of the organocatalyzed IMDA were performed with the highly reactive trienal **29**. It was found that catalyst **1** affords IMDA adduct **53** as a 1:1 mixture of *endo* and *endo* epimer (**54**). The product *ee* is quite low (77%) (eq. 18).

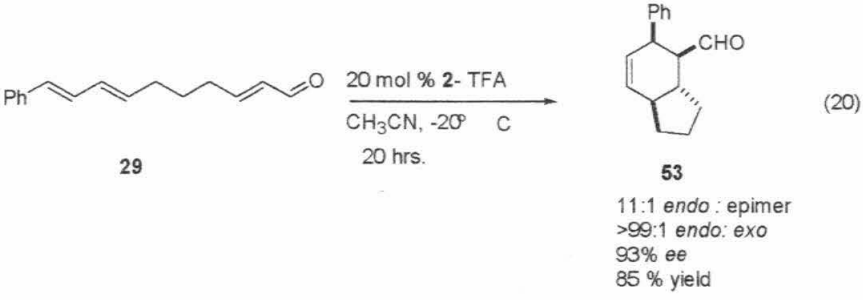


29 **53** **54** (18)

1:1 *endo* (**53**) : epimer(**54**)
>99:1 *endo: exo*
77% *ee*
84 % yield

A preliminary catalyst screen indicated that catalyst **55**, in which a phenyl group replaces the benzyl group at the chiral center, yields products with much better selectivity (94% *ee*, 13:1 *endo:* epimer) (eq. 19)





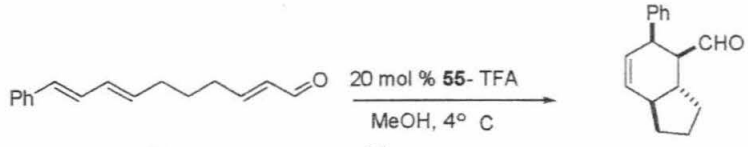
It was later found that the *tert*- Butyl catalyst, **2**, is comparable to **55** in reaction rate and selectivity (eq. 20). The observed differences in selectivity can be rationalized by examining the differences in reactivity of these three catalysts. Catalysts **2** and **55** are significantly more reactive than catalyst **1**. Because triene **29** is so reactive, there appears to be a significant background reaction. Clearly, a more reactive catalyst would be better equipped to compete with the racemic background and produce adducts with high levels of enantiocontrol.

Epimerization is also a major problem in the reaction of catalyst **1** with trienal **29**. Cooling this catalyst system below 4 °C necessitated highly extended reaction times, which resulted in even greater levels of epimerization than those observed.

Interestingly, the superiority of catalyst **55** over **1** was only observed with substrate **29**. Though **55** is able to afford IMDA adducts with a considerable level of enantiocontrol with some of the other substrates examined, catalyst **1** appears to allow better facial coverage of the dienophile, and in all of the other cases, where background was not as much of an issue, catalyst **1** provided superior results to **55**.

A counterion screen of the reaction of **29** with catalyst **55** shows a general correlation between cocatalyst acidity and *endo*: epimer ratios. More acidic cocatalysts give less epimerization product than do mildly acidic cocatalysts. This is expected because the epimerization is believed to proceed through a base- catalyzed deprotonation of the stereocenter adjacent to the aldehyde.

The correlation between cocatalyst acidity and enantioselectivity is less straightforward. The counterion must be acidic enough to allow iminium ion formation, but not so acidic as to participate in an acid- catalyzed background reaction. It was found, in the case of



29 **53**

Cocatalyst	*p*Ka	*ee*	*dr* (*endo*: epimer)
DBA		83.1%	2.2:1
TCA	0.65	84.4%	2.9:1
TFA	-0.25	89.6%	3.8:1
*p*TSA	-2	80.0%	12:1
TfOH	-14	81.1%	12:1

*All reactions were run at 0.5M in MeOH (5% H_2O) at 4°C for 5.5h; *ee* and *dr* determined by GC; conversions were between 80-100%

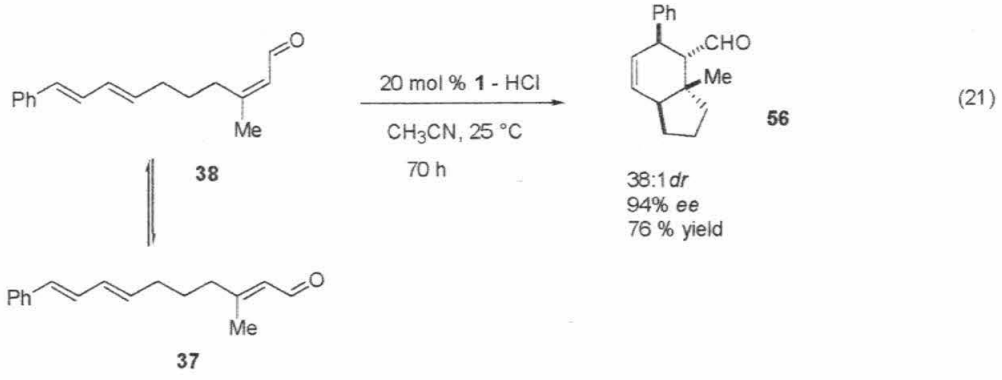
Table 1. Results of a cocatalyst screen of substrate **29**.

substrate **29**, when the triene is subjected to catalytic amounts of HCl in methanol, without any amine catalyst, there is a significant background. TFA, however, with a mid-range pK_a appeared to be ideal in facilitating iminium ion formation and mediating background reaction. These studies were performed with catalyst **55**, but similar trends were observed with **1** and **2**.

It should be noted that, while epimerization is an issue in this reaction, there is no *exo* product observed from the reaction of triene **29**. The fact that the second diastereomer is epimer is supported by NOESY studies and by a simple experiment where an isomerically pure IMDA adduct was resubjected to reaction conditions. NMR analysis after several hours indicated a change in dr that should not be observed if the

diastereomers were *endo* and *exo* (There was no starting material recovered from the resubjection, confirming that the IMDA is not reversible under such conditions).

Substrates **37** and **38** were subsequently studied in hopes of being able to set a quaternary carbon center at the ring juncture of the fused bicyclic product. Each dienophile isomer was separately subjected to reaction conditions with catalyst **1** and within minutes there was equilibration between **37** and **38**. However, from each reaction,



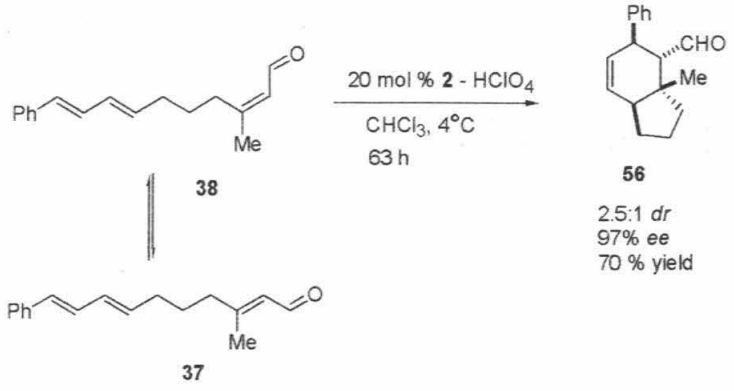
(21)

only one product formed predominantly (eq. 21). NOE studies indicate that the product observed is **56**, from the reaction of substrate **38**, where the aldehyde is *cis* to the tether. The reaction of the *cis* dienophile (**38**) in preference to the *trans* (**37**) can be explained by observing the level of congestion in the transition state for the *trans* dienophile (figure 8a). Because the transition state for the IMDA is asynchronous, the internal bond will be

Figure 8. *anti* Transition state structures for (a) **37** and (b) **38.**

more fully formed in the transition state, and the methyl group of the forming quaternary carbon center can be expected to add significant steric crowding to either transition state. If the *cis* dienophile reacts in an *exo* sense, through a sterically preferred *anti* transition state, the severe congestion can be alleviated (figure 8b). This is indeed found to be the case in the reaction of trienes **37** and **38** with catalyst **1**. NOE studies indicate that the reaction of **38** proceeds completely through an *anti* (*exo)* transition state (figure 8b) to

afford the *trans* fused product **56**. The product is formed in about 38:1 *dr*. The minor isomer appears to be the result of IMDA reaction of the *trans* dienophile (**37**, figure 8a).



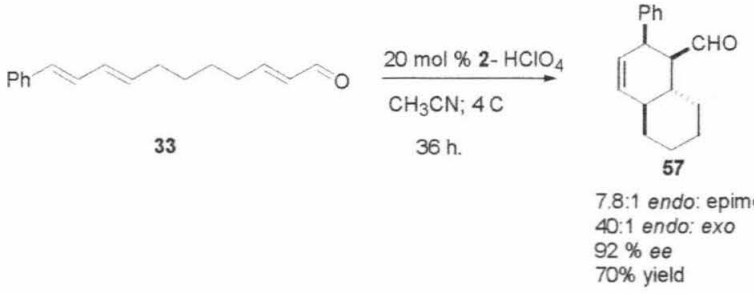
(22)

Interestingly, the product ratios decrease significantly when the substrate is subjected to reaction conditions with catalyst **2** (eq. 22). In this case, while the enantioselectivities remain the same (94% *ee*), the diastereoselectivity decreases significantly to about 2.5:1 *dr*. Again, the minor diastereomer is believed to result from the IMDA reaction of the *trans* dienophile (**37**). Perhaps the more reactive catalyst is better able to tolerate a more sterically unfavorable transition state.

