On the Development of Catalytic Carba-6π Electrocyclizations

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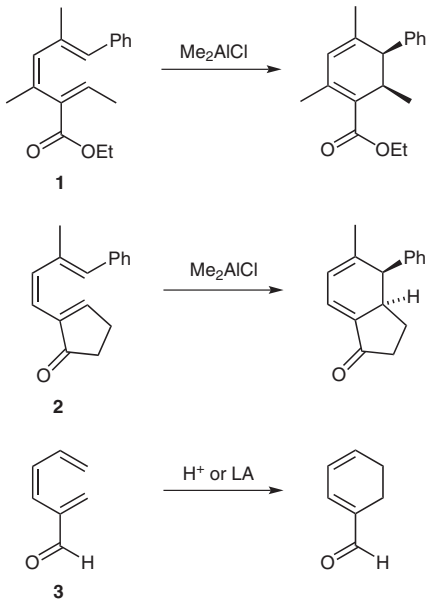
Dedicated to Rolf Huisgen on the occasion of his 90th birthday

Abstract: Hexatriene substrates substituted in the 2-position with carbonyl groups were studied in the context of catalytic 6π electrocyclizations. The nature of the carbonyl group and the substitution pattern on the hexatriene have significant effects on the ability of these substrates to succumb to catalysis. A novel 2-formyl hexatriene dimerization was observed. The first example of a catalytic asymmetric carba-6π electrocyclization is reported along with the discovery of an unusual kinetic resolution via a catalytic photochemical electrocyclic ring-opening.

Key words: electrocyclic reactions, catalysis, dimerization, asymmetric catalysis, kinetic resolution.

The ability to catalyze pericyclic reactions has greatly increased their synthetic utility and has allowed for the development of asymmetric versions. Among the different types of these reactions, Diels–Alder cycloadditions, Claisen rearrangements, and Nazarov cyclizations have been rendered asymmetric by using a variety of chiral Lewis acids, Brønsted acids and aminocatalysts.[1,2] Our group has contributed to this topic by introducing 2-alkoxy-1,4-pentadien-3-ones as excellent substrates for Nazarov cyclizations, which have yielded the first highly enantioselective examples of these 4π electrocyclizations.[2] More recently, 6π electrocyclizations have come into focus. In 2009, List and Smith independently reported asymmetric catalysis in aza-6π electrocyclizations.[3] Prior to this, we demonstrated that carba-6π electrocyclizations could be catalyzed with Lewis acids (Scheme 1).[4,5] Using esters (e.g., **1**) and ketones (e.g., **2**) as Lewis bases and Me_2AlCl as a Lewis acid, we showed that rate accelerations up to 55-fold could be achieved. Our experimental results were accompanied by theoretical calculations on simple aldehydes, such as **3**, which indeed showed that placement of a formyl group in the 2-position should result in significant rate accelerations upon binding of a Lewis acid or a proton.

It is generally believed that aldehydes are preferred substrates for asymmetric Lewis acid catalyzed reactions, since the geometry of their complexation is well-defined. In addition, unsaturated aldehydes, such as **3**, allow for aminocatalysis, which is more problematic with ketones due to their decreased electrophilicity and increased steric hindrance. We have therefore investigated 2-formyl hexatrienes in the context of catalytic 6π electrocyclizations. Herein, we report on our experiences with these substrates and provide an update on our continued studies of catalytic and asymmetric catalytic carba-6π electrocyclizations. In the course of these investigations, we have established that certain substituents on the hexatriene system are required to promote electrocyclizations and prevent side reactions, such as double bond isomerizations or Prins-type cyclizations. Powerful new Lewis acid catalysts have been identified that have led to rate accelerations an order of magnitude higher than previously described. In addition, we have launched preliminary investigations into asymmetric variants of our methodology and have discovered an unusual kinetic resolution that proceeds via a catalytic photochemical electrocyclic ring-opening.



Scheme 1 Catalysis of carba-6π electrocyclizations; LA = Lewis acid

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Variation of Lewis Basic Hexatrienes

In an attempt to expand the range of hexatriene substrates beyond ester **1**, we began to explore hexatrienes with a formyl group at the 2-position. Accordingly, formyl hexatriene **7** was synthesized by subjecting stannane **5** and iodide **6** to modified Liebeskind coupling conditions (Scheme 2).[6,7] The synthesis and purification of stannane **5** was complicated by its propensity to undergo protodestannylation as well as the sensitivity of iodide **4**. Therefore, **4** and **5** were carried through to the coupling reaction with minimal purification. Nevertheless, hexatriene **7** was isolated cleanly and underwent the expected thermal disrotatory electrocyclization efficiently at 105 °C, yielding cyclohexadiene **8**. The rate constants for the electrocyclization of **7** in solvents of varying polarity were measured (Table 1). As expected, they proved to be insensitive to solvent polarity.[8]

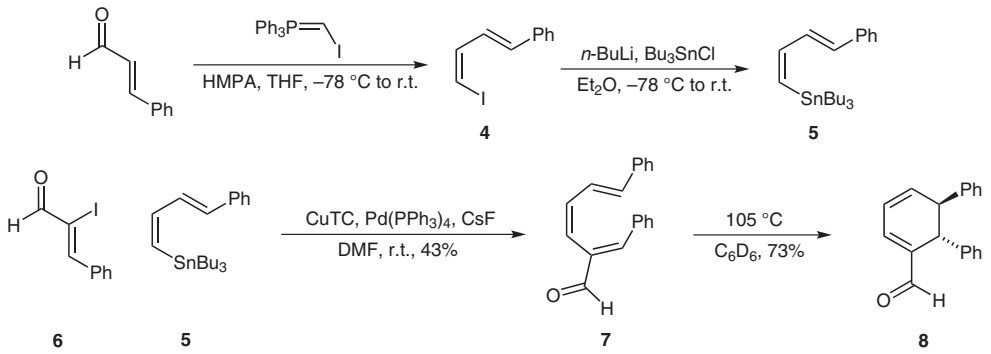
Table 1 First-Order Observed Rate Constants for the Electrocyclization of **7** in Various Solvents at 100 °C

Entry	Solvent	k_{obs} (sec^{-1})
1	CD_2Cl_2	$2.9(2) \times 10^{-5}$
2	CD_3NO_2	$3.0(1) \times 10^{-5}$
3	CD_3OD	$3.1(1) \times 10^{-5}$
4	acetone-d_6	$2.9(1) \times 10^{-5}$

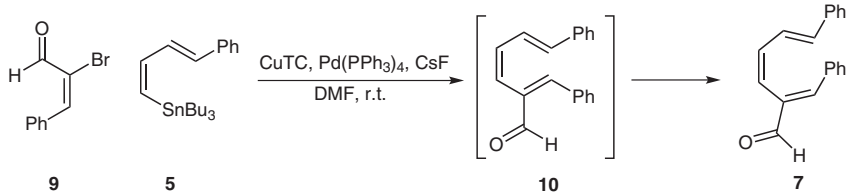
While its thermal electrocyclization proceeded cleanly, hexatriene **7** proved to be an unsuitable substrate for catalysis. Submitting **7** to Me_2AlCl, as well as to other Lewis acids such as $Sc(OTf)_3$ and $Cu(OTf)_2$, resulted in decomposition. Treatment of **7** with a variety of primary and secondary amines as well as Brønsted acids also resulted in the formation of numerous products that were not further identified.

In an effort to lower the energy barrier associated with electrocyclization over other competing decomposition pathways, we next attempted to synthesize the *E*,*Z*,*Z* isomer of **7**, compound **10** (Scheme 3). The rationale for this was that hexatrienes that bear large *cis* substituents in the terminal position have higher electrocyclization energy barriers compared to unsubstituted or *trans*-substituted analogues.[9] Accordingly, stannane **5** was coupled with vinyl bromide **9**, resulting in a complex mixture containing hexatriene **7**, presumably the result of isomerization of hexatriene **10** taking place in situ. Attempts to cleanly isolate **10** using silica or alumina gel chromatography yielded only hexatriene isomer **7** (Scheme 3).

In an alternative strategy that was designed to lower the electrocyclization energy barrier and disfavor decomposition pathways, we next explored the use of hexatrienes with substitution patterns that would favor the requisite conformation for cyclization. For instance, a 2-formyl hexatriene possessing a methyl substituent in the 5-position is expected to more highly populate the *s-cis* conformation **12**, based on unfavorable steric interactions present between the methyl group and the hexatriene terminus in the *s-trans* conformation **11** (Scheme 4). Those interactions are not present in the corresponding unsubstituted hexatriene **14**, whose neighboring single bonds therefore adopt primarily *s-trans* conformation **13**. The *s-cis* hexatriene conformer more closely resembles the electrocyclization transition state and, therefore, appropriately substituted hexatrienes are expected to be entropically biased towards electrocyclization over other reaction pathways, relative to unsubstituted hexatrienes. Substitutions of this type are also expected to lower the enthalpy of activation due to ground-state destabilization of the substi-

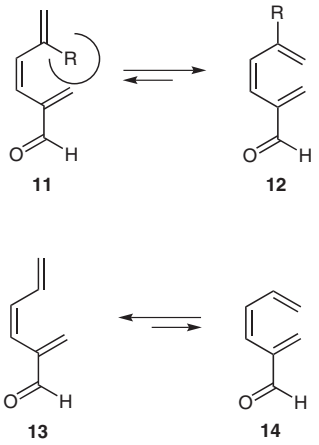


Scheme 2 Synthesis and thermal cyclization of hexatriene **7**; CuTC = copper(I) thiophene-2-carboxylate



