Enantioselective Intramolecular Aldehyde α-Alkylation with Simple Olefins: Direct Access to Homo-Ene Products

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Ⓢ *Supporting Information*

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 toward 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.[1] A 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.[2] 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 prefunctionalization of the olefin component.[3] This fundamental transformation has been widely studied, and a number of catalytic enantioselective carbonyl-ene protocols have been developed.[4,5] Expanding upon this general concept, we sought to invent a one-carbon extended, "homo-ene" variant, wherein unactivated substrates undergo asymmetric α-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 great value to the chemical synthesis community.

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

through a LUMO-lowered 2π-electron pathway, the SOMO activation mode is distinguished by an electrophilic 3π-electron species (**1-he**). On the basis of precedent from our lab,[6–13] 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[14] 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 (see Figure 1). Central to the proposed strategy was our expectation
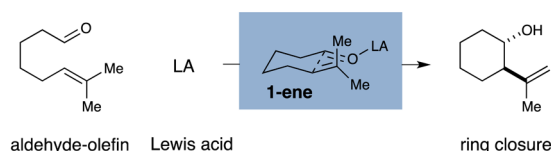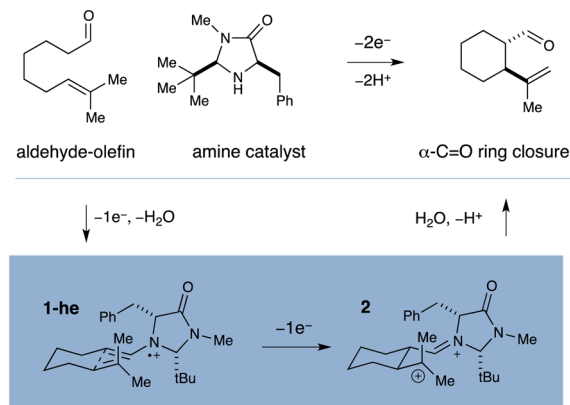
Figure 1. Impetus and design elements of home-ene reaction.

that cyclization would proceed via a highly ordered chair-*E* transition state[15] (**1-he**) to deliver the product with trans diastereoselectivity in a fashion that is highly analogous to the venerable ene 2π-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.[16]

Table 1. Effect of Catalyst Structure and Counterion on Cyclization

formyl-olefin (3)   catalyst·TFA   ring adduct (4)

entry	catalyst (R)	X⁻	yield (%)[a]	ee (%)[b]
1	5 (H)	SbF_6^-	41	89
2	6 (Ph)	SbF_6^-	41	97
3	7 (1-naphthyl)	SbF_6^-	43	99
4	7 (1-naphthyl)	ClO_4^-	12	99
5	7 (1-naphthyl)	PF_6^-	73	99
6	7 (1-naphthyl)	Tf_2N^-	95[c]	99

[a]Determined by ^{1}H NMR using internal standard. Diastereoselectivity >20:1 in all cases. [b]Determined by chiral SFC analysis of the corresponding alcohol, absolute configuration determined by chemical correlation. [c]Isolated in 93% yield.

Table 2. Scope of the Enantioselective Homo-Ene Ring Products

20 mol% 7 (R = 1-naphthyl)   homo-ene adduct

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

[a]Determined by chiral HPLC analysis of the alcohol or aryl ester. [b]Determined by ^{1}H NMR analysis. [c]Determined by ^{1}H NMR analysis using an internal standard.

Table 3. Scope of π-Nucleophile, Selectivity of Olefin Transposition

20 mol% 7[a]

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

[a]R = 1-naphthyl. [b]Determined by chiral HPLC analysis of the alcohol or aryl ester. Diastereoselectivities determined by ^{1}H NMR analysis. [c]Determined by ^{1}H NMR analysis using an internal standard.

The proposed transformation was first evaluated in the context of the amine-tethered prenyl aldehyde substrate 3. Treatment of this aldehyde with base and Fe(III)trisphenanthroline in the presence of an imidazolidinone catalyst (5, 6, or 7, see Table 1) led to the stereoselective formation of piperidine 4 with high levels of trans diastereoselectivity and enantiocontrol. Optimal selectivities were obtained with 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 tris-bistriflamide 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 Table 2 shows, the method readily accommodates significant structural diversity in the linker, offering enantioselective access to a wide range of 5- and 6-membered carbocyclic and heterocyclic

Table 4. Production of Rings with Three Contiguous Stereocenters[a]

substrate	With *S*,*S*-**7** as catalyst	With *R*,*R*-**7** as catalyst
99% ee	1 — 94% yield, >20:1 dr	2 — 91% yield, >20:1 dr[a]
99% ee	3 — 77% yield, 13:1 dr	4 — 52% yield, 14:1 dr
99% ee	5 — 62% yield,[b] 16:1 dr	6 — 65% yield,[b] 17:1 dr
99% ee	7 — 67% yield, >20:1 dr	8 — 75% yield, >20:1 dr

8 favored for *S*,*S*-cat **7**   **9** favored for *R*,*R*-cat **7**

[a]Diastereoselectivities determined by ¹H NMR analysis. [b]Determined by ¹H NMR analysis using an internal standard.