In any case, we have demonstrated that the organocatalytic IMDA can tolerate β-substitution on the dienophile to form a quaternary carbon center at the ring juncture. Standart reaction conditions, with acidic cocatalysts (such as HCl and $HClO_4$) will isomerize β- disubstituted dienophiles. The less reactive catalyst **1** is the preferable catalyst for this type of substrate, as it is able to selectively react one isomer in preference to the other.

In order for this catalytic system to be general, it must successfully form both [4.3.0] bicycles and the less readily generated [4.4.0] bicycles. Decatriene **33** was synthesized to test the ability of the catalyst to form these larger ring systems. Initial attempts to cyclize substrate **33** with catalyst **1** were largely unsuccessful. This substrate is less reactive and more prone to polymerization than the nonatriene equivalent. The yields obtained from reaction with catalyst **1** were only 57%, and reaction times were extended such that epimerization became a major problem.

In moving to the highly reactive catalyst **2**, however, it was possible to increase the rate of the reaction such that the yield became useful while the *endo:* epimer ratio remained high (eq. 23)[31]



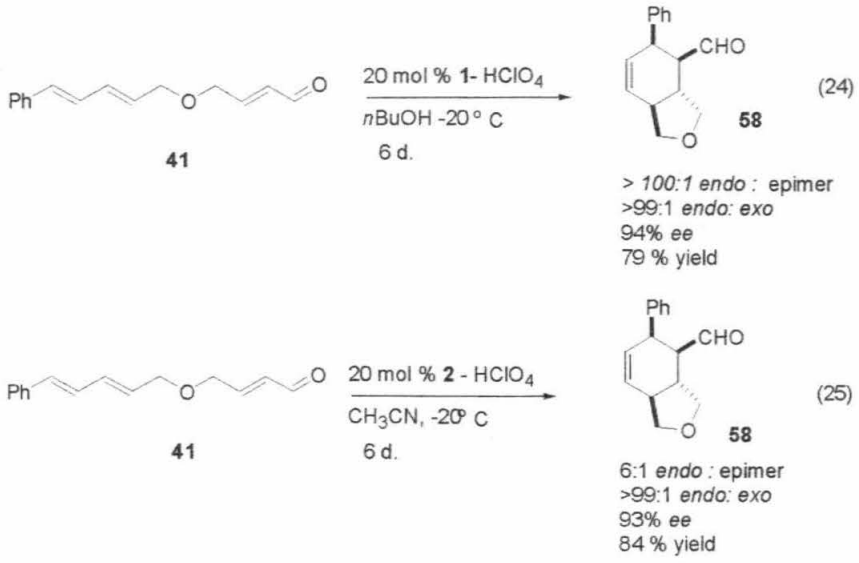
33 **57** (23)

7.8:1 *endo*: epimer
40:1 *endo: exo*
92 % *ee*
70% yield

As expected for the decatrienes, the *endo* : *exo* issue, essentially a nonissue in the nonatriene reactions, becomes quite important. Because the decatrienes cyclize through a chair transition state, the steric requirements are much less stringent than their counterparts with three- atom tethers. As noted earlier, the stereocontrol of the IMDA is based mainly on steric constraints, so it is not surprising that these decatriene substrates react with lower *endo*: *exo* ratios. It was found that the alcoholic sovents gave lower *endo: exo* ratios (*i*PrOH, for instance gives only 4:1 *endo: exo*), but CH_3CN is effective in minimizing the amount of *exo* diastereomer formed.

One of the main advantages of organic catalysis is that amines can tolerate a much broader range of functionality that Lewis acids. One functionality that presents a problem for traditional Lewis acid catalysis is the ether. IMDA reactions with ether-containing substrates typically cannot be catalyzed by Lewis acids due to chelation, but there should be no such compatibility issues with the MacMillan amine catalysts. Substrate **41** was subjected to IMDA with catalysts **1** and **2**.

[31] Studies on the decatriene substrate were performed by Wendy Jen.

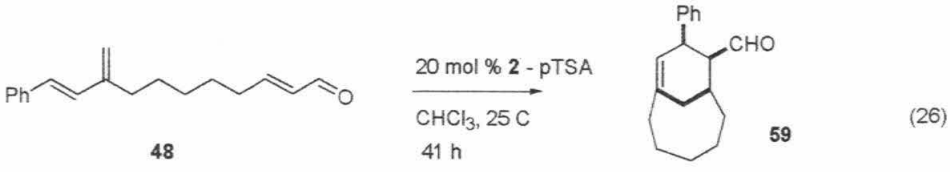


The ether substrate is extremely reactive at room temperature. In fact, the substrate tends to cyclize on silica gel during purification, and thus must be used as soon as it is synthesized. Due to the extraordinary reactivity, the reactions were performed at -20°C, where virtually all background reaction appears to cease. It was found that the selectivities and reactivities were similar for the catalysts **1** and **2**. To our knowledge, this is the first example of an asymmetric catalytic IMDA involving a substrate with a heteroatom in the tether.

Finally, no asymmetric catalytic variants of the Type II IMDA are known. We believed that the amine catalyst could be successfully applied to this reaction, despite the increased reaction times for the Type II. The Type II IMDA is an extremely powerful reaction that can form medium rings containing up to three stereocenters and an anti-Bredt olefin. Clearly an asymmetric catalytic version of this potent reaction would be highly desirable.

Indeed, the reaction of **48** is fairly slow, and reactivity decreases significantly when the reaction is run at low temperatures, where the major product becomes polymer. Due to the relatively low reactivity of this substrate, strong acid cocatalysts were not useful, as they enhance the rate of polymerization. When weakly acidic cocatalysts (such as TFA) were used, Diels-Alder dimerization products were observed (see eq. 17). However, *p*TSA, with a moderate acidity, was able to successfully catalyze the desired reaction without catalyzing either the acid-promoted polymerization or the base-promoted dimerization pathway. With catalyst **2** and *p*TSA at room temperature, the

Type II IMDA cyclization of substrate **48** proceeds to afford adduct **59** as one diastereomer with extremely high levels of enantiocontrol (98.4% *ee*) (eq 26). To our knowledge, this is the first example of an asymmetric catalytic Type II IMDA.



(26)

>99:1 product: epimer
>99:1 *dr*
98.4% *ee*
72 % yield
(based on 90% conversion)

III. Conclusions

In conclusion, we have further demonstrated the generality and utility of MacMillan organocatalysis. We have developed a novel asymmetric organocatalytic intramolecular Diels-Alder reaction and shown that the imidazolidinone catalysts can tolerate a range of functionality, including β - dienophile substitution, an ether-containing substrate, and a Type II triene. A general comparative study of first and second generation catalysts indicates that the second generation imidazolidinone **2** is more reactive, and usually preferable to catalyst **1**, as it allows reactions to be run at lower temperatures and requires shorter reaction times.

IV. Experimental Section

tert-Butyl-(8-chloro-oct-2-enyloxy)-dimethyl-silane (43)

A solution of 23.7 g (115.8 mmol) 8-Chloro-oct-2-enoic acid ethyl ester **42** in 600 mL CH_2Cl_2 was cooled to -78°C. 45 mL (252.9 mmol) DIBAl-H was added slowly and the reaction was warmed to 25°C, quenched with MeOH (200 mL), and stirred with 300 mL Rochelle's salt solution (sat) for 8 hours. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 300 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, and concentrated to afford 18.35 g (97%) of 8-Chloro-oct-2-en-1-ol as a clear oil with the following spectral data that was

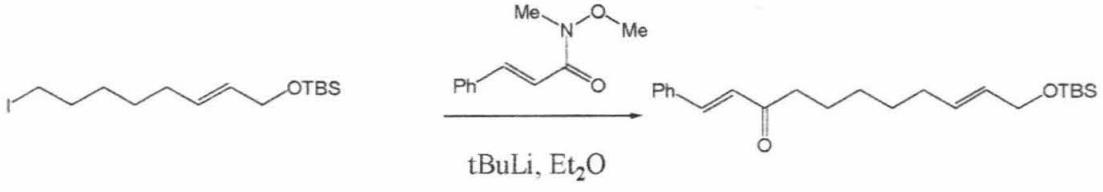
used with further purification: IR (film): 3328, 2933, 2857, 1461, 1309, 1089, 1002, 970, 731, 651 cm^{-1}; ^1H NMR (300 MHz) δ 5.63 (m, 2H, C_6-*H*, C_7-*H*), 4.05 (d, *J* = 4.8 Hz, 2H, C_8- H_2), 3.50 (t, *J* = 6.8 Hz, 2H, C_1-H_2Cl), 2.03 (m, 2H, C_5-H_2), 1.75 (m, 2H, C_2-H_2), 1.45-1.34 (m, 4H, C_3-H_2, C_4-H_2); ^{13}C (300 MHz, $CDCl_3$) δ 132.8, 129.5, 63.9, 45.3, 32.8, 32.3, 28.7, 26.7.