Scheme 3 Synthesis of hexatriene **7** via isomerization of hexatriene **10**; CuTC = copper(I) thiophene-2-carboxylate

tuted hexatriene relative to the unsubstituted hexatriene; this would be caused by unfavorable steric interactions analogous to those discussed above. Finally, inclusion of an electron-donating methyl group in the 5-position along with the electron-withdrawing formyl group in the 2-position is expected to lower the electrocyclization energy barrier due to the 'captodative substitution' effect outlined by Fu and Liu.[10]

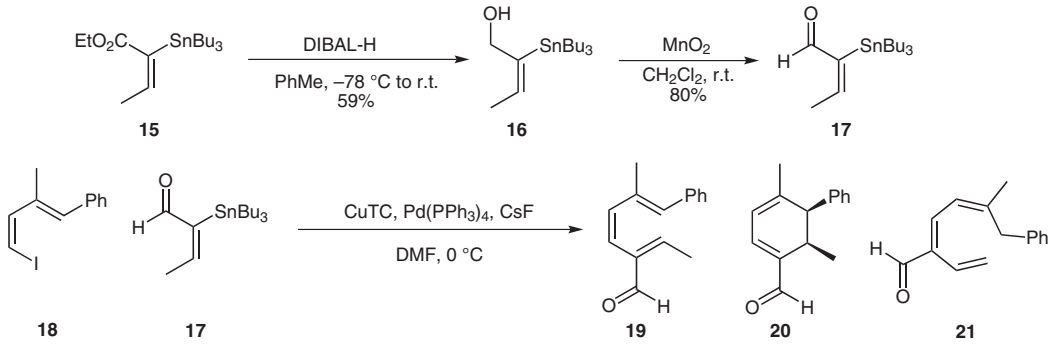


Scheme 4 Conformations of 5-substituted and 5-unsubstituted 2-formyl hexatrienes

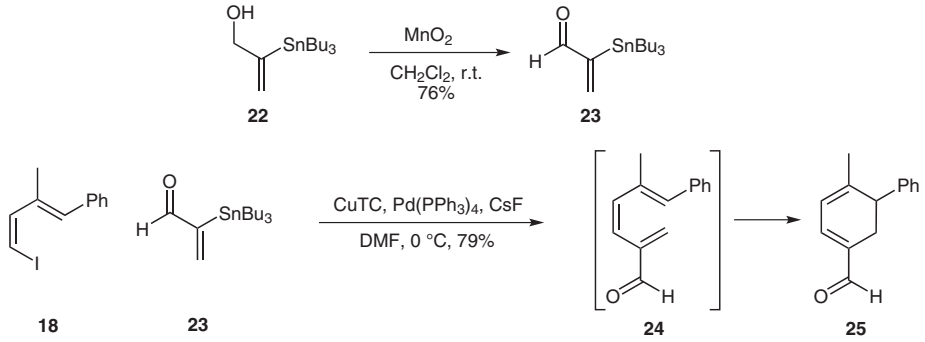
In designing our next substrate, we also decided to replace one of the terminal phenyl groups with a methyl group to prevent isomerization of the terminal double bond. Synthesis of hexatriene **19** began with reduction and re-oxidation of vinyl stannane **15** to give α-stannyl aldehyde **17**, which was coupled with vinyl iodide **18**. After aqueous workup, the crude reaction mixture contained hexatriene **19** contaminated with approximately 25% cyclohexadiene **20** and 35% hexatriene isomer **21**, the latter being formed by alkene isomerization and subsequent 1,7-hydride shift (Scheme 5). Attempts to purify hexatriene **19** resulted in its further conversion into **20** and **21**. As this isomerization pathway would likely be active under our Lewis acidic catalytic conditions, further investigations using this substrate system were not pursued.

In order to completely avoid problems associated with the alkene isomerizations outlined above, we next targeted β-unsubstituted hexatriene **24** (Scheme 6). However, the crude reaction mixture formed upon coupling of **18** and **23** (the MnO_2 oxidation product of **22**) showed only cyclohexadiene **25**, the product of the in situ electrocyclization of **24**. The facile nature of this electrocyclization can be attributed to a lack of unfavorable steric interactions between the hexatriene termini in the electrocyclization transition state.

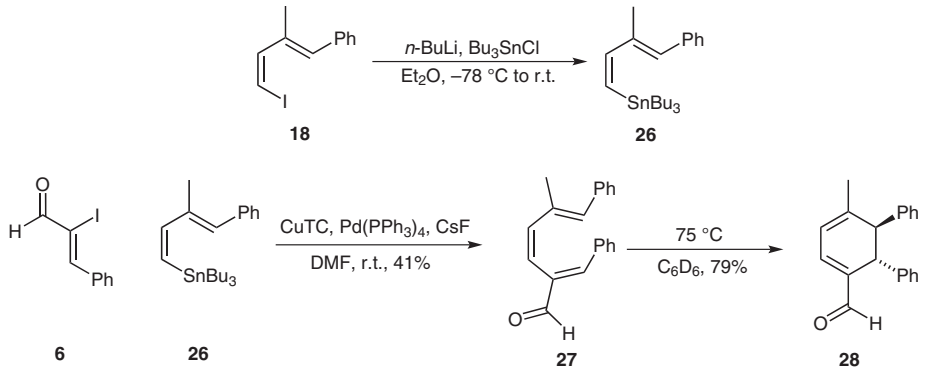
Returning to β-phenyl-substitution, we next targeted hexatriene **27** (Scheme 7), which possessed a methyl substituent that we hoped would bias this substrate towards electrocyclization. Lithium–iodine exchange of vinyl iodide **18** followed by a tributyltin chloride quench gave vinyl stannane **26**. Synthesis and purification of stannane **26** was complicated by its propensity to undergo protodestannylation, as was the case for stannane **5**. Therefore, crude stannane **26** was coupled with iodide **6** to give hexatriene **27** in low yield. The thermal electrocyclization



Scheme 5 Synthesis of hexatriene **19** and its electrocyclization, isomerization and hydride shift products; DIBAL-H = diisobutylaluminum hydride, CuTC = copper(I) thiophene-2-carboxylate



Scheme 6 Synthesis of cyclohexadiene **25** via hexatriene intermediate **24**; CuTC = copper(I) thiophene-2-carboxylate



Scheme 7 Synthesis and thermal cyclization of hexatriene **27**; CuTC = copper(I) thiophene-2-carboxylate

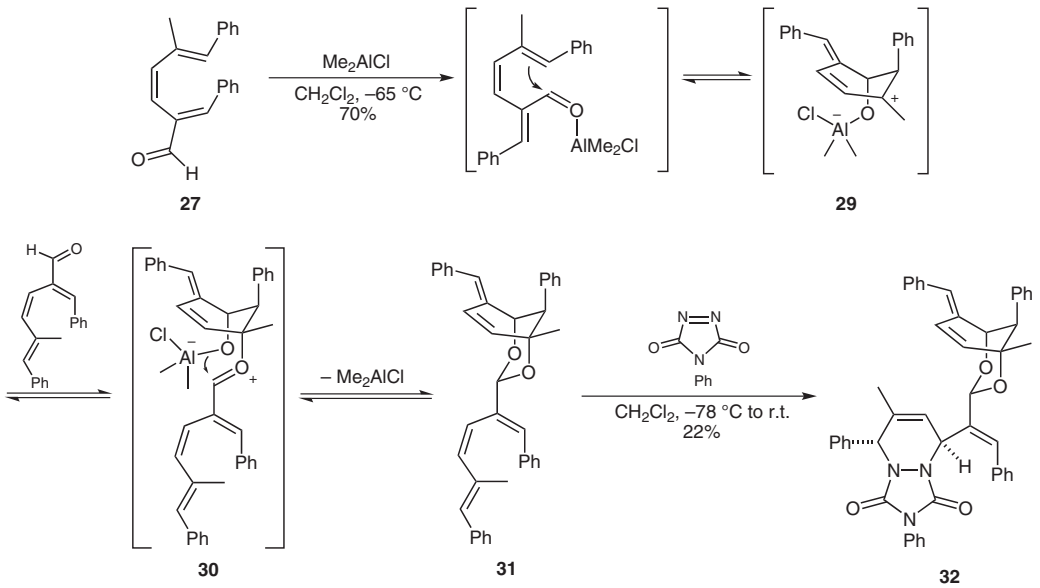
of **27** was effected at only 75 °C, as compared to the 105 °C needed for cyclization of the des-methyl analogue **7** (Scheme 2 and Scheme 7). This difference can be attributed to the influence of the methyl substituent, as discussed above (Scheme 4).

Unfortunately, substrate **27** again failed to undergo Lewis acid catalyzed electrocyclization under a variety of conditions. Interestingly, however, catalytic amounts of Me_2AlCl at low temperature effected the clean formation of acetal **31** (Scheme 8). Presumably, cation **29**, generated by a Prins-type intramolecular nucleophilic attack of aldehyde **27**, is intercepted by a second equivalent of aldehyde to give oxocarbenium aluminate **30**, which gives way to bicyclic acetal **31** as a single diastereomer. It is likely that the entire reaction is reversible under conditions of Me_2AlCl catalysis and, therefore, its outcome is under thermodynamic control. Low temperature acetal cleavage by Me_2AlCl is known.[11] In addition, previous work by the Snider group suggests that the alkylaluminum halide-induced nucleophilic attack of alkenes on carbonyl compounds to give zwitterionic species is a reversible process.[12]

Attempts to characterize **31** using one- and two-dimensional NMR techniques were unsuccessful due to the complexity of the spectra. In addition, dimer **31** failed to crystallize. The compound was therefore treated with the highly reactive dienophile *N*-phenyltriazolinedione in the hope that the latter would react with the diene moiety proposed to be present in **31**. Indeed, this reaction yielded two crystalline products. The major product, **32**, was studied by single crystal X-ray analysis and is shown in Figure 1. The minor product is presumably a diastereomeric Diels–Alder product.

