Organocatalysis

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Cycle-Specific Organocascade Catalysis: Application to Olefin Hydroamination, Hydro-oxidation, and Amino-oxidation, and to Natural Product Synthesis**

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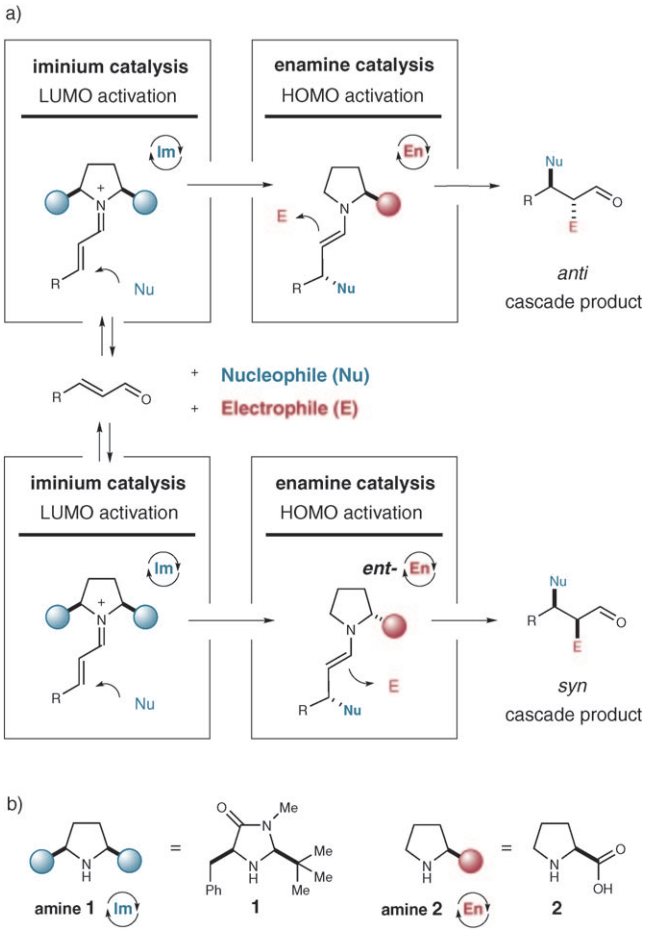
The discovery of new strategies that emulate nature's capacity to rapidly construct architectural complexity continues to be a central focus for research and development in the chemical sciences.[1] Recently, our laboratory disclosed the concept of organocascade catalysis,[2–4] a new chemical paradigm that combines two modes of catalyst activation (iminium and enamine catalysis) into one mechanism, thereby allowing the rapid conversion of simple achiral starting materials into stereochemically complex, single-enantiomer products (≥99% *ee*, Scheme 1a).[5] As a critical design feature, we revealed that the merger of these two activation modes can render a variety of transformations that are not yet possible using monocyclic catalysis pathways (e.g. enantioselective HCl, HF, and aryl–Cl addition across olefins).[2] Moreover, we realized the ideal of cycle-specific catalysis, wherein each cycle in the cascade sequence is moderated by a different chiral amine catalyst, a scenario that enables selective access to any product enantiomer or diastereomer by judicious catalyst selection. Our initial studies on cycle-specific catalysis employed a combination of two chiral imidazolidinone catalysts, a system that was particularly effective for olefin hydrohalogenation.[3a] Herein we describe the use of imidazolidinone **1**[6] and proline (**2**)[7] as a dual-catalyst system that allows access to a greatly expanded array of valuable transformations including olefin hydroamination, hydro-oxidation, and amino-oxidation. As a further milestone, we report the first use of this organocascade catalysis as a strategy for natural product synthesis by the enantioselective construction of the sesquiterpene (−)-aromadendranediol.