A solution of 460 mg (2.83 mmol) 8-Chloro-oct-2-en-1-ol, 0.8 mL (5.66 mmol) Et_3N, and 34 mg (2.83 mmol) DMAP in 3 mL CH_2Cl_2 was cooled to 0°C. 512 mg (3.39 mmol) of TBSCl was added and the reaction was warmed to room temperature and stirred for hrs. The reaction mixture was poured into 5 mL H_2O and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (15 mL), dried with Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was flushed through a silica plug (10% EtOAc/ hexanes) to afford 773 mg (99%) of **43** as a clear oil: IR (film) 2955, 2929, 2857, 1471, 1463, 1255, 1117, 1099, 1061, 970, 836, 776 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 5.69-5.50 (m, 2H, C_6-*H*, C_7-*H*), 4.13 (dd, *J* = 4.9, 1.1, 2H, C_8H_2), 3.54 (t, *J* = 6.8, 2H, C_1-H_2), 2.05 (dt, *J* = 6.4, 2H, C_5-H_2), 1.78 (m, 2H, C_2-H_2), 1.51-1.36 (m, 4H, C_3-H_2, C_4-H_2), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.08 (s, 6H, $Si(CH_3)_2$); ^{13}C (300 MHz, $CDCl_3$) δ 131.1, 129.7, 64.3, 45.4, 32.8, 32.3, 28.8, 26.8, 26.4, 18.8, -4.7; LRMS (EI) *m/z* 219 (M- *t*Bu); HRMS (EI) exact mass calcd for [($C_{14}H_{29}ClOSi$) -tBu$^+$] requires *m/z* 219.0972, found *m/z* 219.0968.

***tert*-Butyl-(8-iodo-oct-2-enyloxy)-dimethyl-silane (44)** A solution of 62.4 g (225.3 mmol) **43** and 67.6 g (451.2 mmol) NaI in 220 mL acetone was stirred at reflux in the absence of light for 46 h. The reaction mixture was cooled to room temperature and poured into 100 mL of water. 150 mL of Et_2O was added and the layers were separated. The aqueous layer was extracted (3 x 100 mL) and the combined organics were dried with Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was flushed through a silica plug (10% EtOAc/ hexanes) to afford 68.1 g (82%) of **44** as a pale, yellow oil:

IR (film) 2955, 2928, 2856, 1472, 1462, 1255, 1105, 1059, 969, 836, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68-5.50 (m, 2H, C_6-*H*, C_7-*H*), 4.13 (dd, *J* = 4.9, 0.8 Hz, 2H, C_8-H_2), 3.19 (t, *J* = 7.2 Hz, 2H, C_1-H_2), 2.05 (m, 2H, C_5-H_2), 1.88-1.79 (m, 2H, C_2H_2), 1.44-1.38 (m, 4H, C_3H_2, C_4H_2), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.08 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 130.9, 129.6, 64.2, 33.7, 32.2, 30.3, 28.4, 26.3, 18.8, 7.4, -4.7; LRMS (EI) *m/z* 311 (M- *t*Bu); HRMS (EI) exact mass calcd for [($C_{14}H_{29}IOSi$) -*t*Bu^+] requires *m/z* 311.0328, found *m/z* 311.0332.

11-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-undeca-1,9-dien-3-one (45)



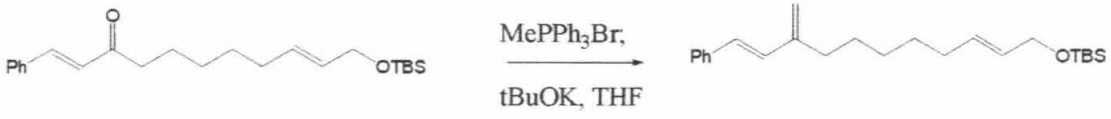
To a solution of 10.0 g (27.1 mmol) **44** in 170 mL Et_2O at –78 °C was added 35.39 mL (60.16 mmol) of *t*-BuLi (1.7 M in pentane). The solution was stirred for 30 minutes at –78 °C, upon which 10.4 g (54.3 mmol) amide[32] was added in 20 mL Et_2O. The solution was warmed to 25 °C after 10 minutes and stirred for an additional 1 hour. The reaction mixture was poured into 150 mL of 1N NH_4Cl. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The organic layers were combined, washed with brine (200 mL), dried with Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. Purification of the resulting residue by flash chromatography (gradient, 2.5-5% EtOAc/ hexanes) afforded 3.47 g (35%) of **45** as a yellow oil:

IR (film) 2929, 2856, 1691, 1668, 1255, 1100, 1055, 972, 836, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57-7.52 (m, 3H, Ph*H*, C_{11}-*H*), 7.40-7.37 (m, 2H, Ph*H*), 6.74 (d, *J* = 16.2 Hz, 1H, C_{10}-*H*), 5.69-5.49 (m, 2H, C_2-*H*, C_3-*H*), 4.12 (dd, *J* = 4.9, 1.1 Hz, 2H, C_1-H_2), 2.66 (t, *J* = 7.6 Hz, 2H, C_8-H_2), 2.05 (dt, *J* = 6.6 Hz, 2H, C_4-H_2), 1.68 (tt, *J* = 7.4 Hz, 2H, C_7-H_2), 1.39 (m, 4H, C_6-H_2, C_5-H_2), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.07 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.4, 142.3, 134.6, 131.2, 130.4, 129.3, 129.0, 128.3, 126.2, 64.2, 41.1, 32.2, 29.2, 29.1, 26.2, 24.4, 18.7, -4.8 ; LRMS (EI) *m/z* 315(M- *t*Bu);

[32] Euro. J. Org. Chem. 1999, 2309-2914.

HRMS (EI) exact mass calcd for [($C_{23}H_{36}O_2Si$) -*t*Bu$^+$] requires *m/z* 315.1780, found *m/z* 315.1783.

tert-Butyl-dimethyl-(9-methylene-11-phenyl-undeca-2,10-dienyloxy)-silane (47).



To a solution of 108 mg (0.97 mmol) of *t*BuOK in 10 mL THF was added 345 mg (0.97 mmol) of $MePPh_3Br$. The yellow solution was stirred at room temperature for 1 h, then cooled to 0°C, and 300 mg (0.81 mmol) of **45** was added in 4 mL THF. The solution was warmed to room temperature and stirred for an addition 1 hour, then poured into 10 mL of water. 15 mL of Et_2O were added and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organics were dried with Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. Purification of the resulting residue by flash chromatography (2.5 % EtOAc/ hexanes) afforded 218 mg (61%) of **47** as a cloudy oil:

IR (film) 2929, 2856, 1641, 1255, 1098, 1057, 1098, 1057, 962, 836, 776, 753, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.22 (m, 5H, Ph*H*), 6.84 (d, *J* = 16.2 Hz, 1H, C_{11}-*H*), 6.61 (d, *J* = 16.5 Hz, 1H, C_{10}-*H*), 5.74-5.54 (m, 2H, C_2-*H*, C_3-*H*), 5.17 (s, 1H, C=C*H*H), 5.09 (s, 1H, C=CH*H*), 4.17 (dd, *J* = 5.1, 1.0 Hz, 2H, C_1- H_2), 2.36 (t, *J* = 7.1 Hz, 2H, C_8-H_2), 2.09 (dt, *J* = 6.4 Hz, 2H, C_4-H_2), 1.65-1.55 (m, 2H, C_7-H_2), 1.49-1.37 (m, 4H, C_5-H_2, C_6-H_2), 0.96 (s, 9H, SiC(CH_3)$_3$), 0.12 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.3, 137.5, 131.4, 131.2, 129.3, 128.7, 128.0, 127.4, 126.5, 116.3, 64.3, 32.4, 32.2, 29.4, 29.3, 28.4, 26.3, 18.7, -4.7; LRMS (EI) *m/z* 313(M- *t*Bu); HRMS (EI) exact mass calcd for [($C_{24}H_{38}OSi$) -*t*Bu$^+$] requires *m/z* 313.1988, found *m/z* 313.1981.

9-Methylene-11-phenyl-undeca-2,10-dien-1-al (48).

