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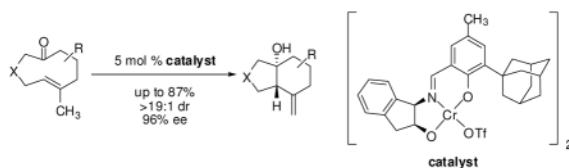
## Enantioselective Catalytic Transannular Ketone-Ene Reactions

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### Abstract



Highly enantio- and diastereoselective transannular ketone-ene reactions are catalyzed by a new chromium(III) triflate tridentate Schiff-base complex. Electronically unactivated keto-olefins undergo hetero-ene reactions at ambient temperature to afford enantioenriched bicyclic alcohols, common structural motifs in natural products. The kinetic resolution of a configurationally stable planar-chiral cyclodecenone is also described.

Transannular chemical reactions are noteworthy for generating structurally and stereochemically rich products from relatively simple precursors in a single transformation.<sup>1</sup> Recently, we and others identified the first applications of chiral catalysts to promote transannular transformations, thereby achieving absolute stereocontrol in Diels–Alder, aldol, and Claisen-rearrangement reactions.<sup>2,3,4</sup> Motivated by the power of ene-type reactions in organic synthesis, we became interested in extending the asymmetric catalytic transannular reaction concept to this important class of C–C bond-forming reactions (Figure 1).<sup>5,6</sup>

Ketones are generally very poor reacting partners in Lewis acid-catalyzed processes, including hetero-ene reactions, and to date enantioselective catalytic ketone-ene reactions have only been achieved with highly electrophilic ketones bearing strongly electron-withdrawing substituents that often allow for two-point binding to the catalyst.<sup>7,8</sup> Given that the transannular disposition of reacting partners can confer significant entropic advantage and corresponding reactivity enhancements, we considered the possibility of effecting enantioselective transannular ene reactions of electronically unactivated ketones. We were particularly interested in studying the intramolecular ketone-ene reaction of (*E*)-cyclodecenones, as the resulting products contain a decalinol framework that is prevalent in terpene natural products (Figure 1).<sup>9</sup> This effort would necessarily take into consideration the known temperature-dependent planar chirality of medium-ring cyclic (*E*)-olefin substrates.<sup>10</sup> In that context, Barriault has studied diastereoselective ketone-ene reactions of (*E*)-cyclodecenones and has shown that those cyclic structures were configurationally flexible under the elevated temperatures of the thermal reaction (140–220 °C).<sup>11</sup> For

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Supporting Information Available Complete experimental procedures, characterization data, <sup>1</sup>H and <sup>13</sup>C NMR spectra of all ketone-ene substrates and products, and crystallographic data for the *p*-bromo-benzoate of **4a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

efficient, enantioselective transannular ene reactions to be possible, the reaction must necessarily occur under conditions where interconversion of the enantiomeric conformers of the substrate takes place. Herein, we report highly diastereo- and enantioselective transannular ketone-ene reactions catalyzed by a new chromium(III) tridentate Schiff-base complex.

5-methyl-(*E*)-cyclodecenone **1a** was chosen as a model substrate and was readily synthesized from cyclohexene oxide in four steps (Scheme 1).<sup>12</sup> A copper-catalyzed epoxide-opening with isopropenyl magnesium bromide and a subsequent Swern oxidation afforded unconjugated enone **2**. Vinylmagnesium bromide addition provided the desired *trans*-substituted cyclohexanol **3** in 20:1 dr and 55% isolated yield over the three steps. Exposure of the divinyl alcohol to potassium hydride and 18-crown-6 promoted an anionic oxy-Cope rearrangement and yielded cyclodecenone **1a** as the exclusive olefin isomer.<sup>13</sup>

Chiral chromium(III) tridentate Schiff-base complexes,<sup>14</sup> which have been shown to activate aldehydes and quinones through single-point binding, were uniquely effective in catalyzing the ketone-ene reaction of **1a** (Table 1).<sup>15</sup> For example, in the presence of dimeric chromium chloride complex **5a**,<sup>16</sup> *trans*-decalinol **5a** was obtained in modest enantioenrichment, excellent diastereoselectivity, and as a single olefin regioisomer (entry 2). Pronounced effects of the catalyst counterion on the reaction outcome, were observed, with reactivity increasing steadily with decreasing coordinating ability of the counterion. Catalysts **5e** and **5f**, bearing PF<sub>6</sub><sup>-</sup> and SbF<sub>6</sub><sup>-</sup> counterions, respectively, promoted complete conversion within 24 h, albeit with diminished enantioselectivities (entries 7 and 8).<sup>17,18</sup> Complexes bearing sulfonate counterions were somewhat less reactive, but induced significantly improved enantioselectivities (entries 3 and 4), with triflate complex **5c** identified as the optimal catalyst. The high substrate conversion along with high product enantioenrichment confirmed that substrate **1a** is configurationally dynamic under the reaction conditions.<sup>19</sup> The use of activated desiccant was found to be essential for catalytic activity, as the corresponding reaction conducted in the absence of activated 4 Å molecular sieves afforded significantly lower conversion (entry 5).<sup>20</sup>