Given our difficulties with aldehydes **7**, **10**, **19**, **24**, and **27**, it became clear that the catalytic electrocyclizations of 2-formyl substrates would be difficult. This prompted us to turn our attention to cyclic ketones in the hope that these substrates would be less prone to competitive intramolecular side reactions and double bond isomerization.

First, ketone **34** was prepared by coupling of vinyl iodide **4** with stannane **33** (Scheme 9). Isolation of **34** was not hampered by facile electrocyclization because heating to 100 °C was required to effect its electrocyclization to cy-



Scheme 8 The Me_2AlCl-catalyzed dimerization of **27** and its Diels–Alder derivatization

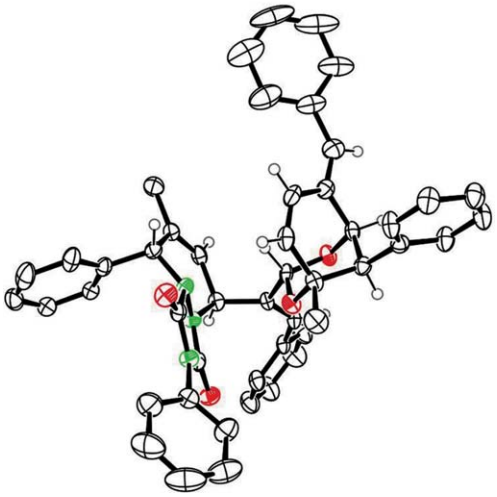


Figure 1 ORTEP diagram of **32** at the 50% probability level; some hydrogen atoms have been removed for clarity

clohexadiene **35**. However, attempts to catalyze the electrocyclization of **34** with Me_2AlCl resulted only in nonspecific substrate decomposition.

We attributed the decomposition of hexatriene **34** under catalytic conditions to the above-described absence of a substituent that would enforce the *s-cis* conformation of the neighboring single bond and entropically bias the substrate towards electrocyclization. To address this, hexatriene **2** was synthesized via coupling of **18** and **33** (Scheme 10). Indeed, inclusion of the δ-methyl substituent allowed the thermal cyclization of **2** to be efficiently carried out at only 52 °C, compared to the 100 °C necessary for the cyclization of the des-methyl analogue **34**. The relatively low electrocyclization energy barrier of **2** resulted in it being isolated along with small amounts of **36** as a result of thermal electrocyclization during isolation.

It was found that inclusion of this methyl group indeed resulted in successful catalysis, as described in our earlier report.[4] A 55-fold rate acceleration was observed for this substrate in the presence of one equivalent of Me_2AlCl at 28 °C. This rate acceleration is significantly larger than the 13-fold rate acceleration observed for hexatriene **1**.

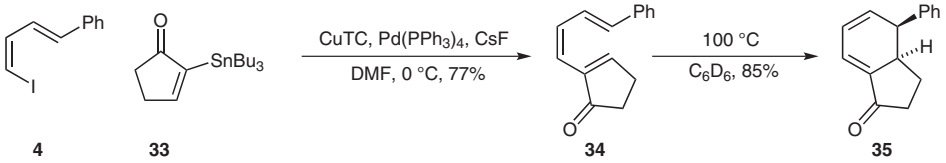
Lewis Acid Optimization

With hexatriene substrate **2** in hand, we sought to further refine our catalytic conditions (Table 2). Notably, $Sc(OTf)_3$ (entry 2) catalyzed the electrocyclization of **2** to the same extent as did Me_2AlCl (entry 5), while $Cu(OTf)_2$ (entry 1) exhibited only mild catalytic activity. Boron-centered Lewis acids were highly effective, with tris-pentafluorophenylborane and boron trifluoride etherate resulting in 400- and 100-fold rate accelerations, respectively (entries 3 and 4). Me_2AlOTf (entry 6) exhibited catalytic activity nearly equal to that of Me_2AlCl. However, the addition of one equivalent of $MeAlCl_2$ or $PhAlCl_2$ resulted in 200- and 300-fold rate accelerations, respectively (entries 7 and 8). In the hope that an alkylaluminum dihalide bearing larger halogen atoms would provide a more Lewis acidic center,[13] we synthesized $MeAlI_2$. This

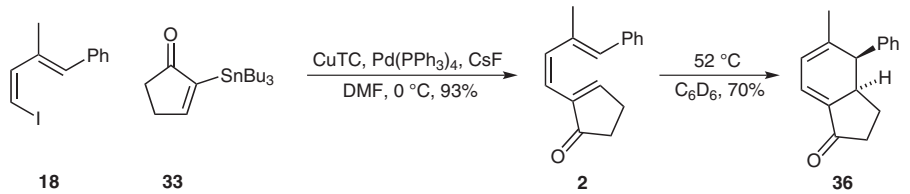
Table 2 Screen for Catalysis of the Electrocyclization of **2** in Benzene-d_6 in the Presence of Lewis Acids (1 equiv); OTf = trifluoromethanesulfonate

Entry	Lewis acid	Approx. $t_{1/2}$ (min)	Temp. (°C)	Approx. rate acceleration
1	$Cu(OTf)_2$[a]	20	45	4
2	$Sc(OTf)_3$[a]	20	r.t.	55
3	$B(C_6F_5)_3$	2.5	r.t.	400
4	$BF_3{\cdot}OEt_2$[a]	8	r.t.	100
5	Me_2AlCl	20	r.t.	55
6	Me_2AlOTf	15	r.t.	70
7	$MeAlCl_2$	24	9	200
8	$PhAlCl_2$	4	r.t.	300
9	$MeAlI_2$	7	9	600

[a] 2,6-Di-*tert*-butyl-4-methylpyridine (1.2 equiv) added.



Scheme 9 Synthesis and thermal electrocyclization of hexatriene substrate **34**



Scheme 10 Synthesis and thermal electrocyclization of hexatriene substrate **2**

proved to be the most competent catalyst yet discovered for this reaction, and resulted in a 600-fold rate acceleration.

Chiral Lewis Acid Survey

A variety of chiral Lewis and Brønsted acids, as well as hydrogen-bonding catalysts, were screened for the catalysis of the electrocyclization of **2**; all but one system resulted in little or no enantioenrichment (≤17% ee; 1 equiv catalyst; see Supporting Information). The exception was the pyridine bis(oxazoline) scandium(III) trifluoromethanesulfonate (**37**; scandium-pybox) catalyst system (Table 3). One equivalent of Lewis acid was used for these studies. The first promising result was obtained using benzene-d_6 solvent (35% ee, entry 1). No further increase in enantioinduction was observed using a variety of different solvents (entries 2–5). Of the first five solvents screened, the highest enantiomeric excess was achieved in dichloromethane-d_2 (42%, entry 5). However, repeating this experiment yielded enantiomeric excesses in the range 32–42%. We hypothesized that the reproducibility issues were due to the presence of varying amounts of adventitious water, because performing the reaction with scandium(III) trifluoromethanesulfonate that had not been dried under vacuum at 150 °C resulted in no catalysis or enantioinduction. This prompted us to include dimethyl zirconocene in our reaction mixtures to serve as a desiccant. This compound reacts rapidly and quantitatively with water, and so observation of its upfield methyl signals in the ^{1}H NMR spectra verifies the dryness of our reaction mixtures. However, while the addition of dimethyl zirconocene increased the level of enantioinduction, it did not improve the reproducibility (entry 6). Finally, switching to 1,1,2,2-tetrachloroethane-d_2 solvent further increased the enantiomeric excess to 57–77% (entry 7). These initial results, however modest, represent the first example of an enantioselective carba-6π electrocyclization.

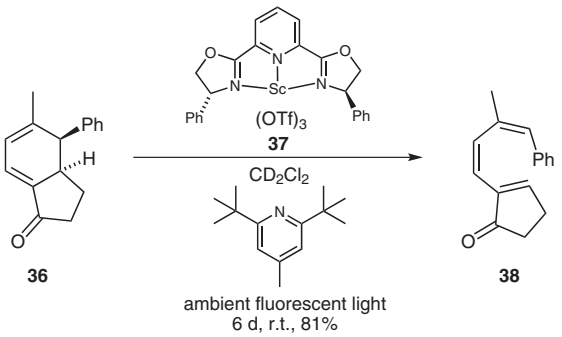
Table 3 Solvent Screen for the Enantioselective Electrocyclization of **2** in the Presence of Scandium-pybox (**37**) and 2,6-Di-*tert*-butyl-4-methylpyridine (0.7 equiv)[a]

Entry	Solvent	ee (%)[b]
1	C_6D_6	35
2	THF-d_8	13, 18
3	CD_3NO_2	35
4	CD_3CN	21
5	CD_2Cl_2	32–42
6[c]	CD_2Cl_2	47–66
7[c]	$(CDCl_2)_2$	57–77

[a] Conditions: 5 h, r.t.
[b] Values are corrected to account for initial thermal conversion of starting material using the formula % ee = (100 × measured ee) / (100 – % of initial conversion).
[c] Cp_2ZrMe_2 (0.5 equiv) added.