To a stirred solution of 1.34 g (3.62 mmol) of **47** in 7.2 mL THF at 0°C was added 2.36 g (9.03 mmol) of TBAF•H_2O. After 10 minutes, the ice bath was removed the reaction was stirred at room temperature for an additional 40 minutes, then15 mL H_2O was added and the resulting solution was extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine (15 mL), dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. Purification of the residue by flash chromatography (20% EtOAc/ hexanes) afforded 800 mg (86%) of 9-Methylene-11-phenyl-undeca-2,10-dien-1-ol as a clear oil:

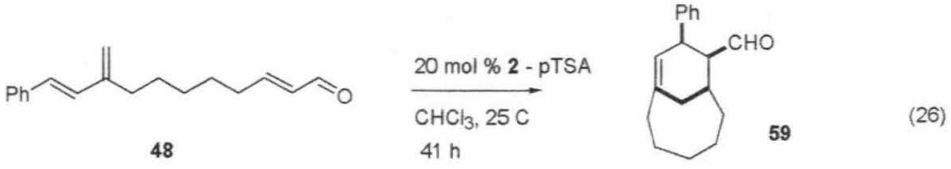
IR (film) 3025, 2929, 2856, 1602, 1448, 963, 886, 754, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.2 (m, 5H, Ph*H*), 6.81 (d, *J* = 16.5 Hz, 1H, C_{11}-*H*), 6.57 (d, *J* = 16.5 Hz, 1H, C_{10}-*H*), 5.76-5.59 (m, 2H, C_2-*H*, C_3-*H*), 5.14 (s, 1H, C=C*H*H), 5.06 (s, 1H, C=CH*H*), 4.09 (m, 2H, C_1-H_2), 2.32 (t, *J* = 7.7, 2H, C_8-H_2), 2.07 (dt, *J* = 6.9, 2H, C_1-H_2), 1.56 (m, 2H, C_7-H_2), 1.46-1.37 (m, 4H, C_5-H_2, C_6-H_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.3, 137.5, 133.5, 131.2, 129.0, 128.7, 128.0, 127.5, 126.5, 116.3, 64.1, 32.5, 32.2, 29.4, 29.3, 28.4; LRMS (EI) *m/z* 256; HRMS (EI) exact mass calcd for [($C_{18}H_{24}O$)] requires *m/z* 256.1827, found *m/z* 313.1981.

To a solution of 800 mg (3.12 mmol) of the free alcohol, 9-Methylene-11-phenyl-undeca-2,10-dien-1-ol, in 6 mL CH_2Cl_2 was added 731 mg (6.24 mmol) N-methylmorpholine-N-oxide and 80 mg 4A molecular sieves. After 15 minutes, 55 mg (0.16 mmol) of tetrapropylammonium perruthenate was added. After 15 minutes more, the crude reaction mixture was flushed through a 3" silica plug with Et_2O (200 mL) and the eluent was concentrated to afford 760 mg (96%) of **48** as a pale yellow oil:

IR (film) 3025, 2932, 2858, 1690, 1639, 1602, 1494, 1448, 1157, 1120, 966, 886, 754, 697 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$) δ 9.51 (dd, *J* = 2.5, 8.0, 1H, C_1-*H*), 7.45-7.20 (m, 5H, Ph-*H*), 6.91-6.80 (m, 1H, C_3-*H*), 6.81 (d, *J* = 16.2, 1H, C_{11}-*H*), 6.58 (d, *J* = 16.5, 1H, C_{10}-*H*), 6.18-6.08 (m, 1H, C_2-*H*), 5.15 (s, 1H, C=C*H*H), 5.06 (s, 1H, C=CH*H*), 2.39-2.32 (m, 2H, C_4-H_2), 2.34 (t, *J* = 7.1, 2H, C_8-H_2), 1.64-1.51 (m, 4H, C_7-H_2, C_5-H_2), 1.48-1.37

(m, 2H, C_6-H_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 194.1, 158.9, 146.0, 137.4, 133.1, 131.0, 128.7, 128.0, 127.5, 126.5, 116.4, 33.0, 32.1, 29.3, 28.2, 28.0; LRMS (EI) *m/z* 254; HRMS (EI) exact mass calcd for [($C_{18}H_{22}O$)] requires *m/z* 254.1671, found *m/z* 254.1668.

9-Phenyl-bicyclo[5.3.1]undec-1(10)-ene-8-carbaldehyde (59).



(26)

>99:1 product: epimer
>99:1 *dr*
98.4% *ee*
72 % yield
(based on 90% conversion)

A solution of 3.9 mg (0.016 mmol) of **2** and 3.0 mg (0.016 mmol) of pTSA•H_2O in 0.4mL of $CHCl_3$ (2% H_2O) was added to 20 mg (0.079 mmol) of **48** at room temperature. After 41 hrs, flash chromatography (5% EtOAc/hexanes) afforded 13 mg (65%) of **54** followed by 2 mg (10%) of **48**. GC analysis of **59** showed that it was formed in 98.4% *ee* (Chiral β-DA, 90° isotherm for 20 minutes, then ramp 20°/minute to 180°; t_r (minor) 29.2, t_r (major) 29.6).

$[\alpha]_D^{25}$ +75.1° (*c* = 1.0, $CHCl_3$); IR (film) 2923, 2854, 1722, 1453, 1260, 1021, 775, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.6 Hz, 1H, C*H*O), 7.34-7.19 (m, 5H, Ph*H*), 5.62 (br, C_2-*H*), 3.66 (m, 1H, C_3-*H*), 2.46 (m, 1H, C_4-*H*), 2.33 (m, 1H, C_6-*H*H), 2.29 (m, 1H, C_6-H*H*), 2.21-2.12 (m, 3H), 1.92-0.82 (m, 8H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 202.7, 145.7, 140.4, 128.9, 128.4, 126.6, 126.4, 62.1, 40.4, 36.1, 35.7, 33.0, 29.6, 29.5, 28.9, 25.4; LRMS (EI) *m/z* 254; HRMS (EI) exact mass calcd for [($C_{18}H_{22}O$)] requires *m/z* 254.1671, found *m/z* 254.1673.

10-Phenyl-deca-2,7,9-trienoic acid methyl ester (27).

10.0 g (24.10 mmol) of cinnamyltriphenylphosphonium chloride was added to 2.70 g (24.10 mmol) of *t*-BuOK in 100 mL Et_2O and the resulting solution was stirred at room temperature for 30 min. The reaction mixture was cooled to 0°C and 3.42 g (21.91 mmol) of **26** was added in 10 mL Et_2O. The solution was warmed to room temperature and stirred for 5 hrs. The solution was poured into 100 mL H_2O and extracted with Et_2O (3 x 50 mL). The combined organics were dried over Na_2SO_4, filtered through cotton, and dried *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/ hexanes) to afford **27** as a 1:1 mixture of geometric isomers (diene). The mixture was redissolved in 50 mL of CH_2Cl_2 and 250 mg (0.98 mmol) I_2 was added. After 30 min, 20 mL Na_2SO_3 (saturated) were added and the layers were separated. The aqueous layer was extracted (2 x 20 mL) and the combined organics were dried over Na_2SO_3, filtered through cotton, and concentrated *in vacuo* to afford 3.54 g (63%) of **27** as a yellow oil:
IR (film) 3445, 2950, 1722, 1444, 1274, 1205, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.17 (m, 5H, Ph*H*), 6.98 (dt, *J* = 7.2, 15.6 Hz, 1H, C_3-*H*), 6.75 (dd, *J* = 10.5, 15.9 Hz, 1H, C_9-*H*), 6.45 (d, *J* = 15.6 Hz, 1H, C_{10}-*H*), 6.21 (dd, *J* = 10.2, 15.0 Hz, 1H, C_8-*H*), 5.87-5.73 (m, 2H, C_7-*H*, C_2-*H*), 3.73 (s, 1H, CO_2CH_3), 2.27-2.14 (m, 4H, C_6-H_2, C_4-H_2), 1.65-1.57 (m, 2H, C_5-H_2); ^{13}C NMR (300 MHz, $CDCl_3$) 167.2, 149.3, 137.7, 134.6, 131.5, 130.7, 129.3, 128.7, 127.4, 126.3, 121.4, 51.8, 32.5, 32.0, 27.9.

10-Phenyl-deca-2,7,9-trien-1-ol (28).

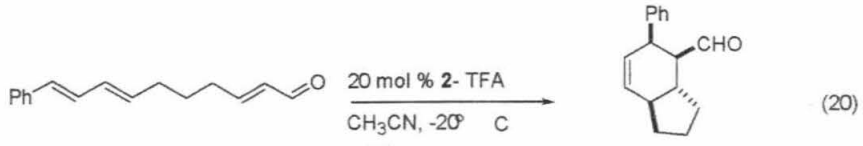
A solution of 1.77 g (6.90 mmol) of **27** in 35 mL CH_2Cl_2 was cooled to -78°C and 2.7 mL (15.19 mmol) of DIBAL-H was added. After one hour, the reaction was allowed to warm to 0°C and 10 mL MeOH was added to quench the remaining DIBAL-H. The slurry was then warmed to room temperature and treated with 50 mL of a solution of saturated aqueous Rochelle's salt. After stirring for 8 hours, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (1 x 40 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 1.50 g (95 %) of **28** as a yellow oil which was used in the next reaction without further purification:

IR (film) 3437, 2943, 1715, 1274, 1205, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.17 (m, 5H, Ph*H*), 6.75 (dd, *J* = 10.4, 15.7 Hz, 1H, C_{10}-*H*), 6.45 (d, *J* = 15.7 Hz, 1H, C_{11}-*H*), 6.20 (dd, *J* = 10.2, 14.5 Hz, 1H, C_9-*H*), 5.87-5.75 (m, 1H, C_8-*H*), 5.70-5.64 (m, 2H, C_2-*H*, C_3-*H*), 4.09 (m, 2H, C_1-H_2OH), 2.17-2.12 (m, 2H, C_7-H_2), 2.07 (m, 2H, C_4-H_2), 1.45-1.42 (m, 4H, C_5-H_2, C_6-H_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.7, 135.7, 133.3, 130.1, 129.4, 128.7, 128.6, 127.2, 126.2, 124.4, 64.0, 33.0, 32.3, 29.1, 28.9; ; LRMS (EI) *m/z* 228; HRMS (EI) exact mass calcd for [($C_{16}H_{20}O$)] requires *m/z* 228.1514, found *m/z* 228.1512.

