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## Enantioselective Intramolecular Aldehyde $\alpha$ -Alkylation with Simple Olefins: Direct Access to Homo-Ene Products

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### Abstract

A highly selective method for the synthesis of asymmetrically substituted carbocycles and heterocycles from unactivated aldehyde–olefin precursors has been achieved via enantioselective SOMO-catalysis. Addition of a catalytically generated enamine radical cation across a pendent olefin serves to establish a general asymmetric strategy towards the production of a wide range of formyl-substituted rings with alkene transposition. Conceptually, this novel mechanism allows direct access to “homo-ene” type products.

Carbocyclic and heterocyclic ring systems bearing asymmetric substitution patterns are widely distributed among medicinal agents and bioactive natural products.<sup>1</sup> A preeminent goal of organic synthesis is the development of technologies to enable the rapid and enantioselective construction of these high-value cyclic substructures from simple starting materials.<sup>2</sup> Along these lines, the powerful carbonyl-ene cyclization delivers stereochemically complex small ring systems from achiral aldehyde–olefin precursors in a routine and predictable fashion through a mechanism that does not require pre-functionalization of the olefin component.<sup>3</sup> This fundamental transformation has been widely studied and a number of catalytic enantioselective carbonyl-ene protocols have been developed.<sup>4,5</sup> Expanding upon this general concept, we sought to invent a one-carbon extended, “homo-ene” variant, wherein unactivated substrates undergo asymmetric  $\alpha$ -carbonyl cyclization through a SOMO-activation mechanism, to stereoselectively generate cyclic adducts bearing synthetically useful aldehyde and olefin functional handles. We describe herein the development of the first asymmetric “homo-ene” cyclization, a transformation we anticipate will be of significant value to the chemical synthesis community.

### Design Plan

In 2007, our laboratory introduced a mode of asymmetric activation termed SOMO (singly occupied molecular orbital) organocatalysis.<sup>6</sup> Subsequent to our initial discovery, we have established SOMO organocatalysis as a remarkably robust and versatile activation platform, capable of facilitating a range of previously elusive transformations, including direct enantioselective  $\alpha$ -allylic alkylation,<sup>7</sup>  $\alpha$ -enolation,<sup>8</sup>  $\alpha$ -vinylation,<sup>9</sup>  $\alpha$ -chlorination,<sup>10</sup> and  $\alpha$ -arylation,<sup>11</sup> as well as polycyclization<sup>12</sup> and cycloaddition<sup>13</sup> to generate cyclohexyl rings and pyrrolidines. Recently, we questioned whether the SOMO platform might be leveraged for the development of an asymmetric  $\alpha$ -carbonyl “homo-ene” cyclization of unactivated aldehyde–olefin substrates. While the traditional carbonyl-ene cyclization proceeds through

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**Supporting Information Available.** Experimental procedures and spectral data are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

a LUMO-lowered  $2\pi$ -electron pathway, the SOMO activation mode is distinguished by an electrophilic  $3\pi$ -electron species (**1-he**). Based on precedent from our lab,<sup>6–13</sup> we anticipated that this enamine radical cation would add stereoselectively from the unshielded *Re*-face to the pendent olefin, thus generating a transient alkyl radical. Operation of a radical-polar crossover mechanism<sup>14</sup> would serve to oxidize the radical to the corresponding carbocation (**2**). Finally, deprotonation and hydrolysis would regenerate the amine catalyst and deliver the enantioenriched cyclized product. Central to the proposed strategy was our expectation that cyclization would proceed via a highly ordered chair-*E* transition state<sup>15</sup> (**1-he**) to deliver the product with *trans* diastereoselectivity in a fashion that is highly analogous to the venerable ene  $2\pi$ -electron pathway (**1-ene**). Notably, this study would require only simple olefins as the tethered SOMO-phile component, a substantial expansion of the scope and utility of this enantioselective oxidation pathway.<sup>16</sup>

## Results

The proposed transformation was first evaluated in the context of the amine-tethered prenyl aldehyde substrate **3**. As presented in Table 1, treatment of this aldehyde with base and Fe(III)trisphenanthroline in the presence of an imidazolidinone catalyst (**5**, **6**, or **7**) led to the stereoselective formation of piperidine **4** with high levels of *trans* diastereoselectivity and enantiocontrol. Optimal selectivities were obtained with the naphthyl-bearing amine catalyst **7**, presumably due to enhanced facial shielding of the SOMO intermediate (**1-he**). Variation of the counterion ( $X^-$ ) in the Fe(III)trisphenanthroline salt revealed the soluble trisbistriflamide salt to be most effective (entry 6).

