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Enantioselective Polyene Cyclization via Organo-SOMO Catalysis

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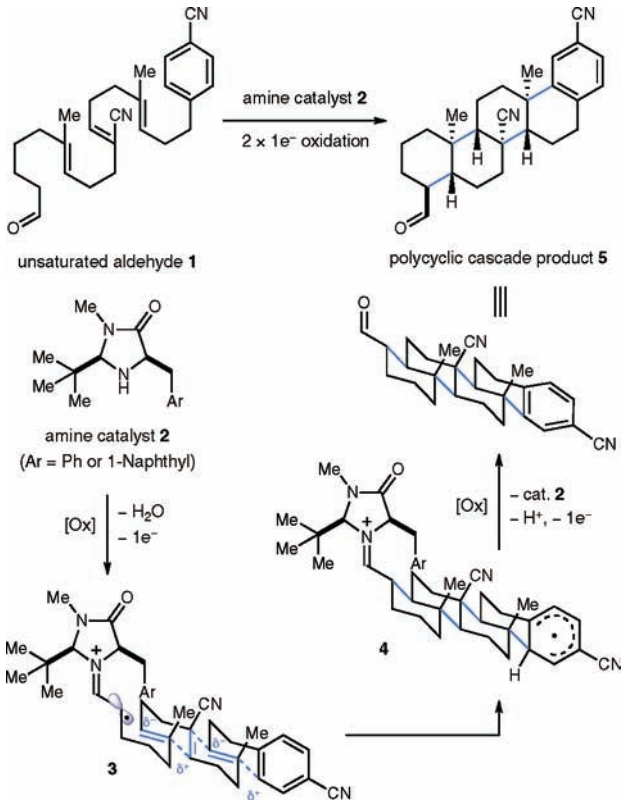
Inspired by the biosynthetic origins of steroids and terpenoidal natural products, synthetic organic chemistry has witnessed considerable efforts in the field of biomimetic polyene cyclization.[1] Most importantly, cationic polycyclizations, originally pioneered by van Tamelen, Johnson, and Goldsmith, have emerged as a valuable tool for the generation of diverse polycylic skeletons.[2,3] While substrate- or auxiliary-mediated induction has traditionally been employed to render such cascade reactions stereoselective, recent advances by Yamamoto, Ishihara, and Gagné have shown that catalytic enantiocontrol can also be exploited in these cation-driven bond constructions.[4] In contrast, radical-mediated polyene cyclizations, as originally proposed (and dismissed) by Breslow as a biosynthetic pathway,[5] have received considerably less attention.[1,6] Moreover, while auxiliary-based cascade radical cyclizations have been reported,[6] enantioselective approaches via catalysis remain largely elusive.[7,8] With the objective of developing a general method for asymmetric catalytic polyene cyclizations, we reasoned that the application of our previously reported SOMO activation strategy[9] should allow us to establish a powerful cascade reaction[10] via a single electron transfer-induced open-shell pathway.[5,6e,f,11] In this communication, we report the successful execution of these ideas and a new application of SOMO catalysis to the enantioselective construction of multiple C−C bonds and contiguous stereocenters in the context of steroidal and terpenoidal architecture.

We hypothesized that a suitably functionalized aldehyde (e.g., **1**) bearing the requisite degree of tethered unsaturation should condense with imidazolidinone catalyst **2** to give α-imino radical intermediate **3** upon oxidation with an appropriate metal oxidant (Scheme 1). At this stage, we expected radical cation **3** to engage in a series of 6-endo-trig radical cyclizations terminated by a suitable arene to give cyclohexadienyl radical **4**. A second oxidation step would then furnish the corresponding cyclohexadienyl cation, which upon rearomatization and liberation of the catalyst would deliver the requisite pentacycle **5**.[12] By analogy to our previous SOMO catalysis studies,[9g] we presumed that catalyst **2** would favor the α-imino radical geometry shown for **3**, in which the polyene chain is oriented away from the bulky *tert*-butyl substituent. At the same time, the aryl moiety on the catalyst framework should effectively shield the *Si* face, leaving the *Re* face exposed to addition across the proximal trisubstituted alkene. As a key design element, the catalyst-induced enantio- and diastereocontrol arising in the production of the first carbocycle should be structurally relayed in subsequent ring formations. Moreover, we recognized that the electronic properties of the tethered polyene would play a pivotal role in partitioning the putative single-electron pathway toward cascade ring construction, in lieu of nonproductive mechanisms such as (i) radical oxidation or (ii) nonregioselective alkene addition. To this end, polyolefins such as **1** that incorporate an alternating sequence of polarity-inverted C═C bonds (acrylonitrile and isobutene moieties) were chosen as suitable substrates that would electronically match nucleophilic olefins with electron-deficient radical intermediates (and vice versa). Moreover, the selection of trisubstituted nucleophilic olefins was expected to favor the desired 6-endo-trig mechanism over