Kinetic Resolution via Catalytic Photochemical Electrocyclic Ring-Opening

In the context of our investigations into enantioselective electrocyclizations, we were interested in the reversibility of the electrocyclization of hexatriene **2**. Thermal electrocyclic ring-opening of **36** was detected only after heating at 150 °C for extended periods. However, when monitoring an enantioenriched solution of cyclohexadiene **36** in the presence of one equivalent of the scandium-pybox complex **37**, a new product whose ^{1}H and ^{13}C NMR resonances were similar to those of hexatriene **2** was observed to grow over the course of several days. Based on this, as well as on an observed NOESY cross-peak between the vinyl and methyl singlets, we have assigned the structure as hexatriene **38**, the product of a photochemical conrotatory 6π electrocyclic ring-opening (Scheme 11). Interestingly, the presence of both scandium triflate and ambient light are required for formation of **38**, the absence of either results in no reaction. In addition, density functional theory calculations (B3LYP/6-31G**) indicate that the ring-opening of **36** to **38** is energetically unfavorable by 12 kcal/mol. Based on these observations and calculations, we believe that this is an example of a photochemical electrocyclic ring-opening reaction promoted by the scandium pybox complex **37**.



Scheme 11 Catalytic photochemical electrocyclic ring-opening of cyclohexadiene **36**

Indeed, the participation of the chiral Lewis acid could be inferred from monitoring the enantiomeric excess of the remaining substrate **36**, which was observed to *increase* over time (Table 4). Notably, the pybox ligand used to produce the enantioenriched cyclohexadiene **36** had the same absolute configuration as that used in the thermal cyclizations described above. In view of that, it is interesting to note that the enantiomer of **36** that is formed preferentially in the catalytic electrocyclization is *not* the enantiomer that preferentially undergoes photochemical electrocyclic ring-opening. This photochemical kinetic resolution takes place over the course of 6–21 days. As the cyclization reactions of hexatriene **2** in the presence of

chiral catalysts proceeds within six hours at room temperature and in the dark, we are confident that the enantioselectivities produced therein are the result of enantioselective electrocyclizations and not of cyclization to racemic product followed by kinetic resolution.

Table 4 Enantiomeric Excess of Remaining Cyclohexadiene **36** under Ambient Light and Scandium-pybox Catalysis as a Function of Conversion into **38**

Entry	Conversion into **38** (%)	ee (%) of **36**
1	0	23
2	32	36
3	51	46
4	73	52

Summary and Conclusions

Our results with Me_2AlCl as a Lewis acid and with various Lewis basic substrates demonstrate that a certain amount of 'substrate engineering' is necessary to promote catalytic carba-6π electrocyclizations. These reactions work well with esters and ketones appended to the hexatriene system. By contrast, 2-formyl hexatrienes have proven to be unsuitable, mostly because of the high reactivity of the carbonyl group towards intramolecular nucleophilic attack, as demonstrated by the formation of an unusual hexatriene dimer. For our ketone substrates, boron-, copper-, scandium-, as well as aluminum-based Lewis acids are all competent catalysts, with $MeAlI_2$ resulting in the most significant rate acceleration. Whether these Lewis acids have a wider substrate scope than Me_2AlCl remains to be determined. Reactants possessing other Lewis basic docking groups, such as amides, imines, lactones, and lactams are currently under investigation in our laboratories.

A first screen of chiral Lewis acids revealed that the scandium-pybox system **37** provides enantiomeric excesses in the 70% range. Despite their low enantiomeric excesses and a lack of turnover, these reactions do, to the best of our knowledge, represent the first catalytic asymmetric carba-6π electrocyclizations and provide a proof of principle that reactions of this type are possible. Future investigations will determine whether these preliminary results can be developed into a truly practical and general methodology for asymmetric synthesis.

All reactions and manipulations, unless otherwise noted, were carried out in an inert atmosphere (N_2) glovebox or using standard Schlenk and high-vacuum techniques. Sealed NMR tubes were prepared by attaching the NMR tube directly to a Kontes high-vacuum stopcock via a cajon ultra-torr reducing union, then flame-sealing on a vacuum line. All glassware was dried in an oven at 150 °C for at least 12 h prior to use or was flame-dried under reduced pressure. ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker DRX-500 (500 MHz), AV-500 (500 MHz), AVB-400 (400 MHz), AVQ-400 (400 MHz), or AV-300 (300 MHz) spectrometers as indicated. ^{1}H NMR chemical shifts (δ) are reported in parts per million relative to residual protiated solvent. Data are reported in the following format: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant; integration. ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to the carbon resonance of the deuterated solvent. Column chromatography was performed with a Biotage SP1 MPLC purification system and pre-packed silica gel columns. IR spectra were obtained with neat samples on NaCl plates using a ThermoNicolet Avatar 370 FT-IR spectrometer. The kinetics experiments were carried out in a circulating oil bath and the temperatures were measured using a calibrated mercury thermometer (±0.1 °C). The temperatures of the kinetics experiments that were carried out in an NMR probe were determined from the ^{1}H NMR chemical shifts of ethylene glycol and MeOH samples (±0.1 °C). The values for k_{obs} were determined by fitting the concentration versus time plots to the equation $C_t = C\pi - (C\pi - C_0)\exp(-k_{obs}t)$ using the program KaleidaGraph (where C_t, $C\pi$, and C_0 are the concentration at time t, time infinity, and time zero, respectively).[14] All well-resolved starting material and product ^{1}H NMR resonances were integrated and fit separately; which ^{1}H NMR resonances were well-resolved depended on the Me_2AlCl/hexatriene ratio; the k_{obs} values shown are averages of those individual values. The reported errors in the k_{obs} values are one standard deviation of the k_{obs} values obtained from each integrated resonance. Enantiomeric excess was determined using a Shimadzu 10A VP Series Chiral HPLC instrument with detection at 230, 254, and 280 nm.

THF, toluene, Et_2O, and CH_2Cl_2 were dried and purified by passage through a column of activated alumina under N_2 pressure, followed by sparging with N_2.[15] Anhydrous DMF was obtained from EMD and used without further purification. C_6D_6, CD_2Cl_2, CD_3NO_2, CD_3OD, acetone-d_6, THF-d_8, CD_3CN, $(CDCl_2)_2$, and $CDCl_3$ were obtained from Cambridge Isotope Labs, Inc. C_6D_6 for use as a reaction solvent or for characterization of alkylaluminum species was sparged with N_2 and stored over activated 4 Å molecular sieve pellets overnight prior to use. CD_2Cl_2 was vacuum-transferred from CaH_2 and degassed with three freeze–evacuation–thaw cycles. CD_3NO_2 and acetone-d_6 were distilled from anhydrous $MgSO_4$, sparged with N_2, and stored over activated 4 Å molecular sieve pellets overnight. CD_3OD was distilled from activated Mg and sparged with N_2. THF-d_8 was vacuum-transferred from purple sodium benzophenone/ketyl, degassed with three freeze–evacuation–thaw cycles, and stored over activated 4 Å molecular sieve pellets. CD_3CN and $(CDCl_2)_2$ were distilled from CaH_2, degassed with three freeze–evacuation–thaw cycles, and stored over activated 4 Å molecular sieve pellets overnight. $CDCl_3$ was stored over K_2CO_3 and used without further purification. Activated 4 Å molecular sieve pellets were obtained from Sigma–Aldrich and heated at 150 °C under vacuum for 24 h. Hexamethylbenzene was obtained from Sigma–Aldrich and was sublimed prior to use. HMPA was obtained from Sigma–Aldrich and distilled from CaH_2 prior to use. 1,1,2,2-Tetrachloroethane, obtained from Sigma–Aldrich, was sparged with N_2 and stored over activated 4 Å molecular sieve pellets overnight prior to use. $Sc(OTf)_3$ was obtained from Sigma–Aldrich and was dried under vacuum at 150 °C for 12 h. $Pd(PPh_3)_4$ and $B(C_6F_5)_3$ were obtained from Strem Chemicals; Bu_3SnCl, CsF, DIBAL-H, *n*-BuLi, NaHMDS, *trans*-cinnamaldehyde, 2,6-di-*tert*-butyl-4-methylpyridine, $Cu(OTf)_2$, Me_3Al, Me_2AlCl, $BF_3{\cdot}OEt_2$, AlI_3, TfOH, and 2,6-bis[(4*R*)-4-phenyl-2-oxazolinyl]pyridine were obtained from Sigma–Aldrich; these reagents were used without further purification. Copper(I) thiophene-2-carboxylate,[6] (iodomethyl)triphenylphosphonium iodide,[16] α-iodocinnamaldehyde (**6**),[17] α-bromocinnamaldehyde (**9**),[18] ethyl 2-tributylstannyl-2-butenoate (**15**),[4] 4-iodo-2-methyl-1-phenyl-1,3-butadiene (**18**),[4] manganese dioxide,[19] phenylaluminum dichloride,[20] 2-tributylstannylpropenol (**22**),[21] 2-tributylstannyl-2-cyclopentenone (**33**),[4] hexatriene **2**,[4] and cyclohexadiene **36**,[4] were synthesized according to literature proce-

dures. Characterization data for these compounds agree with literature values.

