Supporting Information
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On the Development of Catalytic Carba-6π Electrocyclizations

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Supporting Information

S1. Complete Chiral Lewis Acid Survey

We began our screen for asymmetric catalysis of the electrocyclization of triene 2 by employing chiral alkoxyaluminum catalysts (Table S1, entries 1-3). No rate acceleration or enantioenrichment was observed with alkoxyaluminum catalysts, and we attributed this to lone pair donation from oxygen into the empty p orbital of the aluminum center, weakening the Lewis acidity of the catalyst. We therefore turned our attention to chiral aluminum bis-triflamide catalysts, in the hopes that the triflate groups would be sufficiently electron withdrawing to minimize the donation of the nitrogen lone pairs to the aluminum p orbital. Low levels of enantioselectivity as well as decomposition were observed using aluminum bis-triflamide catalysts (Table S1, entries 4-7). Though the level of enantioselectivity is low in these cases, they did serve as an initial indication that highly efficient catalytic asymmetric electrocyclizations might be possible. Corey’s oxazaborolidinium catalyst (Table S1, entry 8) resulted in significant product enantioenrichment. One limitation to the use of this catalyst is its decomposition above 25 ºC, precluding its use with substrates whose thermal electrocyclization barriers are too great, unless larger rate accelerations are achieved or long reaction times employed. The chiral cobalt and chromium-salen complexes shown (Table S1, entries 9, 10) did not catalyze the reaction, and neither did the in-situ-formed copper bis-oxazoline catalyst (Table S1, entry 11). We were pleased to find that scandium bis-oxazoline and the well-established scandium pybox catalysts resulted in significant enantioenrichment (Table S1, entries 12, 13). Thioureas did not catalyze the reaction, presumably due to the relatively high thiourea pKa (Table S1, entries 14, 15). The stronger N-triflyl phosphoramidite Brønsted acid catalysts, which were generously donated by the group of Prof. Hisashi Yamamoto, were met with more success. The phosphoramidite catalyst (Table S1, entry 16) resulted in a low level of enantioselectivity, however the thiophosphoramidite catalyst (Table S1, entry 17) gave no apparent rate acceleration and no enantioenrichment. In all of the above cases, approximate rate accelerations were obtained by measuring a half-life for the reaction via periodic 1H NMR analysis and comparing it to that of the thermal reaction.

Table S1 Trials of catalysts for the electrocyclization of 2 in the presence of catalyst (1 equiv) and 2,6-di-tert-butyl-4-methylpyridine (1.2 equiv). Tf = trifluoromethanesulfonyl; Decomp. = complete substrate decomposition observed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>e.e. (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Catalyst 1" /></td>
<td>C₆D₆; 1 h, r.t., then 6 h, 45 ºC</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Catalyst 2" /></td>
<td>C₆D₆; 1 h, r.t., then 6 h, 45 ºC</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Catalyst 3" /></td>
<td>C₆D₆; 2 h, r.t., then 2 h, 55 ºC</td>
<td>0</td>
</tr>
</tbody>
</table>
4  \[ \text{C}_6\text{D}_6; 3 \text{ h, r.t.} \]

5  \[ \text{C}_6\text{D}_6; 2 \text{ h, r.t., then 1.5 h, 55 °C} \]

6  \[ \text{C}_6\text{D}_6; 1 \text{ h, r.t.} \]  decomp.

7  \[ \text{C}_6\text{D}_6; 2 \text{ h, r.t., then 1 h, 45 °C} \b \]  decomp.

8  \[ \text{C}_6\text{D}_6; 2 \text{ h, r.t.} \]

9  \[ \text{C}_6\text{D}_6; 1 \text{ h, r.t., then 3 h, 45 °C} \b \]

10  \[ \text{C}_6\text{D}_6; 1 \text{ h, r.t., then 3 h, 45 °C} \b \]

11  \[ \text{THF-}d_8; 1 \text{ h, r.t., then 3 h, 45 °C} \]

12  \[ \text{THF-}d_8; 3 \text{ h, r.t.} \]

13  \[ \text{THF-}d_8; 1 \text{ h, r.t., then 1 h, 35 °C} \]

14  \[ \text{C}_6\text{D}_6; 2 \text{ h, r.t., then 2 h, 45 °C} \]

15  \[ \text{C}_6\text{D}_6; 2 \text{ h, r.t., then 2 h, 45 °C} \]

