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Enantioselective Organo-Cascade Catalysis

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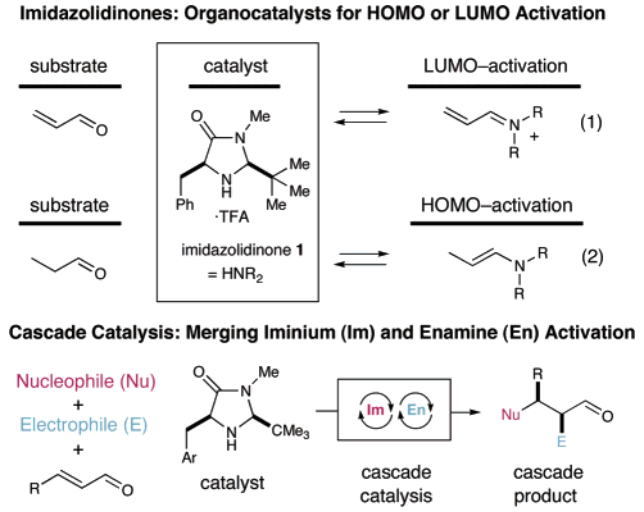
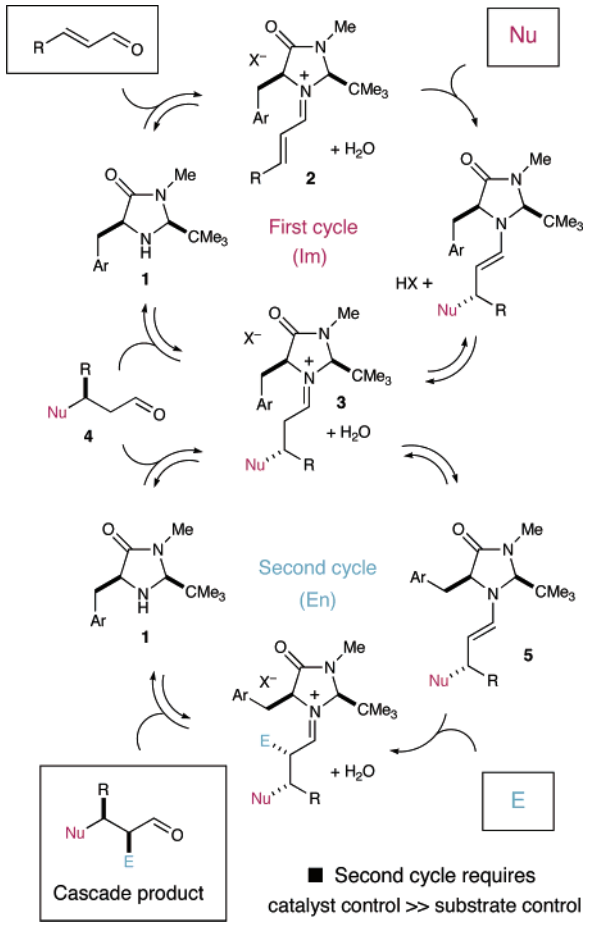
The identification of new chemical strategies that allow increasingly rapid access to structural complexity remains a preeminent goal for the chemical sciences. While the total synthesis approach to molecular complexity has traditionally focused upon a "stop and go" sequence of individual reactions, it is intriguing to consider that biological systems produce elaborate molecules in a continuous process, wherein enzymatic transformations are combined in highly regulated catalytic cascades.[1] Critical to the success of these biocatalytic "assembly lines" is the capacity of discrete transform-specific enzymes to coexist in the same reaction medium[1b] without the unfavorable consequences that might arise when synthetic catalysts are combined (e.g. catalyst−catalyst interactions, ligand exchange, redox processes, etc). Over the past five years, our laboratory has introduced several strategies for asymmetric synthesis based upon the capacity of chiral amines to function as enantioselective catalysts.[2,3] As part of these studies, we have made the unusual finding that imidazolidinones (such as **1**) can enforce orthogonal modes of substrate activation in the forms of iminium (LUMO-lowering) and enamine (HOMO-raising) catalysis[2,3] (eqs 1 and 2). Based on the opportunity that amine catalysts might



coexist without deleterious interactions, we recently questioned whether the conceptual blueprints of biosynthesis might be translated to a laboratory "cascade catalysis" [4] sequence. Herein, we report the execution of these ideals wherein imidazolidinone-based catalytic cycles have been successfully combined to provide powerful, new complexity-generating transforms.