Having identified optimal conditions for the organocatalytic “homo-ene” reaction, we next explored the scope of the reaction with respect to the tethering moiety. As shown in Table 2, the method was found to readily accommodate significant structural diversity in the linker, offering enantioselective access to a wide range of 5- and 6-membered carbocyclic and heterocyclic ring systems. Under our conditions, achiral substrates were cyclized to generate piperidine, pyrrolidine, tetrahydropyran, tetrahydrofuran, cyclopentane, and cyclohexane motifs with good to excellent diastereoselectivity (>20:1), enantioselectivity (85–99%) and yield (62–95%). Notably, the formation of tetrahydrofuran and pyrrolidine adducts was achieved without  $\beta$ -oxy or  $\beta$ -amino elimination from the corresponding aldehyde precursors (entries 2 and 3), demonstrating the mild conditions employed in generating the  $3\pi$ -electron activated intermediate. The products depicted in Table 2 represent important structural motifs that are widely encountered throughout natural product synthesis and drug discovery.<sup>1</sup>

The reaction is also tolerant of a broad array of olefin systems as suitable  $\pi$ -nucleophiles for this homo-ene type cyclization. As highlighted in Table 3, alkylidene cycloalkanes of various ring sizes readily undergo enantioselective C–C bond formation to generate the corresponding bicyclic products in good yield and with excellent stereocontrol (entries 1–3). In addition,  $\alpha$ -carbonyl cyclization using styrenyl olefins is readily accomplished (entry 4). Importantly, non-symmetrical 1,2,2-trisubstituted alkenes, e.g. bearing methyl and cyclohexyl groups, can generate the purported carbocation intermediate (**2**) before undergoing selective deprotonation to generate single olefin-transposition regioisomers (entry 6, >98:2 rr). We note that, at this stage, unfunctionalized 1,2-disubstituted olefins are not effective substrates for this transformation, presumably due to the higher oxidation potential for conversion of secondary radicals to secondary cations in comparison to their tertiary radical counterparts.<sup>17</sup> Despite this current limitation in scope, cycloadducts bearing monosubstituted olefin substituents are nonetheless readily accessible from allyl silane precursors (entry 5).

We next sought to examine the ability of the amine catalyst to override the influence of stereochemical information already present on the intramolecular cyclization substrate. We recognized that if catalyst-controlled stereodifferentiation could be achieved, it should be possible to selectively generate a diverse array of highly complex cyclic systems bearing three or more contiguous stereocenters. As shown in Table 4, enantioenriched aldehyde substrates incorporating  $\beta$ -methyl substitution (99% ee) were subjected to our ring-closing conditions with either the *S,S*-**7** or *R,R*-**7** catalyst. Remarkably, catalyst-mediated cyclization in both enantiomeric series successfully delivered ring systems bearing three contiguous stereocenters, with excellent selectivity for the *trans*-stereochemical relationship across the newly forming bond. In each case, the amine catalyst strongly dictated the diastereochemical outcome, effectively overriding the influence of the substrate  $\beta$ -methyl stereocenter with either catalyst antipode. Presumably, the steric demand of the amine catalyst provides a major conformational lock, enforcing a chair-*E* transition state (see **8** and **9**) and thereby matching or overriding the inherent substrate bias.