The substrate scope of the enantioselective transannular ketone-ene reaction with catalyst **5c** was evaluated (Table 2).<sup>21</sup> Full conversion of cyclodecenone **1a** was achieved by extending the reaction time to 48 h, and product **4a** was obtained in 81% yield and 93% ee. While gem-dimethyl-substituted *trans*-decalinols **4b** and **4c**, were accessed in high yield and enantioselectivity (entries 2 and 3), the closely analogous product **4d** was obtained in low yield and as a racemate (entry 4). Analysis of the chair-chair conformations of these substrates provides a plausible explanation (Figure 2).<sup>22</sup> Only cyclodecenone **1d** possesses a *syn*-pentane relationship between its methyl substituents, and the pseudo-axial methyl substituent at C3 is also likely to interfere with complexation of the Lewis acidic catalyst

With these substitution effects in mind, we probed more highly functionalized substrates (entries 5 and 6). The acid-sensitive acetal **1e** and unconjugated diene **1f** both proved to be effective substrates, affording the corresponding ene products in high enantioselectivities and good yields. Additionally, ether **6** and cyclononene **8** underwent enantioselective ketone-ene reactions to afford the corresponding bicyclic alcohol products, although in diminished yields and enantioselectivities.

Tetrasubstituted alkene **10** proved much less reactive than trisubstituted olefins **1a-f** under the catalytic conditions, undergoing only 19% conversion after 24 h at 50°C. The transannular ketone-ene reaction afforded *trans*-decalinol **11**, bearing a quaternary stereocenter, in 12% yield and 73% ee (Scheme 2). Cyclodecenone (+)-**10** was recovered in 69% yield and in 10% ee, confirming that this substrate undergoes racemization slowly

under the catalytic conditions, and that complex **5c** had induced a measurable kinetic resolution.<sup>23</sup>

In conclusion, we have demonstrated that chiral chromium(III) tridentate Schiff-base complex **5c** catalyzes transannular ketone-ene reactions of medium-sized cyclic keto-(*E*)-olefins in high diastereo- and enantioselectivity to access fused bicyclic alcohols. Significantly, the transannular strategy allows electronically unactivated ketones to be engaged as substrates in a chiral Lewis acid-catalyzed process. This approach is most effective in the case of (*E*)-cyclodecenones that lack  $\alpha$ -substitution, as the reactive components are held in close proximity and in proper alignment for the productive ketone-ene reaction.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