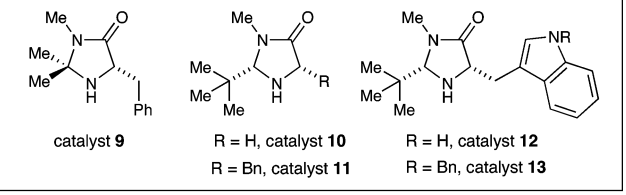
Design Plan (Scheme 1). In accord with our previous studies, we presumed that exposure of α,β-unsaturated aldehydes to imidazolidinone catalysts (of type **1**) would generate activated iminium species **2** that can enantioselectively intercept a wide variety of generic π- or hydrido-nucleophiles (Nu). We assumed that, upon rapid hydrolysis of the resulting iminium **3**, the conjugate addition adduct **4** would then enter a second catalytic cycle wherein enamine activation **5** would enable highly diastereoselective additions to a wide array of electrophiles (E). Central to the utility of this new cascade catalysis process is the mechanistic requirement that induction in the enamine addition step should arise from catalyst control (as opposed to substrate control). Specifically, this would ensure high levels of diastereoselectivity for the overall process regardless of the stereogenicity forged in the first catalytic step. While a single imidazolidinone catalyst could enable both activation cycles (as depicted), we also envisioned that the iminium and enamine steps might be discretely controlled by cycle-specific catalysts. Within this mechanistic scenario, modular control of the enforced sense of enantio- and diastereoinduction (e.g. *R* vs *S*, *syn* vs *anti*) could be achieved via judicious selection of the amine enantiomer involved in each catalytic cycle.

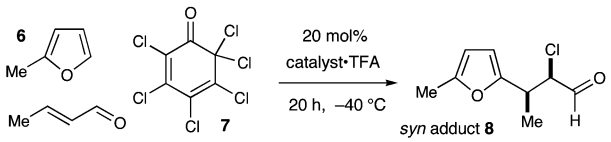
Scheme 1. Cascade Catalysis: Merged Iminium−Enamine Activation



Our bicyclic catalysis strategy was first examined using 2-methylfuran **6** (Nu), crotonaldehyde, the chlorinated quinone **7** (E), and a series of imidazolidinone catalysts (Table 1). Preliminary studies revealed that the proposed catalysis cascade was indeed possible to provide 2-chloro-3-(5-methylfuranyl)butanal **8** with excellent levels of enantioinduction and in good conversion using

Table 1. Organo-Cascade Catalysis: Effect of Catalyst and Solvent

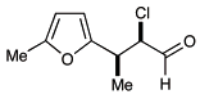
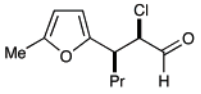
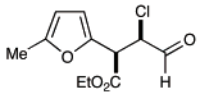
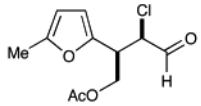
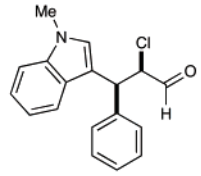
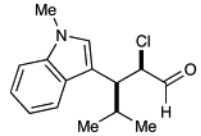




entry	catalyst	solvent	% conversion[a]	dr (*syn*:*anti*)[b]	% ee[c]
1	**9**	EtOAc	3	1:1	88
2	**10**	EtOAc	10	5:1	89
3	**11**	EtOAc	79	9:1	97
4	**12**	EtOAc	78	8:1	97
5	**13**	EtOAc	78	11:1	99
6	**13**	$CHCl_3$	54	8:1	94

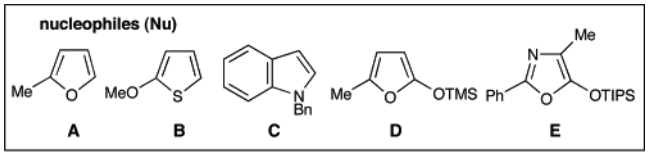
[a] Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). [b] Absolute and relative configuration assigned by chemical correlation. [c] Enantiomeric excess determined by chiral GLC analysis (Bodman β-DM).