Finally, in an extension of the findings shown in Table 4, we have developed a simple two-step organocatalytic protocol by which to achieve the overall conversion of simple achiral aldehydes to stereochemically complex cyclic adducts. As shown in Scheme 1, substrates **10** and **11** were subjected to sequential enantioselective organocatalytic transfer hydrogenation (using catalyst **12**) followed directly by asymmetric homo-ene cyclization (using either enantiomer of catalyst **7**) to generate the observed products in good overall yield and with excellent selectivity. The transformations depicted in Scheme 1 serve to highlight the ability of the SOMO-mediated homo-ene technology to effect the rapid production of stereochemical complexity in cyclic architectures.

In summary, enantioselective SOMO-organocatalysis has been leveraged for the development of a potentially general approach toward the synthesis of stereochemically rich carbocycles and heterocycles from achiral precursors. This protocol bears analogy to the venerable carbonyl-ene cyclization, yet provides access to a differentiated array of complex cyclic scaffolds incorporating valuable aldehyde and olefin functional handles. We anticipate that this method will find broad application among practitioners of organic synthesis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

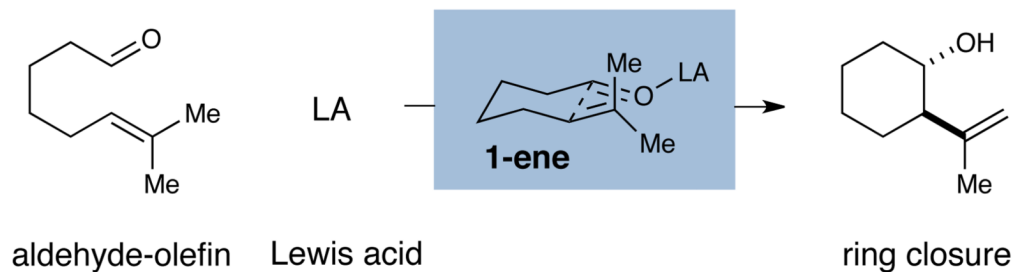
Financial support was provided by the NIHGM5 (R01 GM103558-01) and kind gifts from Merck, Amgen and Abbvie.

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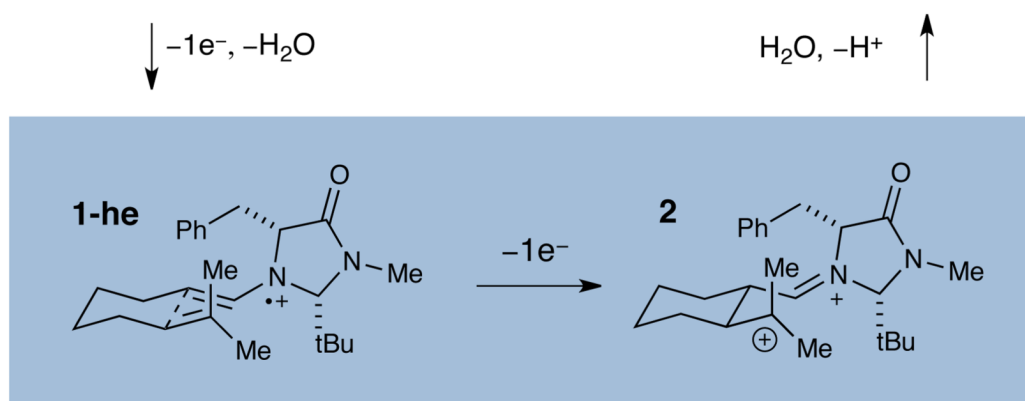
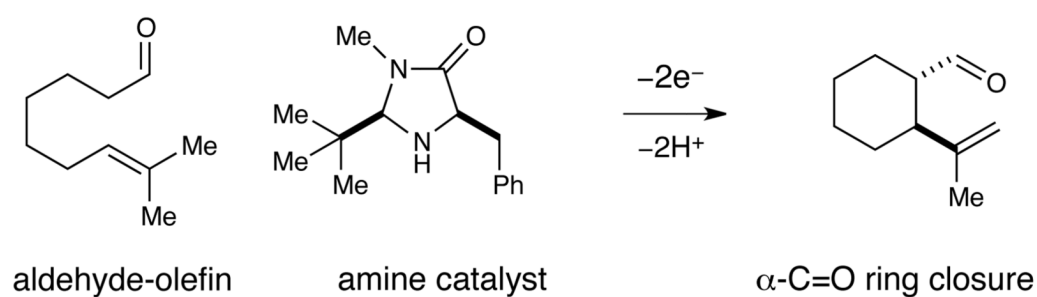
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16. Intramolecular cyclizations using SOMO catalysis have previously been accomplished using  $\pi$ -rich activated olefins such as allylsilanes. This study expands the scope and utility of the enantioselective SOMO oxidation pathway via the use of simple olefins.
17. Unpublished results from our lab have indicated that the initial radical coupling step is reversible when oxidation of the resulting radical to a cation is relatively slow.