10-Phenyl-deca-2,7,9-trienal (29).

To a solution of 1.0 g (4.14 mmol) of **28** in 8 mL CH_2Cl_2 was added 970 mg (8.28 mmol) N-methylmorpholine-N-oxide and 100 mg 4A molecular sieves. After 15 minutes, 73 mg (0.21 mmol) of tetrapropylammonium perruthenate was added. After 50 minutes more, the crude reaction mixture was flushed through a 3" silica plug with Et_2O (100 mL) and the eluent was concentrated *in vacuo*. Purification through flash chromatography (10% EtOAc/ Hexanes) afforded 500 mg (50%) of **29** as a yellow oil: IR (film) 3028, 2935, 2827, 2734, 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.50 (dd, *J* = 2.0, 8.1 Hz, 1H, C_1*H*O), 7.39-7.17 (m, 5H, Ph*H*), 6.90-6.71 (m, 2H, C_3-*H*, C_{10}-*H*), 6.45 (d, *J* = 15.9 Hz, 1H, C_{11}-*H*), 6.26-6.08 (m, 2H, C_9-*H*, C_2-*H*), 5.80 (dt, *J* = 6.9, 15.3 Hz, 1H, C_8-*H*), 2.39-2.32 (m, 2H, C_4-H_2), 2.18 (dt, *J* = 6.9, 6.9, 2H, C_7-H_2), 1.58-1.44 (m, 4H, C_5-H_2, C_6-H_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 194.2, 158.8, 137.7, 135.0, 133.3, 131.2, 130.6, 129.3, 128.8, 127.4, 126.3, 32.9, 32.8, 29.1, 27.7; ; LRMS (EI) *m/z* 226; HRMS (EI) exact mass calcd for [($C_{18}H_{22}O$)] requires *m/z* 226.1358, found *m/z* 226.1356.

5-Phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbaldehyde (53).

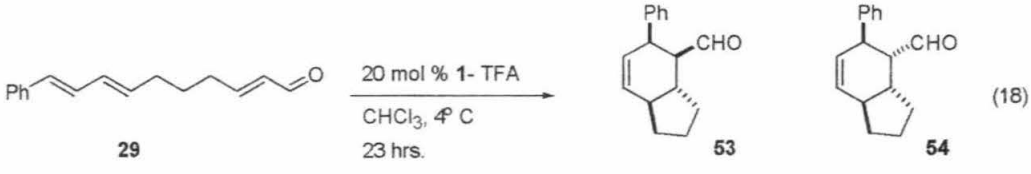


29 53 (20)

11:1 *endo* : epimer
>99:1 *endo: exo*
93% *ee*
85 % yield

A solution of catalyst **2** (10 mg, 0.044 mmol) and TFA (3.4 μL, 0.044 mmol) in 0.44 mL CH_3CN (2% H_2O) , cooled to –20° C, was added to 50 mg (0.22 mmol) of triene **29** (83.3% *E,E* -diene geometry). After stirring for 20 hrs at -20°C, the reaction mixture was warmed to room temperature. The crude reaction mixture was loaded directly onto a silica column and eluted with 10 % EtOAc/ hexanes to afford 35.4 mg (85% yield) of cycloadduct (**53**) as an 11:1 mixture of *endo/ endo* epimer product. GC analysis of (**53**) showed that it was formed in 93% ee (β-PH, 122 °C isotherm with 5°C ramp at 50 min., t_r (major) = 55.80, t_r (minor) = 56.20).

$[\alpha]_D^{25}$ = 4.35° (c = 1, $CHCl_3$),; IR (film) 2952, 2869, 1719, 1640, 1492, 1452, 913, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.05 (d, *J* = 4.1 Hz, 1H, C*H*O), 7.32-7.18 (m, 5H, Ph*H*), 6.14 (d, *J* = 10.1 Hz, 1H, C_1H), 5.59 (m, 1H, C_2-*H*), 4.00 (b, 1H, C_3-*H*), 2.69 (m, 1H, C_4-*H*), 2.04-1.78 (m, 4H), 1.34-1.25 (m, 3H), 1.08 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 205.1, 151.8, 139.8, 131.0, 129.8, 128.7, 127.3, 57.1, 44.8, 44.2, 39.0, 28.9, 27.6, 22.8; Exact mass calcd for $C_{16}H_{18}O$ (M^+) 226.1358; found 226.1353 (EI).



29 53 54 (18)

1:1 *endo* (**53**) : epimer(**54**)
>99:1 *endo: exo*
77% *ee*
84 % yield

A solution of catalyst **1** - TFA (9.5 mg, 0.026 mmol) in 0.27 mL $CHCl_3$, cooled to +4° C, was added to 30 mg (0.133 mmol) of triene **29** (83.3 % E,E -diene geometry). After

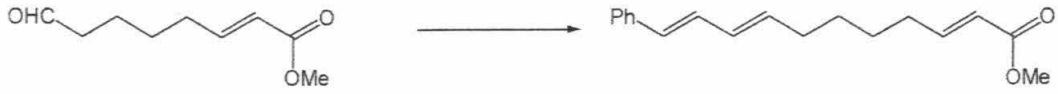
stirring for 23 hr, the reaction mixture was warmed to room temperature. The crude reaction mixture was loaded directly onto a silica column and eluted with 10 % EtOAc/ hexanes to afford 21.0 mg (84% yield) of cycloadduct **53** as a 1:1 mixture of endo/ endo epimer product. GC analysis of **53** showed that it was formed in 77% ee. Physical data match those reported above.

8-Oxo-oct-2-enoic acid methyl ester (30)

25.0 g (304.9mmol) of cyclohexene was dissolved in 120 mL of CH_2Cl_2 and O_3 was bubbled through the solution at -78°C for 11 hrs. 80 g (304.9 mmol) of PPh_3 was added and the reaction mixture was allowed to warm to room temperature and stirred for 8 hrs. 30.5 g (91.2 mmol) of methyl (triphenylphosphoranylidene)acetate was added and the resulting reaction mixture was stirred for 12 hrs longer. Solvent was then removed *in vacuo* and the resulting solid was triturated with Et_2O (3 x 150 mL). The organic liquors were combined and concentrated *in vacuo* and the resulting residue was purified by flash chromatography (20 % EtOAc/ hexanes) to afford 8.57 g (55 %) of **30** as a pale yellow oil:

IR (film) 2943, 2866, 2726, 1722, 1661, 1437, 1274, 1205, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, J = 1.5 Hz, 1H, C_8-H), 6.93 (dt, J = 6.9, 15.9 Hz, 1H, C_3-H), 5.82 (dt, J = 1.6, 15.6 Hz, 1H, C_2-H), 3.71 (s, 3H, -CO_2CH_3), 2.45 (dt, J = 1.5, 7.2 Hz, 2H, C_7H_2), 2.22 (ddt, J = 1.5, 7.5, 7.5 Hz, 2H, C_4-H_2), 1.70-1.59 (m, 2H, C_6-H_2), 1.54-1.44 (m, 2H, C_5-H_2); ^{13}C NMR (300 MHz, $CDCl_3$) 202.2, 167.1, 148.8, 121.5, 51.8, 43.9, 32.2, 27.8, 21.8; LRMS (EI) *m/z* 142 $(M\text{-}CO)^+$; HRMS (EI) exact mass calcd for $[(C_9H_{14}O_3) - CO^+]$ requires *m/z* 142.0994, found *m/z* 142.0997.

11-Phenyl-undeca-2,8,10-trienoic acid methyl ester (31).