16  \[ \text{C}_6\text{D}_6; 1 \text{ h, r.t., then 5 h, 45 °C} \b \]

\[ Ar = 2,4,6-i\text{Pr}_3\text{cymyl} \]
As the scandium pybox catalysts from the above screen provided the most promising lead, we next screened a series of pybox ligands. This screen was conducted in dichloromethane, and phenyl and indenyl pybox ligands proved optimal for this reaction (Table S2). Of note also is the switch in the sense of enantioinduction using phenyl- and isopropyl-substituted pybox ligands of the same enantiomeric series.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>e.e. (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="#" alt="Catalyst 1" /></td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td><img src="#" alt="Catalyst 2" /></td>
<td>-27</td>
</tr>
<tr>
<td>3</td>
<td><img src="#" alt="Catalyst 3" /></td>
<td>-13</td>
</tr>
<tr>
<td>4</td>
<td><img src="#" alt="Catalyst 4" /></td>
<td>42</td>
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</tbody>
</table>

S2. Thermal Electroyclic Ring-Opening

Thermal electrocyclic ring-opening was detected by monitoring the e.e. of a heated enantioenriched solution of cyclohexadiene 36 in C₆D₆ (Scheme S1 and Table S3). No degradation of enantioenrichment was observed until the solution was heated to 150 °C, at which point the e.e. slowly degraded over the course of days. No decomposition of cyclohexadiene was observed by ¹H NMR analysis of the same reaction mixture. These observations are consistent with thermal electrocyclic ring-opening followed by cyclization to racemic cyclohexadiene. The elevated temperatures required for this process lead us to conclude that this pathway is not active in the catalytic studies outlined above.
Scheme S1 Detection of the thermal electrocyclic ring-opening of 36.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>e.e. of unreacted 36 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initial</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>21 h, 100 ºC</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>17 h, 150 ºC</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>34 h, 150 ºC</td>
<td>32</td>
</tr>
</tbody>
</table>

All reactions and manipulations, unless otherwise noted, were carried out in an inert atmosphere (N₂) glovebox. 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 ºC for at least 12 h prior to use. Enantiomeric excess was determined using a Shimadzu 10A VP Series Chiral HPLC with detection at 230, 254, and 280 nm. Benzene was dried and purified by passage through a column of activated alumina under N₂ pressure followed by sparging with N₂. C₆D₆, tetrahydrofuran-d₈, and CD₂Cl₂ were obtained from Cambridge Isotope Labs, Inc. C₆D₆ was sparged with N₂ and stored over activated 4 Å molecular sieve pellets overnight. Tetrahydrofuran-d₈ was vacuum transferred from purple sodium benzophenone/ketyl, degassed with three freeze-evacuation-thaw cycles, and stored over activated 4 Å molecular sieve pellets. CD₂Cl₂ was vacuum transferred from CaH₂ and degassed with three freeze-evacuation-thaw cycles. Activated 4 Å molecular sieve pellets were obtained from Sigma-Aldrich and heated at 150 ºC under vacuum for 24 h. 1,1,2,2-tetrachloroethane, obtained from Sigma-Aldrich, was sparged with N₂ 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 ºC for 12 h. Cu(OTf)₂, Me₃Al, Me₂AlCl, (R,R)-N,N’-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II), (R,R)-N,N’-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocromium(III) chloride, 2,2’-isopropylidenebis[(4S)-4-phenyl-2-oxazoline], 2,6-bis[(4R)-4-phenyl-2-oxazolyl]pyridine, 2,6-bis[(4R)-4-isopropyl-2-oxazolyl]pyridine, 2,6-bis[[4S,5S]-4-methyl-5-phenyl-2-oxazolyl]pyridine, 2,6-bis[(3aS,8aR)-3a,8a-dihydro-8H-indeno(1,2-d)oxazolyl]pyridine, (2S)-3,3-dimethyl-2-[[[(1R,2R)-2-(2-methyl-5-phenyl-1-pyrrolyl)cyclohexyl][thioureido]-N,N-bis(2-isobutyl)butanamide, (S)-2-[[3,5-bis(trifluoromethyl)phenyl][thioureido]-N-benzyl-N,3,3-trimethylbutanamide, and 2,6-di-tert-butyl-4-methylpyridine were obtained from Sigma-Aldrich; (S)-1,1’-bi(2-naphthol) was obtained from Fluka; (4R,5R)-2,2-Dimethyl-α,α’,α”-tetraphenyldioxolane-4,5-dimethanol was obtained from Acros Organics; N-trifyl phosphoramidé and N-triflyl thiophosphoramides catalysts were obtained from Prof. Hisashi Yamamoto at the University of Chicago; these reagents were used without further purification. N,N’-((2S,2'S)-((2,2,2-trifluoroethyl)azanediyl)bis(3-methylbutane-2,1-diyl))bis(1,1,1-trifluoromethanesulfonamide), (1R,1’R)-2,2’-(benzylazanediyl)bis(1-phenylethanol), (1R,2R)-1,2-N,N’-bis(trifluoromethanesulfonylamino)cyclohexane, (1R,2R)-1,2-N,N’-bis(trifluoromethanesulfonylamino)-1,2-diphenylethane, (R)-2,2’-...
bis(trifluoromethanesulfonlamino)-1,1’-binaphthyl,\textsuperscript{12,15} and (S)-3,3-diphenyl-1-o-tolyltetrahydropyrrolo[1,2-c][1,3,2]oxazaborolidinium triflimide,\textsuperscript{3} were synthesized according to literature procedures. Characterization data for these compounds agree with literature values.