4-Iodo-1-phenyl-1,3-butadiene (4)

Synthesized according to the procedure developed by Stork and Zhao.[22] A Schlenk flask was charged with THF (110 mL), (iodomethyl)triphenylphosphonium iodide (6.3 g, 12 mmol), and NaHMDS (1.0 M in THF, 13 mL, 13 mmol). This solution was stirred for 5 min at r.t. and cooled to –60 °C. HMPA (3.2 mL) was then added and the reaction mixture was cooled to –78 °C and stirred for a further 15 min. *trans*-Cinnamaldehyde (1.4 mL, 11 mmol) was added dropwise and the reaction mixture was allowed to warm to r.t. over 1.5 h, after which, hexanes (100 mL) was added and the resultant suspension was filtered through Celite. The filtrate was concentrated in vacuo, hexanes (100 mL) was added, and the organic suspension was washed with H_2O (5 × 10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Hexanes (50 mL) was again added, the resultant suspension was filtered through Celite, and the filtrate was concentrated in vacuo yielding vinyl iodide **4** as an orange oil containing ~15% triphenylphosphine oxide.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.28 (m, 5 H), 7.09–6.90 (m, 2 H), 6.87 (d, *J* = 15.4 Hz, 1 H), 6.41 (d, *J* = 7.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.5, 138.6, 136.9, 136.8, 128.9, 128.6, 127.0, 83.0.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{10}H_9I$: 255.9749; found: 255.9750.

4-Tributylstannyl-1-phenyl-1,3-butadiene (5)

A round-bottom flask was charged with 4-iodo-1-phenyl-1,3-butadiene (**4**; 4.0 g, ~16 mmol) and Et_2O (160 mL). The resultant solution was cooled to –78 °C and *n*-BuLi (2.2 M in hexanes,7.8 mL, 17.2 mmol) was added dropwise. After stirring the reaction mixture for 10 min, Bu_3SnCl (4.7 mL, 17.2 mmol) was added dropwise and the reaction mixture was stirred a further 2 h at –78 °C. The reaction mixture was warmed to 0 °C, then H_2O (10 mL) was added. The organic solution was washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by activity I basic alumina chromatography (EtOAc–hexanes, 0.5%) yielding stannane **5** as a yellow oil containing 15% 1-phenyl-1,3-butadiene. Spectral data for 1-phenyl-1,3-butadiene agree with literature values.[23] The diagnostic ^{1}H NMR resonances of **5** are as follows:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.71–6.62 (m, 2 H), 6.55 (d, *J* = 13.5 Hz, 1 H), 6.21 (d, *J* = 12.5 Hz, 1 H).

Hexatriene 7

A Schlenk flask was charged with 4-tributylstannyl-1-phenyl-1,3-butadiene (**5**; 6.4 g, 15.3 mmol), α-iodocinnamaldehyde (**6**; 2.6 g, 10.2 mmol), DMF (300 mL), and $Pd(PPh_3)_4$ (590 mg, 0.51 mmol). To this solution was added copper(I) thiophene-2-carboxylate (2.9 g, 15.3 mmol), after which the reaction mixture was stirred for 10 min, and CsF (3.1 g, 20.4 mmol) was added. After a further 50 min of stirring, the reaction mixture was diluted with Et_2O (400 mL) and the organic phase was washed with 10% aq KF (3 × 50 mL) and brine (50 mL). The organic solution was then dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by silica gel chromatography (EtOAc–hexanes, 10→40%) yielding **7**.

Yield: 1.14 g (43%); yellow solid.

IR: 1667, 1161, 753, 688 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 9.44 (s, 1 H), 7.37 (d, *J* = 7.6 Hz, 2 H), 7.10–6.91 (m, 8 H), 6.82 (s, 1 H), 6.70 (dd, *J* = 11.2, 15.6 Hz, 1 H), 6.40 (d, *J* = 15.6 Hz, 1 H), 6.30 (t, *J* = 11.2 Hz, 1 H), 6.17 (d, *J* = 11.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.9, 149.5, 137.5, 137.1, 135.5, 134.9, 134.5, 131.1, 130.6, 128.9, 128.7, 128.1, 126.9, 126.3, 121.8.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{19}H_{16}O$: 260.1201; found: 260.1210.

Cyclohexadiene 8

A solution of hexatriene **7** (38 mM in benzene-d_6, 0.5 mL, 0.019 mmol; containing 5 mol% hexamethylbenzene as an internal standard) was heated in a sealed NMR tube at 105 °C for 12 h. The reaction mixture was concentrated in vacuo and purified by silica gel chromatography (EtOAc–hexanes, 5→25%) yielding cyclohexadiene **8**.

Yield: 3.6 mg (73%). Quantitative conversion was observed by ^{1}H NMR analysis.

IR: 1670, 1569, 1161, 726, 697 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ = 9.22 (s, 1 H), 7.29 (d, *J* = 7.0 Hz, 2 H), 7.15–6.98 (m, 8 H), 6.17 (d, *J* = 5.5 Hz, 1 H), 5.86–5.82 (m, 1 H), 5.77–5.73 (m, 1 H), 4.36 (s, 1 H), 3.53 (d, *J* = 5.5 Hz, 1 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 192.6, 143.3, 142.3, 141.7, 138.3, 137.7, 129.1, 128.9, 127.42, 127.38, 127.26, 127.21, 123.4, 48.4, 43.0.

HRMS (FAB$^+$): *m*/*z* [M]$^+$ calcd for $C_{19}H_{16}O$: 260.1201; found: 260.1206.

Hexatriene 7 via Isomerization of Hexatriene 10

Synthesized in a fashion analogous to that of hexatriene **7**, using crude 4-tributylstannyl-1-phenyl-1,3-butadiene (**5**; 149 mg, 0.36 mmol), α-bromocinnamaldehyde (**9**; 50 mg, 0.24 mmol), DMF (6 mL), $Pd(PPh_3)_4$ (14 mg, 0.012 mmol), copper(I) thiophene-2-carboxylate (68 mg, 0.36 mmol), and CsF (72 mg, 0.47 mmol). ^{1}H NMR analysis of the crude reaction mixture revealed a complex mixture of products, including hexatriene **7**. Any attempt to cleanly isolate **10** via silica or alumina gel chromatography yielded hexatriene isomer **7**.

2-Tributylstannyl-but-2-enol (16)

A round-bottom flask was charged with ethyl 2-tributylstannyl-2-butenoate (**15**; 122 mg, 0.30 mmol) and toluene (5 mL). The reaction mixture was cooled to –78 °C and DIBAL-H (1.0 M in toluene, 0.67 mL, 0.67 mmol) was added dropwise. The reaction mixture was warmed to r.t., quenched with sat. aq potassium sodium tartrate (2 mL), and extracted with EtOAc (3 × 10 mL). The organic solution was then dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by silica gel chromatography (EtOAc–hexanes, 20%) yielding **16**.

Yield: 64 mg (59%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64 (qt, J_{H-H} = 2.0, 6.8 Hz, J_{Sn-H} = 34.2 Hz, 1 H), 4.36 (d, J_{H-H} = 7.4 Hz, J_{Sn-H} = 25.2 Hz, 15 H), 1.67 (d, *J* = 6.4 Hz, 3 H), 1.50–1.38 (m, 6 H), 1.33–1.22 (m, 6 H), 0.87 (t, J_{H-H} = 2.0 Hz, J_{Sn-H} = 19.9 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.8, 134.3, 63.7 (J_{Sn-C} = 11.0 Hz), 29.4 (J_{Sn-C} = 9.6 Hz), 27.6 (J_{Sn-C} = 28.5 Hz), 15.4 (J_{Sn-C} = 27.2 Hz), 13.9, 10.2 (J_{Sn-C} = 164 Hz).

2-Tributylstannyl-but-2-enal (17)

A round-bottom flask was charged with 2-tributylstannyl-but-2-enol (**16**; 264 mg, 0.73 mmol), MnO_2 (3.2 g, 36.5 mmol), and CH_2Cl_2 (8 mL). The reaction mixture was stirred at r.t. for 5 h, filtered through Celite, and concentrated in vacuo to yield **17**.

Yield: 210 mg (80%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.34 (s, J_{Sn-H} = 30.4 Hz, 1 H), 6.83 (q, J_{H-H} = 7.1 Hz, J_{Sn-H} = 29.6 Hz, 1 H), 2.18 (d, *J* = 7.2 Hz, 3 H), 1.50–1.37 (m, 6 H), 1.32–1.18 (m, 6 H), 0.93–0.79 (m, 15 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9, 156.7, 147.4, 29.2 (J_{Sn-C} = 9.8 Hz), 27.5 (J_{Sn-C} = 29.8 Hz), 16.7, 13.9, 9.9 (J_{Sn-C} = 167.4 Hz).

Hexatrienes 19 and 21 and Cyclohexadiene 20

Synthesized in a fashion analogous to that of hexatriene **7**, using 2-tributylstannyl-but-2-enal (**17**; 50 mg, 0.14 mmol), 4-iodo-2-methyl-1-phenyl-1,3-butadiene (**18**; 38 mg, 0.14 mmol), DMF (2 mL), $Pd(PPh_3)_4$ (8 mg, 0.007 mmol), copper(I) thiophene-2-carboxylate (29 mg, 0.15 mmol), and CsF (42 mg, 0.28 mmol). The reaction mixture was stirred for 1 h at 0 °C instead of 1 h at r.t. ^{1}H NMR analysis of the crude reaction mixture revealed resonances consistent with **19**, **20**, and **21** in a ratio of 60:25:35. Hexatriene **19** and cyclohexadiene **20** could not be isolated cleanly. Hexatriene **21** was isolated via silica gel chromatography (EtOAc–hexanes, 10→25%).