5.46 g (13.16 mmol) of cinnamyltriphenylphosphonium chloride was added to1.47 g (13.10 mmol) of *t*-BuOK in 45 mL Et_2O and the resulting solution was stirred at room temperature for 30 min. The reaction mixture was cooled to 0°C and 1.72 g (10.11 mmol) of **30** was added in 3 mL Et_2O. The solution was warmed to room temperature and stirred for 5 hrs. The solution was poured into 30 mL H_2O and extracted with Et_2O (3 x 25 mL). The combined organics were dried over Na_2SO_4, filtered through cotton, and dried *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/ hexanes) to afford **31** as a 1:1 mixture of geometric isomers (diene). The mixture was redissolved in 30 mL of CH_2Cl_2 and 167 mg (0.66 mmol) I_2 was added. After 30 min, 15 mL Na_2SO_3 (saturated) were added and the layers were separated. The aqueous layer was extracted (2 x 20 mL) and the combined organics were dried over Na_2SO_3, filtered through cotton, and concentrated *in vacuo* to afford 1.42 g (5.26 mmol) of **31** as a yellow oil:

IR (film) 3028, 2935, 2858, 1722, 1653, 1437, 1274, 1197, 989 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.17 (m, 5H, Ph*H*), 6.98 (dt, *J* = 6.9, 15.6 Hz, 1H, C_3-*H*), 6.75 (dd, *J* = 10.5, 15.6 Hz, 1H, C_{10}-*H*), 6.45 (d, *J* = 15.6 Hz, 1H, C_{11}-*H*), 6.20 (dd, *J* = 10.2, 15.0 Hz, 1H, C_9-*H*), 5.87-5.75 (m, 2H, C_8-*H*, C_2-*H*), 3.73 (s, 1H, CO_2CH_3), 2.24-2.13 (m, 4H, C_7-H_2, C_4-H_2), 1.53-1.44 (m, 4H, C_6-H_2, C_5-H_2); ^{13}C NMR (300 MHz, $CDCl_3$) 167.3, 149.6, 137.7, 135.3, 131.1, 130.4, 129.4, 128.7, 127.3, 126.3, 121.2, 51.8, 32.9, 32.4, 29.1, 27.9; LRMS (CI) *m/z* 270 $(M)^+$; HRMS (CI) exact mass calcd for ($C_{18}H_{22}O_2$) requires *m/z* 270.1620, found *m/z* 270.1620.

11-Phenyl-undeca-2,8,10-trien-1-ol (32).

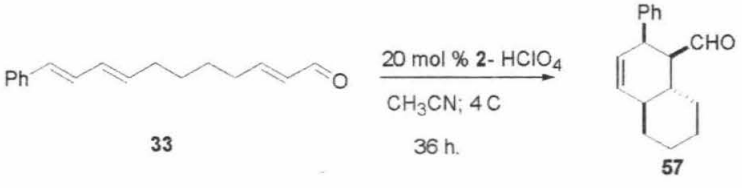
A solution of 2.1 g (7.77 mmol) of **31** in 77 mL CH_2Cl_2 was cooled to -78°C and 3.0 mL (17.09 mmol) of DIBAL-H was added. After one hour, the reaction was allowed to warm to 0°C and 10 mL MeOH was added to quench the remaining DIBAL-H. The slurry was then warmed to room temperature and treated with 50 mL of a solution of saturated aqueous Rochelle's salt. After stirring for 8 hours, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (1 x 40 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 1.88 g (100 %) of **32** as a yellow oil which was used in the next reaction without further purification: IR (film) 3355, 2926, 2854, 1448, 987, 745, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.17 (m, 5H, Ph*H*), 6.75 (dd, J = 10.4, 15.7 Hz, 1H, C_{10}-*H*), 6.45 (d, J = 15.7 Hz, 1H, C_{11}-*H*), 6.20 (dd, J = 10.2, 14.5 Hz, 1H, C_9-*H*), 5.87-5.75 (m, 1H, C_8-*H*), 5.70-5.64 (m, 2H, C_2-*H*, C_3-*H*), 4.09 (m, 2H, C_1-H_2OH), 2.17-2.12 (m, 2H, C_7-H_2), 2.07 (m, 2H, C_4-H_2), 1.45-1.42 (m, 4H, C_5-H_2, C_6-H_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.7, 135.7, 133.3, 130.1, 129.4, 128.7, 128.6, 127.2, 126.2, 124.4, 64.0, 33.0, 32.3, 29.1, 28.9; ; LRMS (EI) *m/z* 242; HRMS (EI) exact mass calcd for [($C_{17}H_{22}O$)] requires *m/z* 242.1671, found *m/z* 242.1668.

11-Phenyl-undeca-2,8,10-trienal (33).

To a solution of 1.0 g (4.14 mmol) of **32** in 8 mL CH_2Cl_2 was added 970 mg (8.28 mmol) N-methylmorpholine-N-oxide and 100 mg 4A molecular sieves. After 15 minutes, 73 mg (0.21 mmol) of tetrapropylammonium perruthenate was added. After 50 minutes more, the crude reaction mixture was flushed through a 3" silica plug with Et_2O (100 mL) and the eluent was concentrated *in vacuo*. Purification through flash chromatography (10% EtOAc/ Hexanes) afforded 500 mg (50%) of **33** as a yellow oil: IR (film): 3014, 2918, 2850, 1688, 1635, 989 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.50 (dd, J = 2.0, 8.1 Hz, 1H,

C_1HO), 7.39-7.17 (m, 5H, Ph*H*), 6.90-6.71 (m, 2H, C_3-*H*, C_{10}-*H*), 6.45 (d, J = 15.9 Hz, 1H, C_{11}-*H*), 6.26-6.08 (m, 2H, C_9-*H*, C_2-*H*), 5.80 (dt, J = 6.9, 15.3 Hz, 1H, C_8-*H*), 2.39-2.32 (m, 2H, C_4-H_2), 2.18 (dt, J = 6.9, 6.9, 2H, C_7-H_2), 1.58-1.44 (m, 4H, C_5-H_2, C_6-H_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 194.2, 158.8, 137.7, 135.0, 133.3, 131.2, 130.6, 129.3, 128.8, 127.4, 126.3, 32.9, 32.8, 29.1, 27.7; ; LRMS (EI) *m/z* 240; HRMS (EI) exact mass calcd for [($C_{17}H_{20}O$)] requires *m/z* 240.1514, found *m/z* 240.1510.

2-Phenyl-1,2,4a,5,6,7,8,8a-octahydro-naphthalene-1-carbaldehyde (57).



33 57 (23)

7.8:1 *endo*: epimer
40:1 *endo: exo*
92 % *ee*
70% yield

A solution of catalyst **2** (6.15 mg, 0.025 mmol) and $HClO_4$ (2.1 μL, 0.025 mmol) in 1.25 mL CH_3CN, cooled to +4° C, was added to 30 mg (0.125 mmol) of triene **33** (76 % E,E - diene geometry). After stirring for 14 hr, the reaction mixture was warmed to room temperature. The crude reaction mixture was loaded directly onto a silica column and eluted with 10 % EtOAc/ hexanes to afford 15.9 mg (70% yield) of cycloadduct **57** as a 7.7:1 mixture of endo/ endo epimer product and a 41:1 mixture of *endo*: *exo* product. The aldehyde was reduced with $NaBH_4$, and HPLC analysis of the resulting alcohol showed that product was formed in 92% ee (AD, 5% EtOH/ Hexanes; t_R (minor) 11.12; t_R (major) 13.37).

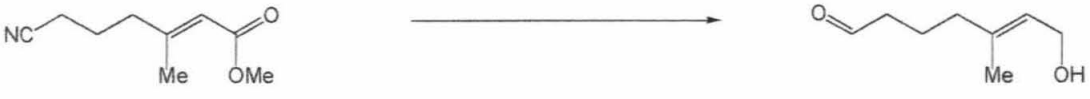
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (d, J = 5.5 Hz, 1H, C*H*O), 7.35-7.12 (m, 5H, Ph*H*), 5.76 (d, J = 9.6 Hz, 1H, C_1H), 5.61 (m, 1H, C_2-*H*), 3.83 (m, 1H, C_3-*H*), 2.48 (m, 1H, C_4-*H*), 0.92-1.92 (m, 10 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 207.4, 138.9, 133.4, 130.1, 128.6, 127.3, 127.0, 56.2, 43.6, 41.9, 35.2, 33.4, 30.6, 27.0, 26.7; LRMS (EI) *m/z* 240 ([M]); HRMS (EI) exact mass calcd for [($C_{17}H_{20}O$)] requires *m/z* 240.1514, found *m/z* 240.1517.

6-Cyano-3-methyl-hex-2-enoic acid methyl ester (34).

170 mL (890 mmol) of methyl diethylphosphonoacetate was added to a solution of 50 mL (439 mmol) of 5-oxohexanenitrile in 1.5 L toluene and the solution was stirred for 10 min. 700 mL NaOMe (prepared from 110.0 g Na and 700 mL MeOH at 0°C) was added to the toluene mixture and the solution was heated to reflux for 2 hrs. The reaction mixture was then cooled to room temperature, poured into 500 mL ice water, and extracted with Et_2O (3 x 300 mL). The combined organic layers were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified through flash chromatography (20 % EtOAc/ hexanes) to afford 58 g (79%) of **34** as a 1.4: 1 mixture of geometric isomers, which was carried onto to the next step without separation:

(major-*E*): IR (film) 2950, 1717, 1652, 1436, 1227, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.53 (m, 1H, C_2-*H*), 3.49 (s, 3H, CO_2CH_3), 2.21 (t, J = 7.1 Hz, 2H, C_6-H_2), 2.12 (t, J = 7.1 Hz, 2H, C_4-H_2), 1.98 (d, J = 1.1 Hz, 3H, C=C(CH_3)CH_2-), 1.67 (tt, J = 7.4, 7.4 Hz, 2H, C_5-H_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.5, 157.2, 119.4, 116.5, 51.0, 39.3, 23.3, 18.5, 16.6; ; LRMS (EI) *m/z* 167; HRMS (EI) exact mass calcd for [($C_9H_{13}NO_2$)] requires *m/z* 167.0946, found *m/z* 167.0942.