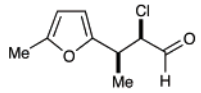
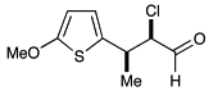
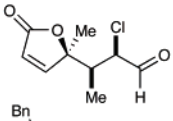
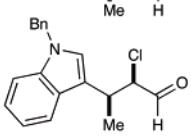
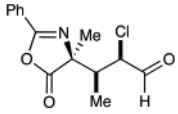
Table 2. Organo-Cascade Catalysis: Scope of Enal Component

entry	R =	product	temp (°C)	% yield	dr[a]	% ee[b]
1	Me		–50	86	14:1	99
2	Pr		–50	74	13:1	99
3	CO_2Et		–60	80	22:1	99
4	CH_2OAc		–40	82	11:1	>99
5	Ph		–40	83	9:1	99
6	*i*-Pr		–40	67	12:1	>99

[a] Absolute and relative configuration assigned by chemical correlation. [b] Enantiomeric excess determined by chiral GLC analysis.

Table 3. Organo-Cascade Catalysis: Representative Nucleophiles



entry	nucleophile	product	temp (°C)	% yield	dr[a]	% ee
1	**A**		–50	86	14:1	99
2	**B**		–50	77	11:1	99
3[b]	**D**		–55	71	>25:1	>99
4	**C**		–60	75	12:1	>99
5	**E**		–40	97	9:1	>99

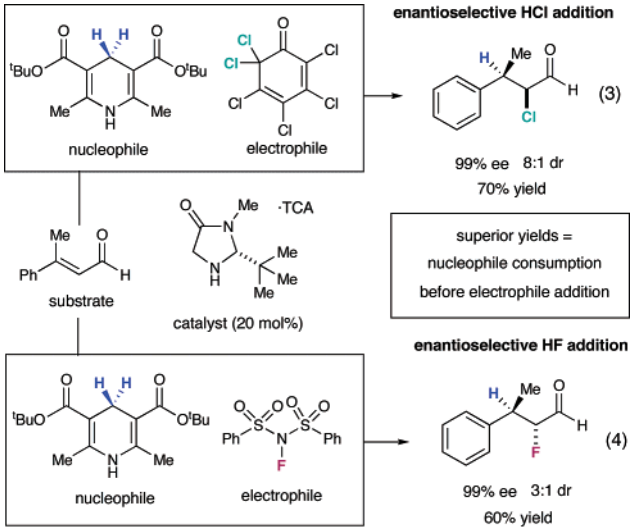
[a] Absolute and relative configuration assigned by chemical correlation. [b] Superior yields were obtained when the electrophile was added after consumption of the silyloxy furan.

imidazolidinones **11**−**13**. A survey of reaction media for this catalysis sequence revealed that EtOAc engenders optimal enantiocontrol at subambient temperatures. The superior levels of stereoselectivity provided by the 1-benzylindole catalyst **13** (entry 5, 99% ee, 11:1 *syn*:*anti*) in EtOAc at −40 °C prompted us to select these conditions for further exploration.[5]

Experiments that probe the scope of the α,β-unsaturated aldehyde component are summarized in Table 2. There appears to be significant latitude in the electronic and steric demands of the β-olefin substituent (entries 1−6, R = Me, CO_2Et, *i*-Pr, CH_2OAc, Ph) to enable access to a broad variety of 3,3′-disubstituted 2-chloropropanals (*syn*:*anti* 9:1 to 22:1, ≥99% ee). In accord with our mechanistic postulate, it is noteworthy that diastereoinduction in the second step appears to be directed primarily by the catalyst architecture and not the stereogenicity forged in the first cycle (1,2-*syn* in all cases).

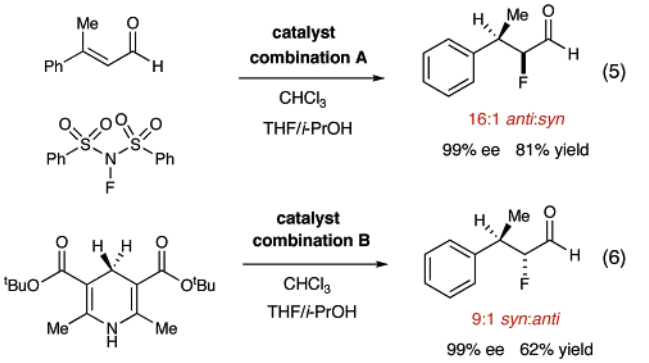
We next examined the impact of the nucleophilic component on this domino catalysis sequence (Table 3). Given that iminium-catalyzed cycloaddition reactions enable the α,β-functionalization of enals directly,[2a] we initially focused on conjugate addition reactions involving a broad variety of aromatic π-nucleophiles (**A**−**E**). To our delight, furans, thiophenes, indoles, butenolides, and tertiary amino lactone equivalents (among other nucleophiles) can be employed in the primary catalytic cycle without apparent impedance of the secondary cycle (entries 1−5, ≥99% ee).