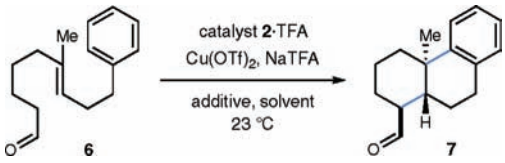
Scheme 1. Enantioselective Polycyclization via SOMO Catalysis



a competing 5-exo-trig mode, as radical additions to fully substituted carbons are strongly disfavored.[13] Similarly, the use of unsaturated nitriles should enforce 6-endo regiocontrol, while functional conversion of C≡N to a range of common steroidal substituents (H, CHO, Me) is known to be operationally trivial.[6f,14]

Our proposed polycyclization strategy was first evaluated using bicyclization substrate **6**, imidazolidinone **2a**, and a series of metal oxidants. Surprisingly, our initial survey revealed that strong oxidants that had been successful in previous SOMO activation studies {e.g., cerium(IV) ammonium nitrate (CAN)[9a−d,f] and $[Fe(phen)_3](PF_6)_3$[9g]} did not generate any of the desired tricyclic product **7**. In both cases, products derived from premature oxidation of the tertiary alkyl radical intermediate or capture of the radical by external nucleophiles were predominant.[9d] In contrast, the use of $Cu(OTf)_2$ in acetonitrile with sodium trifluoroacetate (NaTFA) as a base furnished a small amount of the desired tricycle **7**, albeit with low enantioselectivity (Table 1, entry 1).[15,16] Subsequent optimization studies revealed that slow addition of the oxidant (via syringe pump) greatly improved the yield of desired tricyclic product **7**, presumably as a result of the kinetic preference for a unimolecular cascade process versus an interrupted pathway that involves bimolecular radical oxidation. While it is possible that the carbocation intermediates from an interrupted step may still

Table 1. Reaction Optimization for Enantioselective Bicyclization[a]



entry	catalyst	additive[b]	solvent	yield (%)[c]	ee (%)[d]
1	**2a**, Ar = Ph (20 mol%)	none	MeCN	11	34
2	**2a**, Ar = Ph (20 mol%)	TFA	MeCN	16	35
3[e]	**2a**, Ar = Ph (20 mol%)	TFA	MeCN	42	42
4[e]	**2b**, Ar = 1-Np (20 mol%)	TFA	MeCN	56	74
5[e]	**2b**, Ar = 1-Np (20 mol%)	TFA	*i*-PrCN/DME[f]	54	87
6[e]	**2b**, Ar = 1-Np (30 mol%)	TFA	*i*-PrCN/DME[f]	70	87

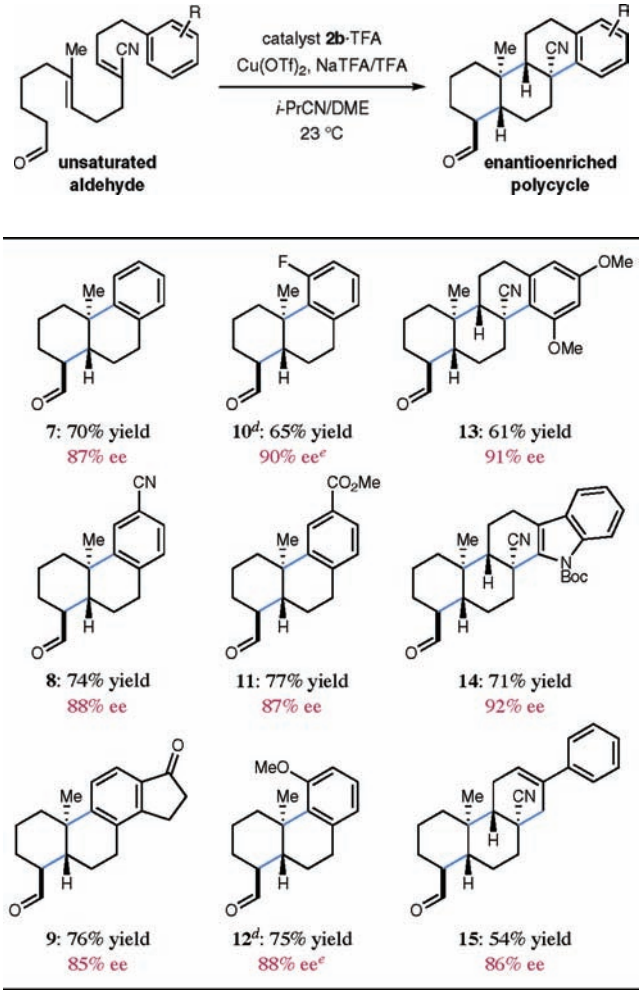
[a] Reactions were peformed on a 0.20 mmol scale using 2.5 equiv of $Cu(OTf)_2$ and 2.0 equiv of NaTFA. [b] Using 3.0 equiv of TFA. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] With slow addition of oxidant and base as a solution in MeCN or *i*-PrCN. [f] A 3:2 *i*-PrCN/DME mixture (0.08 M).