The diagnostic ^{1}H NMR resonances of **19** are as follows:

^{1}H NMR (500 MHz, C_6D_6): δ = 9.23 (s, 1 H), 6.23 (d, *J* = 12.0 Hz, 1 H), 5.84 (m, 2 H).

The diagnostic ^{1}H NMR resonances of **20** are as follows:

^{1}H NMR (400 MHz, C_6D_6): δ = 9.42 (s, 1 H), 6.10 (d, *J* = 5.6 Hz, 1 H), 5.66 (d, *J* = 5.6 Hz, 1 H), 3.23 (d, *J* = 8.0 Hz, 1 H), 3.06 (quin, *J* = 7.3 Hz, 1 H).

The complete ^{1}H NMR spectrum of **21** is as follows:

^{1}H NMR (500 MHz, C_6D_6): δ = 9.39 (s, 1 H), 7.16–6.98 (m, 5 H), 6.92 (d, *J* = 7.0 Hz, 1 H), 6.77 (d, *J* = 12.0 Hz, 1 H), 6.58 (dd, *J* = 11.5, 17.5 Hz, 1 H), 6.45 (dd, *J* = 2.0, 17.8 Hz, 1 H), 6.37 (d, *J* = 12.0 Hz, 1 H), 5.40 (d, *J* = 12.0 Hz, 1 H), 3.20 (s, 2 H), 1.49 (s, 3 H).

2-Tributylstannylacrolein (23)

Synthesized in a fashion analogous to that of **17**, using 2-tributylstannylpropenol (**22**; 72 mg, 0.21 mmol), MnO_2 (274 mg, 3.2 mmol), and CH_2Cl_2 (8 mL), yielding **22** (54 mg, 76%) as a yellow oil. Decomposition of **22** was observed over the course of 1 h at r.t., so it was characterized by ^{1}H NMR and LRMS analyses and employed in the subsequent reaction immediately.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.64 (s, J_{Sn-H} = 26.9 Hz, 1 H), 6.84 (d, J_{H-H} = 2.1 Hz, 1 H), 6.67 (d, J_{H-H} = 2.1 Hz, J_{Sn-H} = 23.8 Hz, 1 H), 1.52–1.38 (m, 6 H), 1.37–1.20 (m, 6 H), 1.00–0.91 (m, 6 H), 0.85 (t, *J* = 7.2 Hz, 9 H).

LRMS (EI$^+$): *m*/*z* [M – Bu]$^+$ calcd for $C_{11}H_{21}OSn$: 289; found: 289.

Cyclohexadiene 25

Synthesized in a fashion analogous to that of hexatriene **7**, using 2-tributylstannylacrolein (**23**; 50 mg, 0.14 mmol), 4-iodo-2-methyl-1-phenyl-1,3-butadiene (**18**; 42 mg, 0.16 mmol), DMF (2 mL), $Pd(PPh_3)_4$ (9 mg, 0.008 mmol), copper(I) thiophene-2-carboxylate (34 mg, 0.18 mmol), and CsF (49 mg, 0.32 mmol). The reaction mixture was stirred for 1 h at 0 °C instead of 1 h at r.t. The crude product was purified by silica gel chromatography (EtOAc–hexanes, 2→18%) yielding cyclohexadiene **25**.

Yield: 22 mg (79%); yellow oil.

IR: 3025, 2918, 2849, 2809, 1668, 1642, 1578 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.44 (s, 1 H), 7.28–7.07 (m, 5 H), 6.80 (d, *J* = 5.6 Hz, 1 H), 6.20 (d, *J* = 6.0 Hz, 1 H), 3.49 (t, *J* = 8.0 Hz, 1 H), 2.76 (d, *J* = 7.2 Hz, 2 H), 1.80 (s, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 192.6, 150.1, 143.3, 142.1, 134.3, 128.8, 127.8, 127.1, 121.2, 44.5, 27.9, 23.2.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}O$: 199.1117; found: 199.1119.

4-Tributylstannyl-2-methyl-1-phenyl-1,3-butadiene (26)

Synthesized in a fashion analogous to that of 4-tributylstannyl-1-phenyl-1,3-butadiene (**5**), using 4-iodo-2-methyl-1-phenyl-1,3-butadiene (**18**; 1.0 g, ~3.7 mmol), Et_2O (40 mL), *n*-BuLi (1.8 M in hexanes, 2.5 mL, 4.4 mmol), and Bu_3SnCl (1.1 mL, 4.1 mmol). The resultant crude yellow oil containing **26**, 2-methyl-1-phenyl-1,3-butadiene, and stannane impurities was not subjected to any chromatographic purification as was **5**, but was instead used directly in subsequent reactions. Spectral data for 2-methyl-1-phenyl-1,3-butadiene was in agreement with literature values.[24] The diagnostic ^{1}H NMR resonances of **26** are as follows:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.15 (m, 5 H), 7.13 (d, *J* = 13.2 Hz, 1 H), 6.48 (s, 1 H), 5.91 (d, *J* = 13.6 Hz, 1 H).

Hexatriene 27

Synthesized in a fashion analogous to that of hexatriene **7**, using crude 4-tributylstannyl-2-methyl-1-phenyl-1,3-butadiene (**26**; 70 mg, ~0.16 mmol), α-iodocinnamaldehyde (**6**; 42 mg, 0.16 mmol), DMF (2 mL), $Pd(PPh_3)_4$ (9 mg, 0.008 mmol), copper(I) thiophene-2-carboxylate (34 mg, 0.18 mmol), and CsF (49 mg, 0.32 mmol). The crude product was purified by silica gel chromatography (EtOAc–hexanes, 5→35%) yielding **27**.

Yield: 18.2 mg (41%); yellow solid.

IR: 3022, 2923, 1684, 1142 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 9.39 (s, 1 H), 7.46 (d, *J* = 7.2 Hz, 2 H), 7.16–6.93 (m, 8 H), 6.84 (s, 1 H), 6.55 (s, 1 H), 6.29 (d, *J* = 11.6 Hz, 1 H), 6.00 (d, *J* = 11.6 Hz, 1 H), 1.86 (s, 3 H).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.56 (s, 1 H), 7.71 (d, *J* = 6.5 Hz, 2 H), 7.41–7.14 (m, 9 H), 6.56–6.50 (m, 2 H), 6.12 (d, *J* = 12.0 Hz, 1 H), 1.89 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.6, 147.0, 140.3, 138.7, 137.5, 136.4, 135.2, 132.2, 130.9, 130.5, 129.4, 129.0, 128.3, 127.0, 121.0, 17.4.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{20}H_{18}O$: 274.1358; found: 274.1352.

Cyclohexadiene 28

Synthesized in a fashion analogous to that of cyclohexadiene **8**, using hexatriene **27** (2.0 mL, 64 mM in benzene-d_6, 0.13 mmol; containing 5 mol% hexamethylbenzene as an internal standard), with the exception that the reaction mixture was heated for 14 h at 75 °C. The crude product was purified by silica gel chromatography (EtOAc–hexanes, 5→35%) yielding cyclohexadiene **28**. Quantitative conversion was observed by ^{1}H NMR.

Yield: 28 mg (79%).

IR: 3059, 3025, 1672, 1579, 1493, 698 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 9.27 (s, 1 H), 7.32 (d, *J* = 7.2 Hz, 2 H), 7.20–7.00 (m, 8 H), 5.25 (d, *J* = 6.0 Hz, 1 H), 5.74 (d, *J* = 5.8 Hz, 1 H), 4.31 (s, 1 H), 3.40 (s, 1 H), 1.37 (s, 3 H).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 9.45 (s, 1 H), 7.35–7.19 (m, 10 H), 7.08 (d, *J* = 5.5 Hz, 1 H), 6.36 (d, *J* = 5.5 Hz, 1 H), 4.00 (s, 1 H), 3.56 (s, 1 H), 1.79 (s, 3 H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ = 192.5, 148.8, 144.0, 143.8, 142.3, 136.6, 129.4, 129.2, 127.74, 127.71, 127.6, 127.4, 121.2, 54.2, 44.8, 23.6.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{20}H_{18}O$: 274.1358; found: 274.1361.

Hexatriene Dimer 31

A Schlenk flask was charged with hexatriene **27** (257 mg, 0.938 mmol) and CH_2Cl_2 (8 mL) and immersed in liquid nitrogen under positive nitrogen pressure until the reaction mixture was completely

frozen. A solution of Me_2AlCl (2.6 mL, 91 mM in CH_2Cl_2, 0.234 mmol) was added dropwise to the frozen reaction mixture, after which the Schlenk flask was sealed and placed in a –65 °C bath. After being stirred for 6 h at –65 °C, the reaction mixture was quenched with H_2O (2 mL) with vigorous stirring, extracted with EtOAc (3 × 10 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by silica gel chromatography (EtOAc–hexanes, 4→15%) yielding dimer **31**.

Yield: 180 mg (70%); colorless oil.