7-Hydroxy-5-methyl-hept-5-enal (35).



10 g (59.81 mmol) of **34** was dissolved in 300 mL CH_2Cl_2 and the reaction mixture was cooled to -78°C. 32.0 mL (179.42 mmol) DIBAL-H was added slowly and the reaction mixture was stirred for 1.5 hrs. 100 mL of MeOH was added to quench the remaining DIBAL-H, then 200 mL of saturated Rochelle's salt solution was added and the resulting

slurry was warmed to room temperature and stirred for 12 hrs. The aqueous and organic layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organics were washed with brine (200 mL), dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (60-80% EtOAc/ hexanes) to afford 3.67 g (41%) of **35** as a mixture of isomers:

(major) IR (film) 3385, 2934, 2856, 1717, 999 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (m, 1H, C*H*O), 5.45-5.29 (m, 1H, C_6-*H*), 4.08 (dd, *J* = 7.0, 14.8 Hz, C_7-H_2), 2.43-2.37 (m, 2H, C_2-H_2), 2.10-1.99 (m, 2H, C_4-H_2), 1.78-1.68 (m, 2H, C_3-H_2), 1.62 (s, 3H, C=C(CH_3)CH_2-); ^{13}C NMR (300 MHz, $CDCl_3$) δ 202.8, 138.2, 124.7, 59.4, 43.5, 39.0, 23.5, 20.3; ; LRMS (EI) *m/z* 124 ([M – H_2O]$^+$); HRMS (EI) exact mass calcd for [($C_{18}H_{22}O$) – H_2O]$^+$ requires *m/z* 124.0888, found *m/z* 124.0884.

3-Methyl-10-phenyl-deca-2,7,9-trien-1-ol (36).

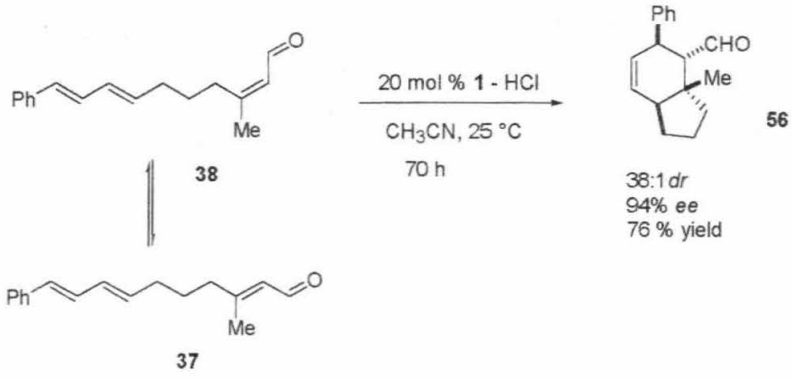
12.85 g (30.97 mmol) of cinnamyltriphenylphosphonium chloride was added to6.95 g (61.94 mmol) of *t*-BuOK in 130 mL THF and the resulting solution was stirred at room temperature for 30 min. The reaction mixture was cooled to 0°C and 3.67g (25.81 mmol) of **35** was added in 5 mL THF. The solution was warmed to room temperature and stirred for 5 hrs. The reaction mixture was poured into 40 mL H_2O and extracted with Et_2O (3 x 40 mL). The combined organics were dried over Na_2SO_4, filtered through cotton, and dried *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/ hexanes) to afford **36** as a 1:1 mixture of geometric isomers (diene): IR (film) 3342, 2931, 2860, 1447, 988, 745, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.17 (m, 5H, Ph*H*), 6.75 (dd, *J* = 10.4, 15.6 Hz, 1H, C_9-*H*), 6.45 (d, *J* = 15.7, 1H, C_{10}-*H*), 6.26-6.15 (m, 1H, C_8-*H*), 5.87-5.77 (m, 1H, C_7-*H*), 5.45-5.41 (m, 1H, C_2-*H*), 4.15 (m, 2H, C_1-

H_2), 2.17-2.03 (m, 4H, C_4-H_2, C_6-H_2), 1.68 (s, 3H, C=C(CH_3)CH_2-), 1.62-1.48 (m, 2H, C_5-H_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 139.9, 135.5, 131.0, 130.3, 130.3, 129.5, 128.8, 128.7, 127.3, 126.3, 123.7, 59.7, 39.3, 32.7, 27.5, 16.5; LRMS (EI) *m/z* 242 (M); HRMS (EI) exact mass calcd for [($C_{17}H_{22}O$] requires *m/z* 242.1671, found *m/z* 242.1679.

3-Methyl-10-phenyl-deca-2,7,9-trienal (37).

To a solution of 1.5 g (6.19 mmol) of **36** in 13 mL CH_2Cl_2 was added 1.45 g (12.38 mmol) N-methylmorpholine-N-oxide and 150 mg 4A molecular sieves. After 15 minutes, 109 mg (0.31 mmol) of tetrapropylammonium perruthenate was added. After 15 minutes more, the crude reaction mixture was flushed through a 3" silica plug with Et_2O (200 mL) and the eluent was concentrated to afford **37** as a 1.4:1 mixture of diene isomers. The mixture was redissolved in 20 mL of CH_2Cl_2 and 79 mg (0.31 mmol) I_2 was added. After 20 min, 15 mL Na_2SO_3 (saturated) was added and the layers were separated. The aqueous layer was extracted (2 x 15 mL) and the combined organics were dried over Na_2SO_3, filtered through cotton, and concentrated *in vacuo*. Purification of the resulting residue (10% EtOAc/ hexanes) afforded 1.20 g (81%) of **37** as a yellow oil:
IR (film): 3028, 2935, 2858, 1668, 1444, 989, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (d, *J* = 8.1 Hz, C_1-*H*O), 7.39-7.199 (m, 5H, Ph*H*), 6.74 (dd, *J* = 10.8, 15.6 Hz, 2H, C_9-*H*), 6.46 (d, *J* = 15.9 Hz, 1H, C_{10}-*H*), 6.22 (dd, *J* = 9.0, 15.0 Hz, 1H, C_8-*H*), 5.92-5.87 (m, 1H, C_2-*H*), 5.78 (dt, *J* =7.2, 15.0 Hz, 1H, C_7-*H*), 2.26-2.14 (m, 4H, C_4-H_2, C_6-H_2), 2.17 (d, *J* = 1.2 Hz, C=C(CH_3)CH_2-), 1.70-1.60 (m, 2H, C_5-H_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 191.4, 164.0, 137.6, 134.3, 131.6, 130.8, 129.2, 128.8, 127.6, 127.4, 126.4, 40.3, 32.6, 27.0, 17.9; LRMS (EI) *m/z* 241 ($[M]^{+\cdot}$); HRMS (EI) exact mass calcd for $[(C_{17}H_{20}O)]^+$ requires *m/z* 240.1514, found *m/z* 240.1520.

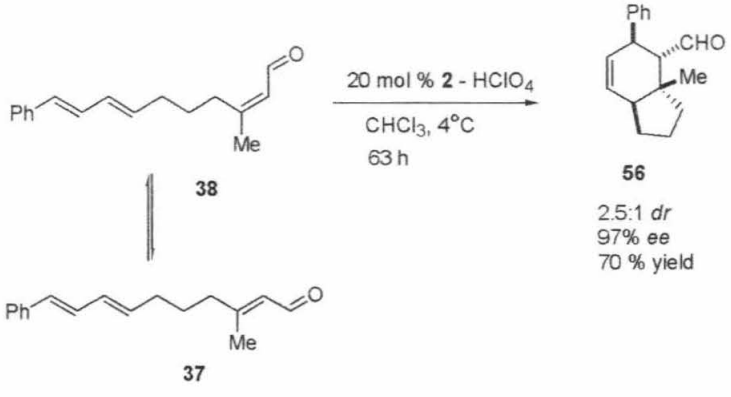
3a-Methyl-5-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbaldehyde(56).



(21)

To a solution of 6.4 mg (0.025 mmol) of **1** in 0.25 mL CH_3CN (2 % H_2O) was added 30 mg (83.3 % E,E; 0.125 mmol) of **38**. The solution was stirred at 25°C for 63 hrs, then the crude reaction mixture was flashed through a silica column and eluted with 10 % EtOAc / hexanes to afford 19.0 mg **56** (76%) as a 38:1 diastereomeric mixture. The product was subjected to acetalization with chiral *R,R* – pentanediol acetal and the resulting acetal was determined to have 94 % *ee* (GC, DB – 1701, t_R (major) 34.74 t_R (minor) 35.04).