participate in a productive cyclization pathway, it is clear that β-H elimination remains the dominant mechanism in this case.[17] A subsequent evaluation of catalyst architecture revealed markedly improved enantioselection with catalyst **2b**, in which the benzyl group of catalyst **2a** has been replaced with the extended shielding of a (1-naphthalene)methyl moiety (74% ee; entry 4). Moreover, a survey of reaction media revealed a pronounced effect on the enantiomeric excess in that a 3:2 mixture of isobutyronitrile with 1,2-dimethoxyethane (DME) gave rise to synthetically useful results (70% yield, 87% ee; entry 6).

We next evaluated the generality of our newly developed organocatalytic protocol in a series of cascade bicyclizations (Table 2). A wide array of arenes readily acted as terminating groups; in addition to electron-neutral phenyl rings (**7**, 70% yield, 87% ee), electron-rich and -poor aryl aldehydes also participated, furnishing **8**−**12** in good yields and comparable enantioselectivity (65−77% yield, 85−90% ee).[18] While the reaction yields for all of the examined aryl terminators were similar, we observed that electron-deficient arenes were successful over a larger range of reaction concentrations, a result that supports the matched interaction of a nucleophilic trialkyl radical with an electron-poor terminator in the final S_RAr cyclization.[19] We presume that in such cases, electron-withdrawing substituents increase the substitution rate and stabilize the newly formed cyclohexadienyl radical intermediate. Notably, when meta-substituted arenes were subjected to these cascade conditions, cyclization at the aryl 2-position was predominant (affording products **10** and **12**), again emphasizing the radical nature of this process (2−4:1 ortho/para selectivity, 65−75% yield, 88−90% ee).[9g,19] Indeed, the prevalent formation of ortho-substituted product **12** was in sharp contrast to the literature precedent for para selectivity when cationic conditions were employed with similar polyene substrates.[2d] It is important to note that all of the products of this survey were obtained as single diastereomers.[20]

We next tested the capacity of our SOMO catalysis strategy to accomplish polyene tricyclization. On the basis of the design principles outlined above, we assumed that aldehydic substrates incorporating an alternating sequence of electron-rich and electron-poor olefinic acceptors (isobutene and acrylonitrile) would be suitably matched to allow intramolecular radical chain propagation prior to coupling and termination with a suitable π-rich aryl ring.[9g,19] To our delight, a range of tricyclization substrates readily furnished the desired products **13**−**15** in moderate to good yields and useful enantioselectivities (54−71% yield, 86−92% ee; Table 2).[21] It should be noted that electron-rich benzene (**13**) and indole (**14**) terminators were tolerated using these mild oxidative conditions. Moreover, the successful generation of tricyclic aldehyde **15** revealed that π-nucleophilic olefins such as 1,1-disubstituted styrenes can also serve as suitable terminating groups.

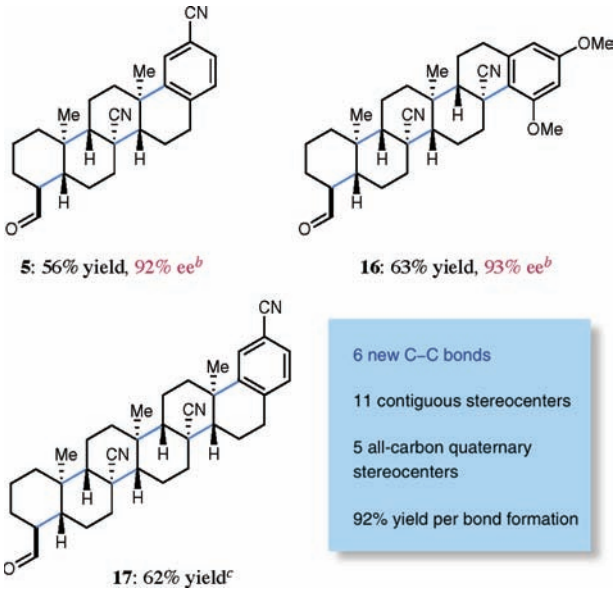
Table 2. Scope Studies in Enantioselective Bi- and Tricyclization[a,b,c]



[a] Conditions: Slow addition (7 h) of $Cu(OTf)_2$ (2.5 equiv), NaTFA (2.0 equiv), and TFA (3.0 equiv) in *i*-PrCN (2 parts) to aldehyde and catalyst (30 mol %) in 1:2 *i*-PrCN/DME to give a 0.08 M solution with subsequent stirring for 17 h at room temperature. [b] Isolated yield. [c] ee was determined by chiral HPLC analysis. [d] Ortho/para mixture (4:1 for **10**; 2:1 for **12**). [e] ee of the ortho product; 91% ee for the para regioisomer of **12**.