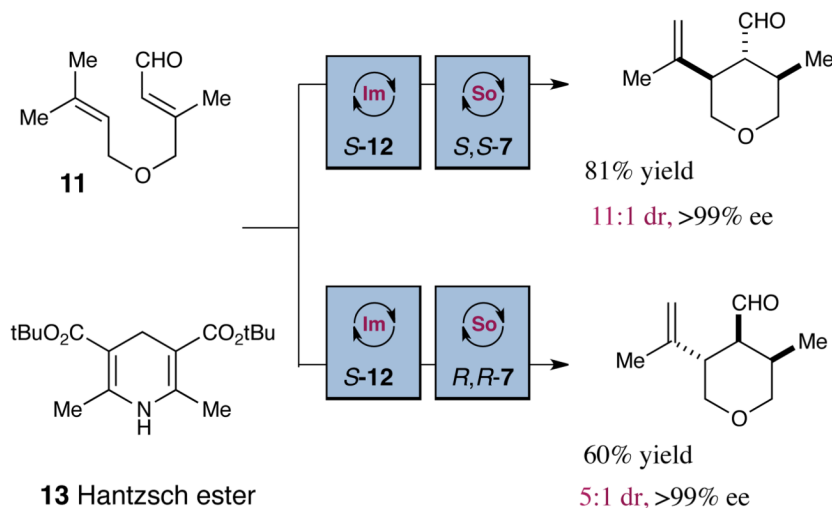
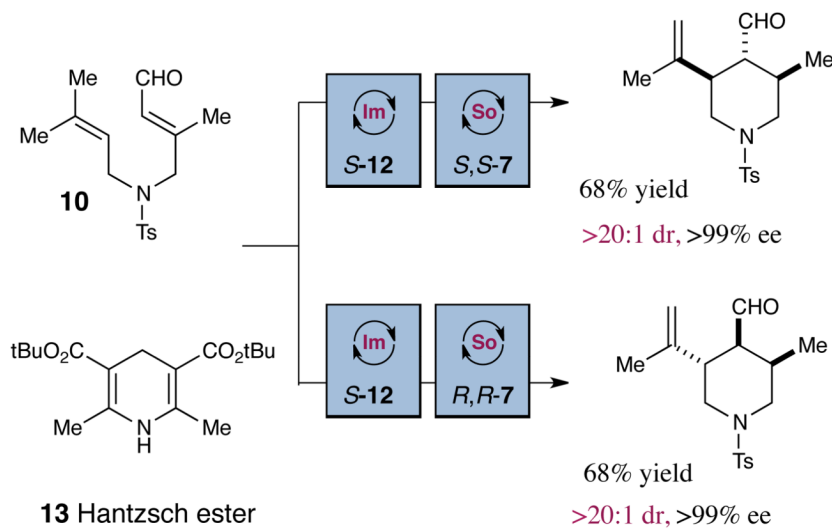
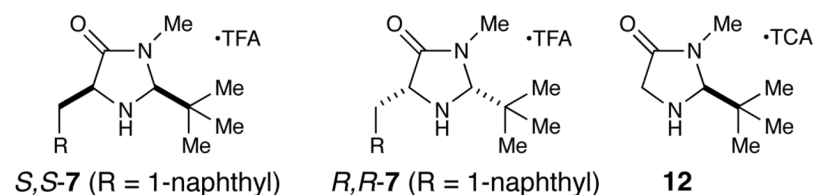
### Lewis Acid (LA) Catalyzed Intramolecular Carbonyl-Ene Cyclization