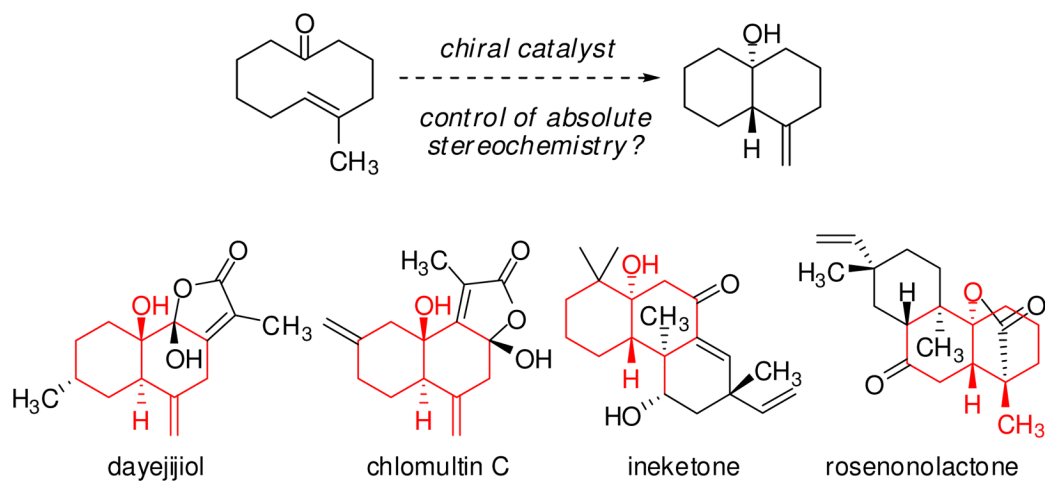
## Acknowledgments

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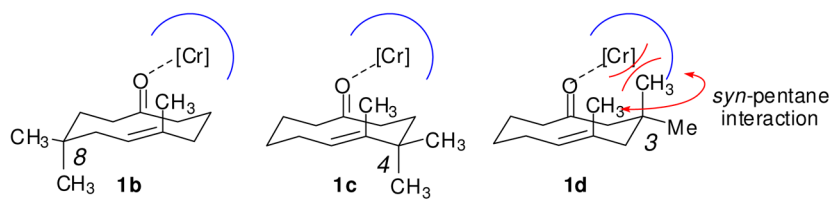
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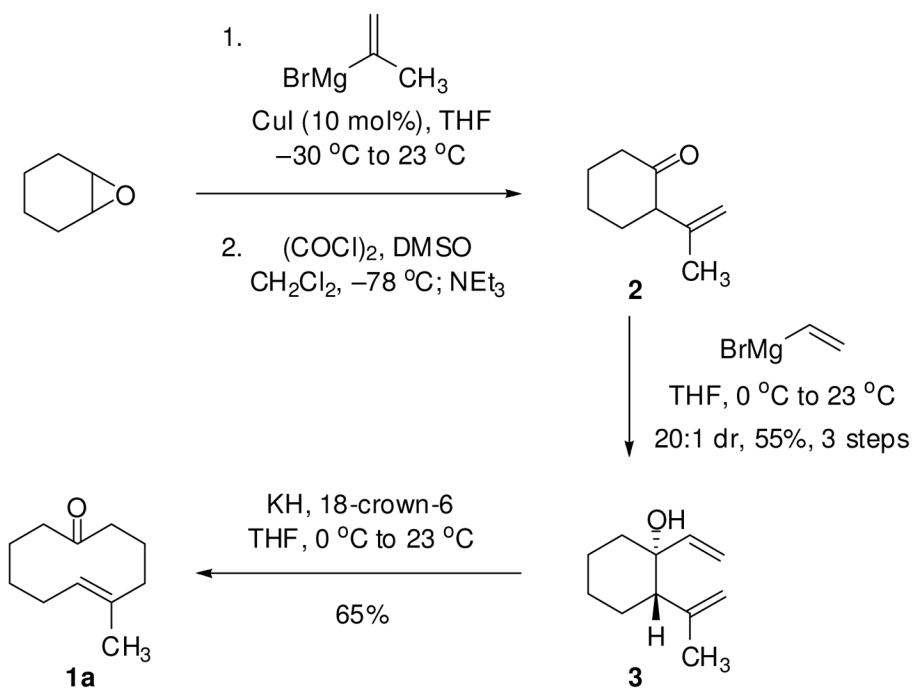
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17. Catalyst **5f** has been shown to induce superior reactivity and enantioselectivity relative to catalyst **5a** in hetero-Diels–Alder reactions. See refs. 14a and 16.
18. The transannular ketone-ene reaction conducted with complex **5f** afforded minor olefin byproducts (<10%). This outcome is an indication of diminished regioselectivity with this more Lewis acidic catalyst and suggests that this catalyst may promote a stepwise ketone-ene reaction.
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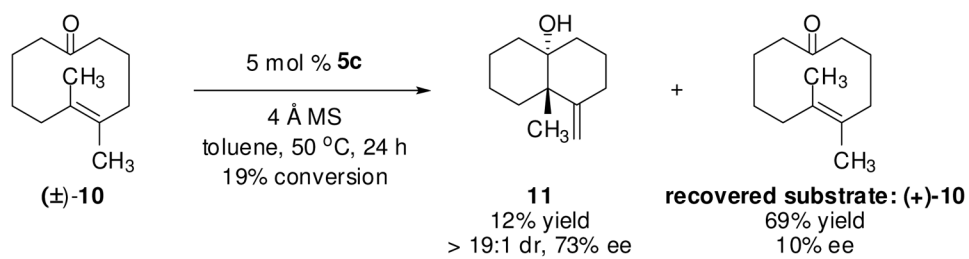
**Figure 1.** Proposed enantioselective catalytic transannular ketone-ene reaction and selected examples of natural products featuring *trans*-decalinol frameworks



**Figure 2.** Conformational analysis to account for the low reactivity observed for cyclodecenone **1d** relative to **1b** and **1c**.