As outlined in Scheme 2, we finally sought to probe the limitations of this radical cyclization strategy via application to extended ring systems such as tetra-, penta-, and hexacycles. Remarkably, for the SOMO-catalyzed tetracyclization of trienal **1**, we observed levels of reaction efficiency and enantiocontrol similar to those obtained in bicycle and tricycle formation (pentacycle **5**: 56% yield, 92% ee, single diastereomer). Moreover, extension of this multi-bond-forming reaction to tetraene cascade ring construction cleanly afforded pentacyclization product **16** in almost identical yield and enantiomeric excess (63% yield, 93% ee). Perhaps most notably, this new SOMO-polyene cyclization concept was successfully extended to the enantioselective[22] production of the hexacyclization adduct **17** as a single diastereomer in 62% yield (corresponding to an average yield of 92% per bond formed). In the course of this cascade bond construction, a total of 11 contiguous

Scheme 2. Extended Ring Systems by Organo-SOMO Catalysis[a]



[a] Conditions: See Table 2, footnotes *a*−*c*. [b] Determined by chiral supercritical fluid chromatography (SFC). [c] Determination of enantiomeric excess in this case was not possible because of the sparing solubility of the polycycle in HPLC or SFC solvents: $[\alpha]_D = -25.3$ ($c = 0.68$, $CHCl_3$); also see ref 22.

stereocenters, of which five are all-carbon quaternary centers, were formed from a simple acyclic starting material under the influence of imidazolidinone **2b**. It is instructive to consider that the last stereogenic center formed in the course of this cascade resides 11.7 Å from the catalyst binding point,[23] thus showcasing the stereoinduction efficiency of this new SOMO cyclization sequence.

In summary, we have developed the first catalytic enantioselective cyclization strategy for accessing steroidal and terpenoidal frameworks using organocatalysis. This strategy represents an ambient-temperature protocol, which is unprecendented in SOMO activation catalysis with respect to carbon−carbon bond formation. Future work will be devoted to the application of this new technology to the synthesis of complex natural products and pharmaceutically relevant entities.

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Supporting Information Available: Experimental procedures, syntheses of starting materials, X-ray crystallographic proof of the absolute configuration of **8**, spectral data for all new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Additon of both base (NaTFA or $NaHCO_3$) and TFA was found to be necessary for high conversion. Replacement of $Cu(OTf)_2$/NaTFA by $Cu(TFA)_2 \cdot H_2O$/NaOTf showed inferior reactivity, presumably because of the kinetic inaccessibility of the active oxidant $[(i\text{-PrCN})_4Cu]X_2$ (outer-sphere complex; X = OTf, TFA) from the inner-sphere complex $Cu(TFA)_2$ (see ref 15a).
(17) Under the reaction conditions, alkene protonation followed by subsequent cationic cyclization is not a feasible process. Under typical cationic cyclization conditions (see ref 4d), cationic cyclization could be achieved in a separate step.
(18) Structural assignments of **8** and **13** as well as the absolute configuration of **8** (after chemical derivatization) were secured by X-ray crystallographic analysis (see the Supporting Information for details).
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(20) General procedure for the enantioselective polyene cyclization: An oven-dried vial equipped with a magnetic stir bar and a rubber septum was charged with a solution of catalyst **2b**·TFA (0.060 mmol, 0.30 equiv) and the polyenal (0.200 mmol, 1.00 equiv) in 1:2 *i*-PrCN/DME (1.5 mL) under an Ar atmosphere. To this mixture, a solution of $Cu(OTf)_2$ (0.500 mmol, 2.50 equiv), NaTFA (0.400 mmol, 2.00 equiv), and TFA (0.400 mmol, 2.00 equiv) in *i*-PrCN (1.0 mL) was slowly added over 7 h using a syringe pump at room temperature. After stirring had been continued for a further 17 h, the light-green solution was subjected to aqueous workup and purified by flash chromatography to afford the cyclization product.
(21) Further evidence against a radical polar crossover reaction mechanism was obtained by the examination of a mismatched tricyclization substrate consisting of two trisubstituted electron-rich alkene moieties: significantly lower reaction efficiency (25% yield of the desired tetracycle) and only partial conversion were observed.
(22) We assume levels of enantiocontrol similar to those observed for **5** and **16**.
(23) Estimated by semiempirical PM3 calculations on **17** using Gaussian 03.

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