### Organocatalytic Aldehyde-Olefin Alkylation: $\alpha$ -Carbonyl Cyclization



**Figure 1.**  
Impetus and design elements of home-ene reaction

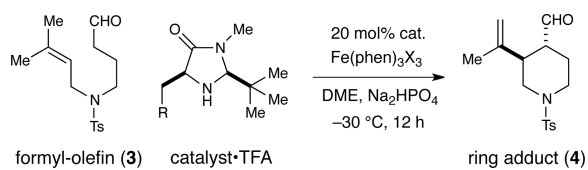
**Scheme 1.**

Sequential organocatalytic hydrogenation-cyclization

Conditions: Step 1) 2.5 equiv. **13**, 20 mol% **12**,  $\text{CHCl}_3$ ,  $-50\text{ }^\circ\text{C}$ , 24 hours. Step 2) 2.5 equiv.  $\text{Fe}(\text{phen})_3(\text{Tf}_2\text{N})_3$ , 2.5 equiv.  $\text{Na}_2\text{HPO}_4$ , 20 mol% **7**,  $-30\text{ }^\circ\text{C}$ , DME, 12 hours. <sup>a</sup>Diastereoselectivities determined by  $^1\text{H-NMR}$  analysis. Enantiomeric excess determined by chiral HPLC analysis of the corresponding alcohol or terephthalic acid monomethyl diester.

Table 1

Effect of catalyst structure and counterion on cyclization



entry	catalyst (R)	X <sup>-</sup>	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	<b>5</b> (H)	SbF <sub>6</sub> <sup>-</sup>	41%	89%
2	<b>6</b> (Ph)	SbF <sub>6</sub> <sup>-</sup>	41%	97%
3	<b>7</b> (1-naphthyl)	SbF <sub>6</sub> <sup>-</sup>	43%	99%
4	<b>7</b> (1-naphthyl)	ClO <sub>4</sub> <sup>-</sup>	12%	99%
5	<b>7</b> (1-naphthyl)	PF <sub>6</sub> <sup>-</sup>	73%	99%
6	<b>7</b> (1-naphthyl)	Tf <sub>2</sub> N <sup>-</sup>	95% <sup>c</sup>	99%

<sup>a</sup>Determined by <sup>1</sup>H NMR using internal standard. Diastereoselectivity >20:1 in all cases.

<sup>b</sup>Determined by chiral SFC analysis of the corresponding alcohol, absolute configuration determined by chemical correlation.

<sup>c</sup>Isolated in 93% yield.

Table 2

Scope of the enantioselective homo-ene ring products

entry	substrate	product	yield / % ee <sup>a</sup>
1			82% yield 97% ee >20:1 dr <sup>b</sup>
2			77% yield 86% ee >20:1 dr <sup>b</sup>
3			75% yield <sup>c</sup> 95% ee >20:1 dr <sup>b</sup>
4			76% yield <sup>c</sup> 96% ee >20:1 dr <sup>b</sup>
5			62% yield <sup>c</sup> 85% ee >20:1 dr <sup>b</sup>
6			84% yield 99% ee >20:1 dr <sup>b</sup>

<sup>a</sup>Determined by chiral HPLC analysis of the alcohol or aryl ester.<sup>b</sup>Determined by <sup>1</sup>H-NMR analysis.<sup>c</sup>Determined by <sup>1</sup>H-NMR analysis using an internal standard.