^{1}H NMR (500 MHz, C_6D_6): δ = 7.61 (d, *J* = 7.5 Hz, 2 H), 7.29 (d, *J* = 10 Hz, 1 H), 7.26–7.20 (m, 3 H), 7.16–6.93 (m, 15 H), 6.71 (s, 1 H), 6.51 (d, *J* = 12.5 Hz, 1 H), 6.38 (s, 1 H), 6.25 (d, *J* = 12.5 Hz, 1 H), 6.11 (s, 1 H), 5.45 (d, *J* = 10 Hz, 1 H), 4.67 (d, *J* = 2.5 Hz, 1 H), 3.82 (d, *J* = 2.5 Hz, 1 H), 2.06 (s, 3 H), 1.35 (s, 3 H).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.54 (d, *J* = 7.8 Hz, 2 H), 7.37–7.19 (m, 15 H), 7.18–7.14 (m, 1 H), 7.14 (d, *J* = 7.0 Hz, 2 H), 6.92 (s, 1 H), 6.63 (s, 1 H), 6.56 (s, 1 H), 6.25 (app q, *J* = 12.5 Hz, 2 H), 5.81 (s, 1 H), 5.68 (d, *J* = 10.0 Hz, 1 H), 4.62 (d, *J* = 2.0 Hz, 1 H), 3.64 (d, *J* = 2.5 Hz, 1 H), 1.87 (s, 3 H), 1.29 (s, 3 H).

^{13}C NMR (125 MHz, CD_2Cl_2): δ = 137.8, 137.6, 137.2, 137.0, 136.2, 136.1, 136.0, 134.4, 131.7, 131.4, 130.9, 129.6, 129.5, 129.3, 129.1, 128.3, 128.1, 128.0, 127.9, 127.6, 127.2, 126.8, 126.4, 125.0, 93.6, 79.2, 73.6, 25.1, 17.1.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{40}H_{36}O_2Na$: 571.2608; found: 571.2596.

Diels–Alder Adduct 32

A round-bottom flask was charged with hexatriene dimer **31** (145 mg, 0.26 mmol) and CH_2Cl_2 (3 mL). After cooling the reaction mixture to –78 °C, a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (1 mL, 0.32 M in CH_2Cl_2, 0.32 mmol) was added dropwise. The reaction mixture was slowly warmed to 10 °C over the course of 6 h, after which it was concentrated in vacuo to give a yellow oil. The crude product was purified by silica gel chromatography to yield a 2:1 mixture of diastereomers, which were separated via reverse-phase HPLC (MeCN–H_2O, 85:15) to yield the major diastereomer **32** (43 mg, 22%) and the minor diastereomer (29 mg, 15%). Characterization data for the minor diastereomer are as follows:

^{1}H NMR (500 MHz, C_6D_6): δ = 7.90 (s, 1 H), 7.85 (d, *J* = 7.6 Hz, 2 H), 7.65 (d, *J* = 7.5 Hz, 2 H), 7.48 (d, *J* = 7.5 Hz, 2 H), 7.38 (d, *J* = 10.0 Hz, 1 H), 7.25–6.85 (m, 17 H), 6.80 (t, *J* = 7.5 Hz, 1 H), 6.69 (s, 1 H), 5.98 (s, 2 H), 5.46 (d, *J* = 10.0 Hz, 1 H), 5.18 (s, 1 H), 5.09 (s, 1 H), 4.51 (s, 1 H), 3.68 (s, 1 H), 1.31 (s, 3 H), 1.22 (s, 3 H).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.0 Hz, 2 H), 7.53–7.47 (m, 3 H), 7.46–7.15 (m, 21 H), 6.71 (s, 1 H), 5.76–5.69 (m, 3 H), 5.62 (s, 1 H), 4.97 (s, 1 H), 4.47 (s, 1 H), 3.68 (s, 1 H), 1.62 (s, 3 H), 1.36 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.7, 150.9, 137.7, 136.6, 136.3, 135.9, 135.7, 133.8, 132.5, 132.3, 132.0, 131.8, 130.7, 130.1, 129.8, 129.12, 129.07, 129.0, 128.93, 128.85, 128.7, 128.6, 128.5, 128.4, 128.1, 127.8, 127.7, 127.3, 125.5, 119.4, 88.8, 79.2, 74.4, 60.2, 53.7, 52.4, 25.8, 20.5.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{48}H_{41}O_4N_3Na$: 746.2989; found: 746.2980.

Characterization data for the major diastereomer **32** are as follows:

^{1}H NMR (500 MHz, C_6D_6): δ = 7.87 (d, *J* = 7.6 Hz, 2 H), 7.78–7.73 (m, 3 H), 7.42 (d, *J* = 10.0 Hz, 1 H), 7.33–7.28 (m, 4 H), 7.22 (t, *J* = 7.5 Hz, 2 H), 7.15–7.00 (m, 10 H), 6.94 (t, *J* = 7.7 Hz, 3 H), 6.81 (t, *J* = 7.5 Hz, 1 H), 6.32 (s, 1 H), 6.04 (s, 1 H), 5.97 (s, 1 H), 5.78 (d, *J* = 10.0 Hz, 1 H), 5.33 (s, 1 H), 5.17 (d, *J* = 4.0 Hz, 1 H), 4.61 (d, *J* = 2.5 Hz, 1 H), 3.80 (d, *J* = 2.5 Hz, 1 H), 1.26 (s, 3 H), 1.12 (s, 3 H).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.0 Hz, 2 H), 7.50–7.14 (m, 24 H), 6.60 (s, 1 H), 5.80 (s, 2 H), 5.73 (d, *J* = 10.0 Hz, 1 H), 5.67 (d, *J* = 4.5 Hz, 1 H), 5.29 (s, 1 H), 4.55 (d, *J* = 2.5 Hz, 1 H), 3.66 (d, *J* = 2.5 Hz, 1 H), 1.68 (s, 3 H), 1.19 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.7, 151.6, 137.7, 136.3, 135.9, 135.6, 135.2, 134.7, 133.0, 131.9, 131.8, 131.5, 131.4, 129.8, 129.54, 129.48, 129.08, 129.06, 128.9, 128.7, 128.63, 128.55, 128.5, 128.0, 127.8, 127.7, 127.2, 125.1, 119.9, 91.1, 79.7, 74.3, 60.6, 53.6, 52.2, 25.6, 20.5.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{48}H_{41}O_4N_3Na$: 746.2989; found: 746.2980.

Hexatriene 34

Synthesized in a fashion analogous to that of hexatriene **7**, using 4-iodo-1-phenyl-1,3-butadiene (**4**; 168 mg, 0.65 mmol), 2-tributylstannyl-2-cyclopentenone (**33**; 162 mg, 0.44 mmol), DMF (5 mL), $Pd(PPh_3)_4$ (25 mg, 0.022 mmol), copper(I) thiophene-2-carboxylate (92 mg, 0.48 mmol), and CsF (132 mg, 0.87 mmol). The reaction mixture was stirred for 1 h at 0 °C instead of 1 h at r.t. The crude product was purified by silica gel chromatography (EtOAc–hexanes, 23→25%) yielding hexatriene **34**.

Yield: 71 mg (77%); yellow oil.

IR: 2960, 2921, 2903, 1695, 1451, 993, 956, 751 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 7.31 (d, *J* = 7.5 Hz, 2 H), 7.27 (dd, *J* = 15.5, 10.5 Hz, 1 H), 7.16–7.12 (m, 2 H), 7.05 (t, *J* = 7.2 Hz, 1 H), 6.97–6.95 (m, 1 H), 6.50 (d, *J* = 15.5 Hz, 1 H), 6.39–6.29 (m, 2 H), 1.94–1.90 (m, 2 H), 1.83–1.80 (m, 2 H).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.46 (d, *J* = 7.2 Hz, 2 H), 7.37 (t, *J* = 7.4 Hz, 2 H), 7.31–7.18 (m, 1 H), 6.75 (d, *J* = 15.6 Hz, 1 H), 6.51 (t, *J* = 11.4 Hz, 1 H), 6.12 (d, *J* = 11.2 Hz, 1 H), 2.81–2.77 (m, 2 H), 2.55–2.48 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.7, 159.4, 141.4, 137.1, 135.9, 133.6, 128.8, 128.2, 126.8, 125.3, 118.6, 34.3, 27.3.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{15}H_{14}O$: 210.1045; found: 210.1046.

Cyclohexadiene 35

Synthesized in a fashion analogous to that of cyclohexadiene **8**, using hexatriene **34** (1.6 mL, 24 mM in benzene-d_6, 0.038 mmol; containing 5 mol% hexamethylbenzene as an internal standard), with the exception that the reaction mixture was heated for 20 h at 100 °C. The crude product was purified by silica gel chromatography (EtOAc–hexanes, 20→23%) yielding cyclohexadiene **35**.

Yield: 6.8 mg (85%).

IR: 3029, 2960, 1705, 1644, 1561, 1226, 764, 700 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ = 7.06–6.92 (m, 3 H), 6.88 (d, *J* = 6.5 Hz, 2 H), 6.73 (t, *J* = 4.5 Hz, 1 H), 5.89 (dd, *J* = 9.5, 5.5 Hz, 1 H), 5.72 (dd, *J* = 9.3, 5.8 Hz, 1 H), 3.19 (dd, *J* = 11.5, 5.5 Hz, 1 H), 2.91–2.80 (m, 1 H), 1.89–1.71 (m, 2 H), 1.38–1.29 (m, 1 H), 0.95–0.85 (m, 1 H).

^{13}C NMR (125 MHz, C_6D_6): δ = 203.6, 137.8, 136.6, 135.8, 129.8, 129.0, 127.8, 124.9, 124.7, 43.1, 40.5, 38.8, 23.2.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{15}H_{14}O$: 210.1045; found: 210.1048.