**Representative Procedure for Chiral Lewis Acid Survey**

An NMR tube was charged with 2,6-di-\textit{tert}-butyl-4-methylpyridine (3 mg, 0.0146 mmol), chiral catalyst (0.0120 mmol), solvent of interest (230 \( \mu \)L), and triene \textit{2} (250 \( \mu \)L, 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 the reaction was monitored at regular intervals via \textit{1H} NMR. The reaction mixture was kept at room temperature initially and heated in a circulating oil bath at increasing temperatures until significant conversion was observed. Upon reaction completion the NMR tube was opened and the reaction mixture was quenched with H\(_2\)O and extracted three times with dichloromethane. The combined organic extracts were dried over MgSO\(_4\), filtered, concentrated \textit{in vacuo}, re-dissolved in dichloromethane, and passed through a small plug of silica gel (20% EtOAc in hexanes). The eluent was concentrated \textit{in vacuo} and dissolved in \textit{iPrOH} for chiral HPLC analysis (Chiralcel OD, flow rate 0.5 mL/min, 98:2 hexanes:\textit{iPrOH}, \textit{Tr} = 20.4, 23.1 min).

**Synthesis of Chiral Aluminum Catalysts (Table S1, entries 1-7).**

A five dram scintillation vial was charged with the diol or bis-triflamide of interest (1 equiv) and benzene such that the solution was 0.1 M in diol or bis-triflamide. To this solution was added Me\(_3\)Al or Me\(_2\)AlCl (1 equiv, 240 mM in benzene) dropwise at room temperature. After stirring the reaction mixture for 5 min, the vial was capped. After a further 2 h, the reaction mixture was concentrated \textit{in vacuo} and dissolved in the deuterated solvent of interest for use in the catalyst screen.

**Thermal Electrocyclic Ring-Opening**

A solution of enantioenriched cyclohexadiene \textit{36} (1.8 mL, 12.4 mM in benzene-\textit{d\(_6\)}, 0.022 mmol; containing 25 mol% 1,1,2,2-tetrachloroethane as an internal standard), obtained from the asymmetric catalyst trials described above, was heated in a sealed J-Young NMR tube in a circulating oil bath. The reaction mixture was monitored for decomposition by \textit{1H} NMR analysis. The enantiomeric excess of the cyclohexadiene was monitored by opening the J-Young NMR tube under an inert atmosphere, removing a 50 \( \mu \)L aliquot of the reaction mixture, and re-sealing the J-Young NMR tube. The aliquot was passed through a small plug of silica gel (20% EtOAc in hexanes). The eluent was concentrated \textit{in vacuo} and dissolved in \textit{iPrOH} for chiral HPLC analysis (Chiralcel OD, flow rate 0.5 mL/min, 98:2 hexanes:\textit{iPrOH}, \textit{Tr} = 20.4, 23.1 min). The results of this experiment can be found in Table S3.

**Representative Kinetic Plots for the Electrocyclization of Triene 7 in Various Solvents.**
Figure S1. Representative kinetic plot and least-squares fit of the electrocyclization of 7 in CD$_2$Cl$_2$ at 100 °C.

Figure S2. Representative kinetic plot and least-squares fit of the electrocyclization of 7 in CD$_3$NO$_2$ at 100 °C.
Figure S3 Representative kinetic plot and least-squares fit of the electrocyclization of 7 in CD$_3$OD at 100 ºC.

Figure S4 Representative kinetic plot and least-squares fit of the electrocyclization of 7 in acetone-d$_6$ at 100 ºC.

Representative Kinetic Plot for the Methylaluminum Diiodide Catalyzed Electrocyclization of Triene 2.
Figure S5 Representative kinetic plot and least-squares fit of the MeAlI₂-catalyzed electrocyclization of 2 in C₆D₆ at 9 ºC.

References