Table 3

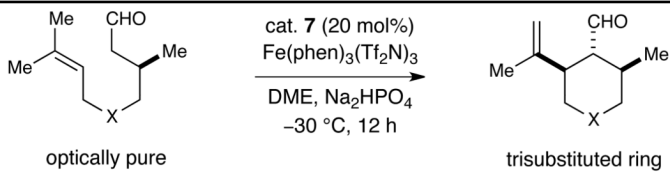
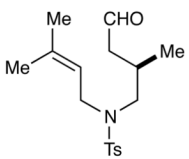
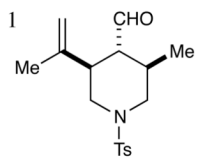
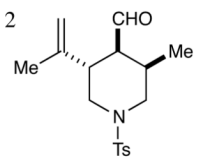
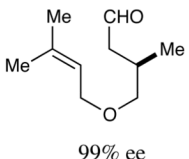
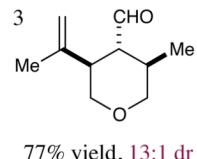
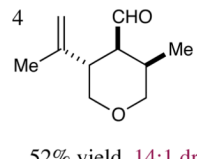
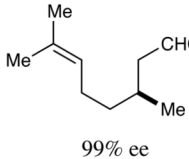
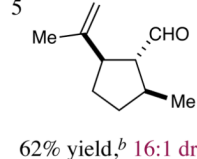
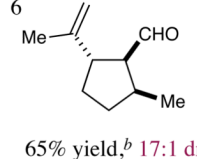
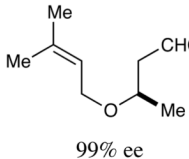
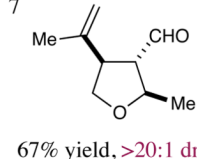
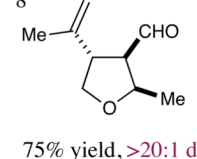
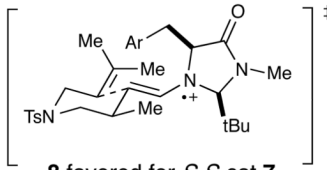
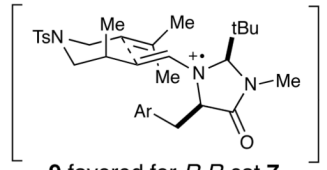
Scope of  $\pi$ -nucleophile, selectivity of olefin transposition

entry	substrate	product	yield / % ee <sup>b</sup>
1			99% yield 98% ee >20:1 dr <sup>c</sup>
2			87% yield 97% ee >20:1 dr <sup>c</sup>
3			90% yield 97% ee >20:1 dr <sup>c</sup>
4			79% yield 96% ee >20:1 dr <sup>c</sup>
5			78% yield 92% ee >20:1 dr <sup>c</sup>
6			77% yield 98% ee >20:1 dr <sup>c</sup>

<sup>a</sup>R = 1-naphthyl.<sup>b</sup>Determined by chiral HPLC analysis of the alcohol or aryl ester. Diastereoselectivities determined by <sup>1</sup>H-NMR analysis.<sup>c</sup>Determined by <sup>1</sup>H-NMR analysis using an internal standard.

Table 4

Production of rings with three contiguous stereocenters<sup>a</sup>

substrate	With <i>S,S</i> -7 as catalyst	With <i>R,R</i> -7 as catalyst
 <p>optically pure</p> <p>trisubstituted ring</p>		
 <p>99% ee</p>	<p>1</p>  <p>94% yield, &gt;20:1 dr</p>	<p>2</p>  <p>91% yield, &gt;20:1 dr<sup>a</sup></p>
 <p>99% ee</p>	<p>3</p>  <p>77% yield, 13:1 dr</p>	<p>4</p>  <p>52% yield, 14:1 dr</p>
 <p>99% ee</p>	<p>5</p>  <p>62% yield,<sup>b</sup> 16:1 dr</p>	<p>6</p>  <p>65% yield,<sup>b</sup> 17:1 dr</p>
 <p>99% ee</p>	<p>7</p>  <p>67% yield, &gt;20:1 dr</p>	<p>8</p>  <p>75% yield, &gt;20:1 dr</p>
 <p>8 favored for <i>S,S</i>-cat 7</p>	 <p>9 favored for <i>R,R</i>-cat 7</p>	

<sup>a</sup>Diastereoselectivities determined by <sup>1</sup>H-NMR analysis.<sup>b</sup>Determined by <sup>1</sup>H-NMR analysis using an internal standard.