Dimethylaluminum Triflate

Procedure adapted from that developed by Yamamoto et al.[25] A solution of $AlMe_3$ (10 mL, 113 mM in CH_2Cl_2, 1.13 mmol) was cooled to 0 °C. To this solution was added TfOH (100 μL, 1.13 mmol) dropwise over the course of 5 min, which resulted in the evolution of a gas from the reaction mixture (CAUTION!: Care should be taken to perform this addition slowly). The reaction mixture was

stirred at 0 °C for 10 min, then warmed to r.t. and stirred for a further 10 min, after which the solution became cloudy. Concentration of the reaction mixture in vacuo yielded the title compound.

Yield: 161 mg (70%); white solid.

^{1}H NMR (400 MHz, C_6D_6): δ = –0.48 (s).

^{19}F NMR (376 MHz, C_6D_6): δ = –76.0 (s).

For reference, spectral data for trimethylaluminum are as follows:

^{1}H NMR (500 MHz, C_6D_6): δ = –0.36 (s).

Methylaluminum Diiodide

A J-Young tube was charged with aluminum iodide (84.8 mg, 0.208 mmol), benzene-d_6 (565 μL), and trimethylaluminum (435 μL, 239 mM in benzene-d_6, 0.104 mmol), giving a heterogeneous mixture. The tube was sealed and stored at r.t. for 2 h, during which time the reaction mixture became homogeneous. Concentration of the reaction mixture in vacuo yielded the title compound.

Yield: 87.3 mg (95%); white solid.

^{1}H NMR (500 MHz, C_6D_6): δ = 0.28 (s).

LRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for CH_3AlI_2: 296; found: 296.

For reference, spectral data for trimethylaluminum are as follows:

^{1}H NMR (500 MHz, C_6D_6): δ = –0.36 (s).

Hexatriene 38

A J-Young NMR tube was charged with $Sc(OTf)_3$ (45 mg, 0.093 mmol), 2,2′-isopropylidenebis[(4*S*)-4-phenyl-2-oxazoline] (82 mg, 0.22 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (23 mg, 0.11 mmol), CD_2Cl_2 (600 μL), and cyclohexadiene **36** (1.2 mL, 77 mM in CD_2Cl_2, 0.093 mmol). The NMR tube was then sealed and kept at r.t. under ambient fluorescent light for 6 d, after which time complete consumption of the starting materials was observed by ^{1}H NMR analysis. The reaction mixture was concentrated in vacuo and purified by silica gel chromatography (EtOAc–hexanes, 15→18%) yielding hexatriene **38**.

Yield: 17 mg (81%); yellow oil.

IR: 2922, 1700, 1440, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61–7.58 (m, 1 H), 7.34 (d, *J* = 7.6 Hz, 2 H), 7.29–7.24 (m, 2 H), 7.18 (t, *J* = 7.3 Hz, 1 H), 6.46 (d, *J* = 12.2 Hz, 1 H), 6.37 (s, 1 H, vinyl CH, NOE to CH_3), 6.13 (d, *J* = 12.2 Hz, 1 H), 2.60–2.55 (m, 2 H), 2.37–2.34 (m, 2 H), 1.97 (s, 3 H; CH_3, NOE to vinyl CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.6, 159.6, 141.2, 137.8, 135.0, 134.4, 129.4, 128.7, 128.3, 127.0, 119.1, 34.1, 27.3, 23.5.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{16}H_{16}O$: 224.1201; found: 224.1200.

Kinetic Analysis of the Electrocyclization of Hexatriene 7 in Various Solvents

A solution of hexatriene **7** (550 μL, 35 mM in the desired solvent, 0.0192 mmol; containing 5 mol% hexamethylbenzene as an internal standard) was added to an NMR tube, which was sealed under vacuum. The NMR tube was completely submerged in a circulating oil bath equilibrated to 100 °C; the tube was removed from the oil bath and cooled rapidly to r.t. under a stream of hexanes; the reaction was monitored for disappearance of **7** and appearance of **8** (single scan ^{1}H NMR spectroscopy using an AVB-400 spectrometer) and the tube was replaced in the oil bath. Only time spent in the oil bath was included in the concentration versus time plots. The first-order rate constants are given in Table 1.

Achiral Lewis Acid Survey

An NMR tube was charged with 2,6-di-*tert*-butyl-4-methylpyridine (3 mg, 0.0146 mmol; only added for reactions using $Cu(OTf)_2$, $Sc(OTf)_3$, and $BF_3{\cdot}OEt_2$), Lewis acid (0.0120 mmol), C_6D_6 (230 μL), and hexatriene **2** (250 μL, 48 mM in C_6D_6, 0.0120 mmol; containing 25 mol% 1,1,2,2-tetrachloroethane as an internal standard). The NMR tube was then sealed under vacuum and the reaction was monitored at regular intervals by ^{1}H NMR analysis. The reaction mixture was kept at r.t. initially, then heated in a circulating oil bath at increasing temperatures until significant conversion was observed.

The rate acceleration of the methylaluminum diiodide-catalyzed reaction shown in Table 2 was measured by assembling the reaction mixture as described above, after which the NMR tube was placed in an AV-500 NMR probe pre-equilibrated to 8.7 °C, and the reaction was monitored for disappearance of **2** and appearance of **36** (single scan ^{1}H NMR spectroscopy). The pseudo-first-order rate constant for this reaction was $1.2(2) \times 10^{-3}$ s^{-1}, which represents a 600-fold rate acceleration when compared to the first-order rate constant of 2.1×10^{-6} s^{-1} at 8.7 °C obtained by extrapolation of the Eyring plot for the thermal cyclization of **2**.[4]

Chiral Lewis Acid Survey

For the experimental procedures and results of the complete chiral Lewis acid survey, see the Supporting Information. All experiments whose results can be found in Table 3 were carried out as follows: An NMR tube was charged with 2,6-di-*tert*-butyl-4-methylpyridine (3.0 mg, 0.0146 mmol), $Sc(OTf)_3$ (5.9 mg, 0.0120 mmol), 2,6-bis[(4*R*)-4-phenyl-2-oxazolinyl]pyridine (4.4 mg, 0.0120 mmol), solvent of interest (230 μL), and hexatriene **2** (250 μL, 48 mM in solvent of interest, 0.0120 mmol; containing 25 mol% 1,1,2,2-tetrachloroethane as an internal standard). The NMR tube was then sealed under vacuum and held at r.t. for 5 h. The NMR tube was opened and the reaction mixture was quenched with H_2O (0.5 mL) and extracted with CH_2Cl_2 (3 × 1 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated in vacuo, redissolved in CH_2Cl_2 (0.4 mL), and passed through a small plug of silica gel (EtOAc–hexanes, 20%). The eluent was concentrated in vacuo and dissolved in *i*-PrOH for chiral HPLC analysis (Chiralcel OD; flow rate: 0.5 mL/min; hexanes–*i*-PrOH; t_R = 20.4, 23.1 min).

Catalytic Photochemical Electrocyclic Ring-Opening

A J-Young NMR tube was charged with $Sc(OTf)_3$ (15 mg, 0.031 mmol), 2,6-bis[(4*R*)-4-phenyl-2-oxazolinyl]pyridine (23 mg, 0.062 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (8 mg, 0.039 mmol), CD_2Cl_2 (500 μL), and enantioenriched cyclohexadiene **36** (800 μL, 39 mM in CD_2Cl_2, 0.031 mmol; containing 25 mol% 1,1,2,2-tetrachloroethane as an internal standard), obtained from the asymmetric catalyst trials described above. The reaction mixture was kept at r.t. under ambient fluorescent light and monitored over the course of 30 d. Conversion into hexatriene **38** was measured by ^{1}H NMR analysis. The enantiomeric excess of the cyclohexadiene was monitored by opening the J-Young NMR tube under an inert atmosphere, removing a 50 μL aliquot of the reaction mixture, and re-sealing the J-Young NMR tube. The aliquot was passed through a small plug of silica gel (EtOAc–hexanes, 20%). The eluent was concentrated in vacuo and dissolved in *i*-PrOH for chiral HPLC analysis [Chiralcel OD; flow rate: 0.5 mL/min; hexanes–*i*-PrOH, 98:2; t_R (cyclohexadiene **36**) = 20.4, 23.1 min, t_R (hexatriene **38**) = 25.9 min]. The results of this experiment can be found in Table 3.

X-ray Crystal Structure Determination of 32

A colorless block was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 s per frame using a scan width of 0.5°. Data collection was 97.9% complete to 25.00° in π. Indexing and unit cell refinement by CELL_NOW indicated a twinned crystal with two unique domains, both of which having the same primitive, triclinic lattice parameters. The twin law that relates the two domains is given by the 3 × 3

matrix [–1.002 –0.739 –0.003 0.005 1.002 0.005 0.005 –0.004 –1.000]. The space group was found to be P-1 (No. 2). The twinned data were integrated and separated into domains using the Bruker SAINT[26] software program and scaled using the TWINABS software program. Solution by direct methods (SHELXS-97)[27] produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97).[28] All hydrogen atoms were placed using a riding model; their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.[28] Crystallographic data for **32** can be found at the Cambridge Crystallographic Data Centre (CCDC 736749).

Supporting Information associated with this article, including the complete chiral Lewis acid survey, detection of thermal electrocyclic ring-opening, and representative kinetic plots, can be found at http://www.thieme-connect.com/ejournals/toc/synthesis.

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