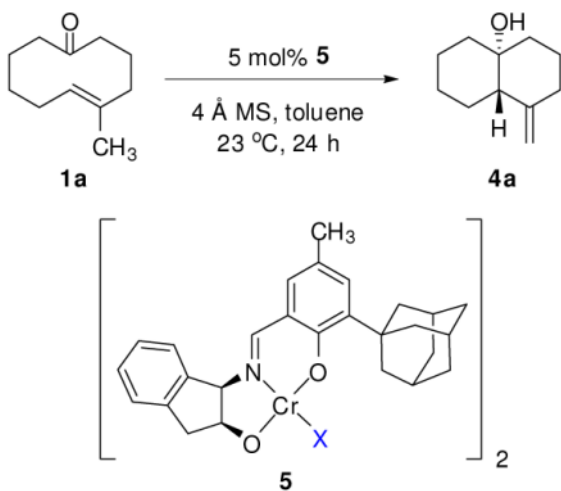
**Scheme 1.**  
Synthesis of Cyclodecenone **1a**



**Scheme 2.**  
Kinetic Resolution of Planar Chiral Cyclodecenone ( $\pm$ )-**10** by a Cr(III)-Catalyzed Transannular Ketone-Ene Reaction



Table 1

Catalyst Evaluation for the Enantioselective Transannular Ketone-Ene Reaction of Cyclodecenone **1a**.<sup>a</sup>

entry	catalyst	conv (%) <sup>b</sup>	dr <sup>c</sup>	<b>4a</b> ee (%) <sup>d</sup>
1	none	<1	–	–
2	<b>5a</b> (X = Cl)	50	>19:1	60
3	<i>ent-5b</i> (X = OTs)	67	>19:1	–84
4	<b>5c</b> (X = OTf)	76	>19:1	93
5 <sup>e</sup>	<b>5c</b> (X = OTf)	6	>19:1	n.d.
6	<b>5d</b> (X = NTf <sub>2</sub> )	98	>19:1	46
7	<b>5e</b> (X = PF <sub>6</sub> )	100	>19:1	50
8	<b>5f</b> (X = SbF <sub>6</sub> )	100	>19:1	56

<sup>a</sup>Reactions were performed on a 0.2 mmol scale with 5 mol % catalyst **5** (10 mol % based on Cr) and in the presence of powdered 4 Å molecular sieves at 23 °C in anhydrous toluene ([**1a**] = 4 M).

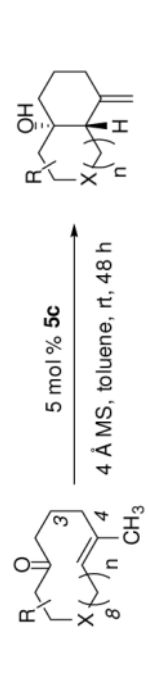
<sup>b</sup>Determined by GC analysis of the crude reaction mixtures using dodecane as an internal standard.

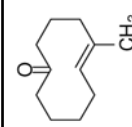
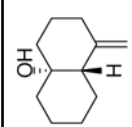
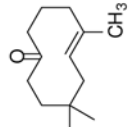
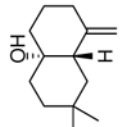
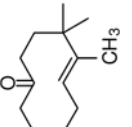
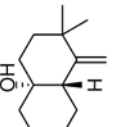
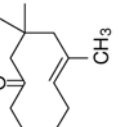
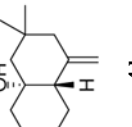
<sup>c</sup>Determined by <sup>1</sup>H NMR analysis of the crude reaction mixtures.

<sup>d</sup>Determined by GC analysis using commercial chiral columns.

<sup>e</sup>Reaction performed in the absence of powdered 4 Å molecular sieves. n.d = not determined.

Table 2

Substrate Scope of the Enantioselective Transannular Ketone-Ene Reaction<sup>a</sup>


entry	substrate	product <sup>b</sup>	yield (%) <sup>c</sup>	dr <sup>d</sup>	ee (%) <sup>e</sup>
1			81	>19:1	93
2			96	>19:1	94
3			84	>19:1	94
4			32 <sup>f</sup>	>19:1	0

entry	substrate	product <sup>b</sup>	yield (%) <sup>c</sup>	dr <sup>d</sup>	ee (%) <sup>e</sup>
5			87	>19:1	96
6			62	>19:1	94
7 <sup>g</sup>			13	>19:1	49
8 <sup>g</sup>			18	>19:1	68

<sup>a</sup>Reactions were performed on a 0.2 mmol scale with 5 mol % catalyst **5c** (10 mol % based on Cr) and in the presence of powdered 4 Å molecular sieves at 23 °C in anhydrous toluene ([**substrate**] = 4 M). Unless otherwise noted, reactions showed complete conversion after 48 h and the bicyclic alcohol product was obtained as a single regioisomer.

<sup>b</sup>The absolute configuration of **4a** was determined by X-ray crystallographic analysis of the corresponding *p*-bromobenzoate. The stereochemistry of all other products is assigned by analogy.

<sup>c</sup>Isolated yield of the ketone-ene products following purification by flash chromatography

<sup>d</sup>Determined by <sup>1</sup>H NMR analysis of the crude reaction mixtures.

<sup>c</sup>Determined by GC analysis using commercial chiral columns.

<sup>f</sup>Combined yield of **4d** and an inseparable regioisomeric product. This reaction went to 70% conversion after 48 h.

<sup>g</sup>Reaction time was 24 h.