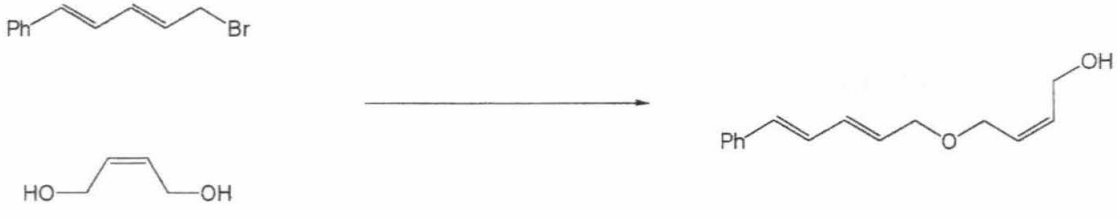
IR (film) 3024, 2958, 2873, 1716, 750, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.96 (d, 1H, J = 2.4 Hz, C*H*O), 7.35-7.16 (m, 5H, Ph*H*), 5.98 (m, 2H, C*H*=C*H*), 4.05(m, 1H, C*H*Ph), 2.78(m, 1H, C*H*CHO), 2.21-1.32 (m, 6H), 0.81(s, 3H, C-CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 203.6, 145.9, 130.2, 129.7, 128.7, 128.1, 126.2, 64.4, 44.4, 43.7, 39.1, 34.1, 25.1, 22.0, 21.5; LRMS (EI) *m/z* 240; HRMS (EI) exact mass calcd for [($C_{17}H_{20}O$)] requires *m/z* 240.1514, found *m/z* 240.1509.



(22)

To a solution of 6.1 mg (0.025 mmol) of **2** and 2.0μL $HClO_4$ (0.025 mmol) in 0.25 mL $CHCl_3$ (2 % H_2O) was added 30 mg (83.3 % E,E; 0.125 mmol) of **38**. The solution was stirred at 4°C for 63 hrs, then the crude reaction mixture was flashed through a silica column and eluted with 10 % EtOAc / hexanes to afford 17.5 mg (70 %) **56** as a 2.5:1 diastereomeric mixture. The product was subjected to acetalization with chiral *R,R* – pentanediol acetal and the resulting acetal was determined to have 97 % *ee*. Physical data were identical to those reported above.

4-(5-Phenyl-penta-2,4-dienyloxy)-but-2-en-1-ol (40).

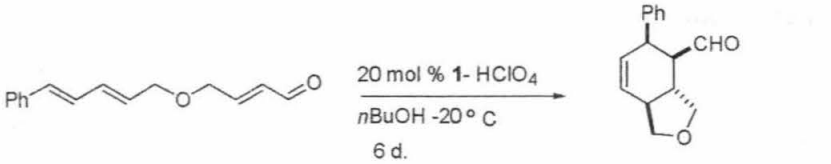


11.6 g (131.65 mmol) of 2-butene-1,4-diol was combined with 354 mg (1.1 mmol) of Bu_4NH_4Br, 15 mL of 50% NaOH (aqueous), and 10 mL CH_2Cl_2. 5.3 g (23.76 mmol) **39** was added slowly at room temperature and the reaction mixture was stirred for 3 hrs, then poured into 30 mL H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 70 mL). The combined organic layers were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. Purification by flash chromatography (gradient, 20-40% EtOAc/ hexanes) afforded 2.4 g (44%) of **40** as a yellow oil: IR (film) 3375, 3028, 2866, 1684, 1452, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.20 (m, 5H, Ph*H*); 6.78 (dd, J = 15.6, 10.5 Hz, 1H, C_8-*H*), 6.55 (d, J = 15.6 Hz, 1H, C_9-*H*), 6.42 (dd, J = 15.0, 10.5 Hz, 1H, C_7-*H*), 5.93-5.69 (m, 3H, C_6-*H*, C_3-*H*, C_2-*H*), 4.22 (d, J = 6.0 Hz, 2H, C_1-H_2), 4.09 (d, J = 6.0 Hz, 4H, C_4-H_2, C_5-H_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.2, 133.6, 133.2, 132.5, 129.7, 128.8, 128.6, 128.2, 127.9, 126.6, 71.0, 65.9, 59.1; LRMS (EI) *m/z* 230 $(M)^+$; HRMS (EI) exact mass calcd for ($C_{15}H_{18}O_2$) requires *m/z* 230.1307, found *m/z* 230.1305.

4-(5-Phenyl-penta-2,4-dienyloxy)-but-2-enal (41).

A solution of 0.21 mL (2.39 mmol) oxalyl chloride in 40 mL CH_2Cl_2 was cooled to –60 °C. 0.34 mL (4.77 mmol) DMSO was added, along with a solution of 500 mg (2.17 mmol) alcohol **40** in 5 mL CH_2Cl_2. After 15 minutes, 1.5 mL (10.85 mmol) Et_3N was added and the reaction was allowed to warm to room temperature over 40 minutes. The slurry was then poured into 30 mL water, extracted with CH_2Cl_2 (3 x 20 mL), and concentrated *in vacuo*. The product was then run through a basic alumina plug (level IV), eluted with 5 – 10 % EtOAc/ hexanes, concentrated, and used immediately in the IMDA without further purification.

5-Phenyl-1,3,3a,4,5,7a-hexahydro-isobenzofuran-4-carbaldehyde(58).

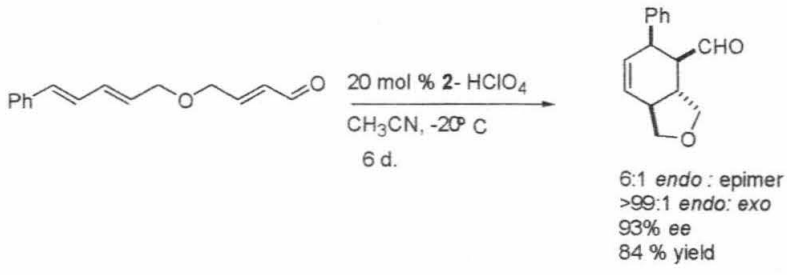


> 100:1 endo : epimer
>99:1 *endo: exo*
94% *ee*
79 % yield

To a solution of 5.9 mg (0.17 mmol) of **1** - $HClO_4$ in 0.23 mL *n*BuOH (5 % H_2O) was added 190 mg (0.83 mmol) of **41** in 0.6 mL *n*BuOH. The solution was stirred at -20°C for 6 days, then the crude reaction mixture was warmed to room temperature, flashed through a silica column and eluted with 10 % EtOAc / hexanes to afford 150 mg (79 %) **58** as one diastereomer. The product was subjected to acetalization with chiral *R,R* – pentanediol acetal and the resulting acetal was determined to have 94 % *ee*.

$[\alpha]_D^{25}$ =284.02° (c = 1, $CHCl_3$); IR (film) 2935, 2866, 1722, 1274, 1027, 911 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.36(d, 1H, *J* = 1.8 Hz, C*H*O), 7.34-7.19(m, 5H, Ph*H*), 6.10(d, 1H, *J* = 9.6 Hz, C*H*=CH), 5.72(dt, 1H, *J* = 3.3, 6.6 Hz, CH=C*H*), 4.24(m, 1H, C*H*Ph), 4.23(t, 1H, *J* = 6.9 Hz, C*H*HOCH$_2$), 4.13(t, 1H, *J* = 7.2 Hz, C*H*HOCH$_2$), 3.47(dd, 1H, *J* = 7.2, 11.4 Hz, CH$_2$OCH*H*), 3.36(dd, 1H, *J* = 7.2, 7.4 Hz, CH$_2$OCH*H*), 2.94(ddd, 1H, *J* = 1.5, 7.5, 11.4 Hz, C*H*CHO), 2.51-2.43 (m, 1H, -C*H*CH$_2$O-), 2.36-2.22(m, 1H, C=CHC*H*CH$_2$O-); ^{13}C NMR

(300 MHz, $CDCl_3$) δ 201.7, 139.4, 130.8, 129.4, 128.9, 127.7, 125.6, 70.0, 69.9, 54.7, 44.3, 43.6, 39.2.



6:1 *endo* : epimer
>99:1 *endo: exo*
93% *ee*
84 % yield

A solution of 10.8 mg (0.044 mmol) of **2** and 3.8μL (0.044 mmol) $HClO_4$ (70 %) in 0.3 mL CH_3CN (2 % H_2O) was added to 50 mg (0.22 mmol) of **41** in 0.1 mL CH_3CN. The solution was stirred at -20°C for 6 days, then the crude reaction mixture was warmed to room temperature, flashed through a silica column and eluted with 10 - 35 % EtOAc / hexanes to afford 42 mg (84 %) **58** as a 6:1 diastereomeric mixture. The product was subjected to acetalization with chiral *R,R* – pentanediol acetal and the resulting acetal was determined to have 93 % *ee*. Physical data match those reported above.