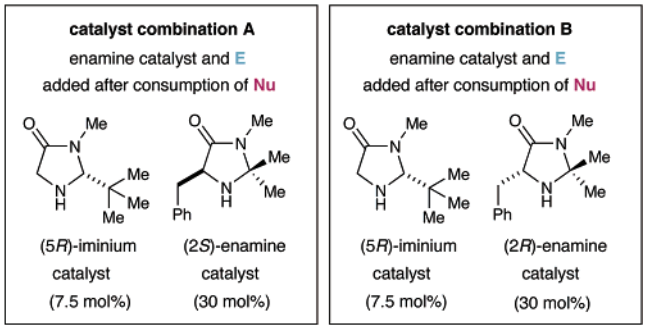
A demonstration of the potential utility and versatility of this organo-cascade catalysis strategy is presented in the design of two transformations that, to our knowledge, have no precedent in asymmetric synthesis. Specifically, we hypothesized that implementation of our recently reported transfer hydrogenation conditions using Hantzsch esters[2c] in conjunction[6] with electrophilic sources of chlorine or fluorine would effectively allow the asymmetric addition of HCl and HF across trisubstituted olefin systems (eqs 3 and 4). As revealed in eqs 3 and 4, this design plan has been fruitful



to provide the accordant hydro-halogenated products with excellent levels of enantio- and diastereoselectivity (HCl, 8:1 *anti*:*syn*, 99% ee; HF, 3:1 *syn*:*anti*, 99% ee).

Perhaps most importantly, we have found that two discrete amine catalysts can be employed to enforce cycle-specific selectivities. As revealed in eq 5, implementation of catalyst combination **A**, incorporating amines (2*S*)-**9** and (5*R*)-**10** (30 and 7.5 mol % respectively), allows the formal addition of HF to a trisubstituted enal with 16:1 *anti* selectivity (99% ee). Remarkably, the *syn* HF





addition product can be accessed with 9:1 selectivity and in 99% ee by simply changing the enantiomeric series of either amine employed in this catalyst combination (eq 6, catalyst combination **B**). Conceptually, this result demonstrates that cascade catalysis pathways that function with cycle-specific amine catalysts can be *readily modulated to provide a required diastereo- and enantioselective outcome via the judicious selection of simple amine catalysts*. We believe that this type of cycle-specific catalysis will be of great benefit to practitioners of syntheses that require rapid access to diversity while maintaining predictable control of stereoselectivity.

Last, a remarkable benefit of combining multiple asymmetric catalytic events into one sequence is the mathematical requirement for enantioenrichment in the second cycle, as demonstrated by the enantioselectivities obtained throughout this study (≥99% ee in all cases). Indeed, simple calculations reveal that such cascade sequences can provide the major diastereomer with exquisite levels of enantiocontrol despite combining catalytic cycles that might be only moderately selective (e.g. 86% ee + 86% ee = 99% ee).[7]

In summary, we have developed a new strategy for organocatalysis based on the biochemical blueprints of cascade catalysis. This strategy allows increasingly rapid access to structural complexity from simple starting materials and catalysts, while achieving exquisite levels of enantiocontrol. This strategy also allows modular control of absolute and relative stereoinduction in transformations that can function with cyclic-specific catalysts. Studies in the area of triple cascade catalysis will be reported shortly.

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Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) General procedure: to a 2-dram vial equipped with a magnetic stir bar and charged with catalyst (0.05 mmol) were added EtOAc (0.25 mL) and TFA (0.05 mmol), and then the solution was cooled to the indicated temperature. To this solution was added the enal (0.75 mmol) followed by the nucleophile (0.25 mmol) and the electrophile (0.5 mmol). Upon consumption of starting materials, the solution was passed through Iatrobeads with Et_2O, and then concentrated in vacuo. The resulting residue was purified by Iatrobead chromatography.

(6) Superior yields were obtained when the electrophile was added after consumption of the Hantzsch ester (as determined by TLC or GLC).

(7) For example, if two catalytic cycles, each 86% ee selective, were combined, the resulting cascade would furnish a 7:1 mixture of diastereomers, with the major diastereomer being formed in 99% ee.

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