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 β-oxy or β-amino elimination from the corresponding aldehyde precursors (entries 2 and 3), demonstrating the mild conditions employed in generating the 3π-electron-activated intermediate. The products in Table 2 represent important structural motifs that are widely encountered throughout natural product synthesis and drug discovery.[1]

The reaction is also tolerant of a broad array of olefin systems as suitable π-nucleophiles for this homo-ene-type cyclization. As shown 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

Scheme 1. Sequential Organocatalytic Hydrogenation–Cyclization[a,b]

S,*S*-**7** (R = 1-naphthyl)   *R*,*R*-**7** (R = 1-naphthyl)   **12**
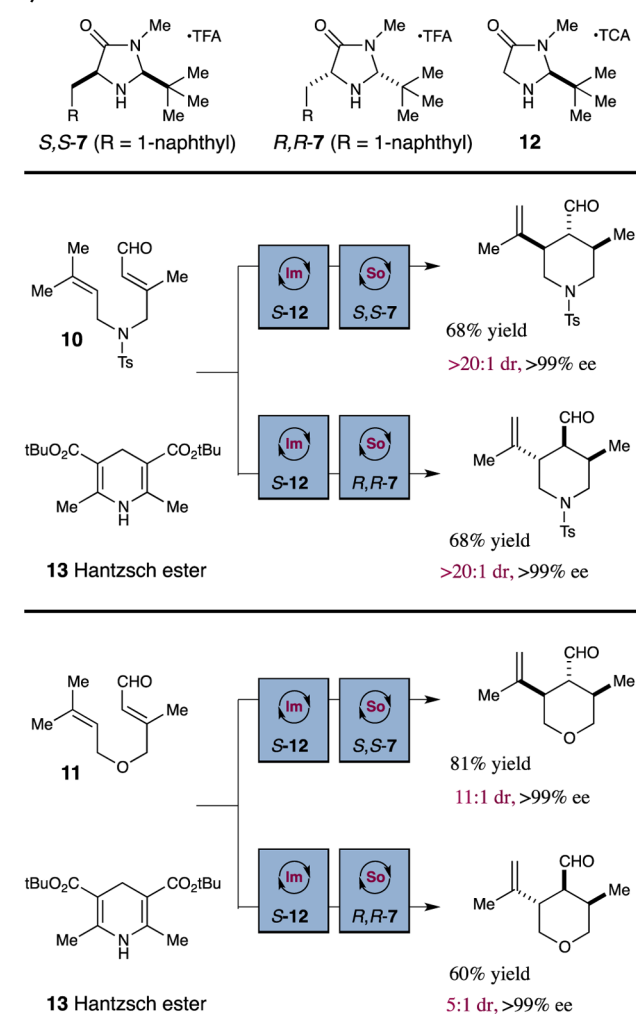
[a]Conditions: (Step 1) 2.5 equiv **13**, 20 mol % **12**, CHCl₃, −50 °C, 24 h. (Step 2) 2.5 equiv Fe(phen)₃(Tf₂N)₃, 2.5 equiv Na₂HPO₄, 20 mol % **7**, −30 °C, DME, 12 h. [b]Diastereoselectivities determined by ¹H NMR analysis. Ee determined by chiral HPLC of the corresponding alcohol or terephthalic acid monomethyl diester.

with excellent stereocontrol (entries 1–3), and α-carbonyl cyclization using styrenyl olefins is readily accomplished (entry 4). Importantly, nonsymmetrical 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). 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.[17] Despite this current limitation in scope, cycloadducts bearing monosubstituted olefin substituents are nonetheless readily accessible from allyl silane precursors (entry 5).

Next we examined the ability of the amine catalyst to override the influence of stereochemical information already present on the intramolecular cyclization substrate. We recognized 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 β-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 β-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**), 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.

■ ASSOCIATED CONTENT

ⓢ Supporting Information
Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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(16) Intramolecular cyclizations using SOMO catalysis have previously been accomplished using π-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.