Over the last 10 years, imidazolidinones (such as **1**) have been established as LUMO-lowering iminium catalysts that can be employed in a wide variety of enantioselective transformations including conjugate additions, Friedel–Crafts alkylations, hydrido reductions, and cycloadditions.[8] While imidazolidinones can also serve as enamine catalysts,[9] they do not contain the necessary structural features to participate in bifunctional enamine catalysis (wherein activation of the electrophilic reaction partner is also performed by the amine catalyst). In contrast, proline (**2**) has been shown to be an enamine catalyst for which bifunctional activation is a standard mode of operation across a variety of transformation types;[7] yet, remarkably, this amino acid is generally ineffective as an iminium catalyst with enals or enones. Given these mutually orthogonal reactivity profiles, we hypothesized that the combination of imidazolidinone **1** and proline should provide a dual-catalyst system that fully satisfies the chemoselectivity requirements for cycle-specific catalysis (i.e. **1** is



Scheme 1. a) Absolute and relative stereocontrol in cycle-specific cascade catalysis. b) Imidazolidinone **1** and proline (**2**) as catalysts. LUMO = lowest unoccupied molecular orbital, HOMO = highest occupied molecular orbital.

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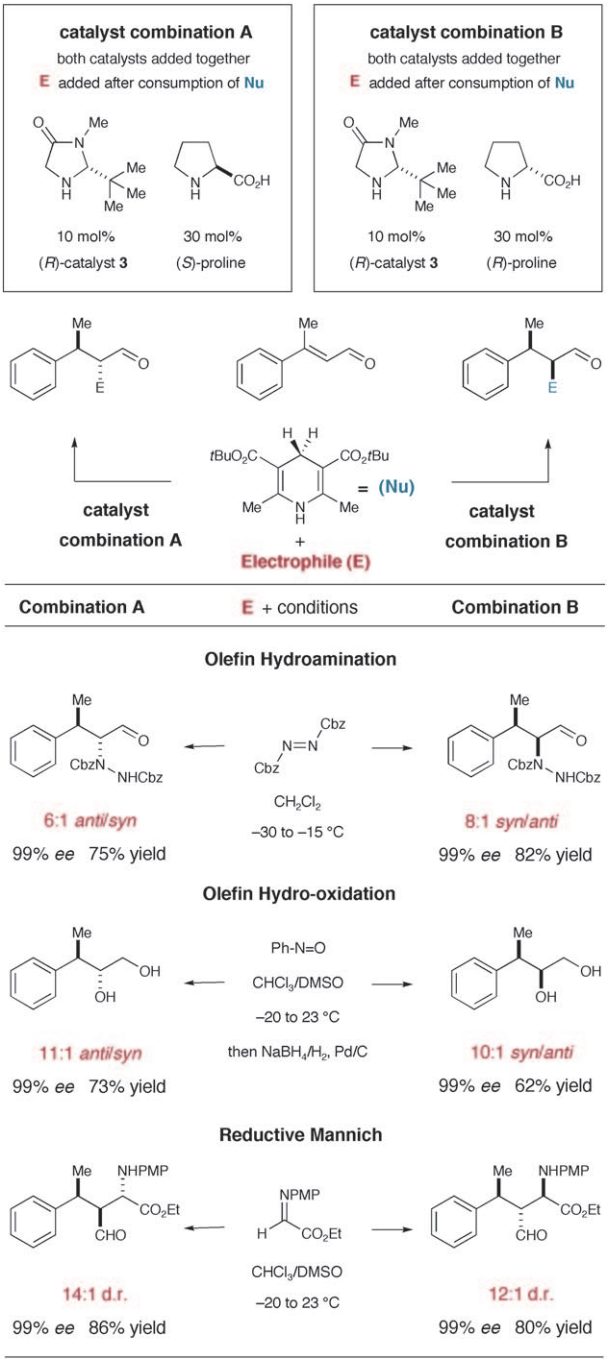
responsible for exclusive iminum activation, proline assumes exclusive bifunctional enamine activation). Moreover, we hoped that this catalyst union would enable the invention of powerful new transformations that combine many of the fundamental bond constructions that have become available by means of iminium and enamine catalysis.

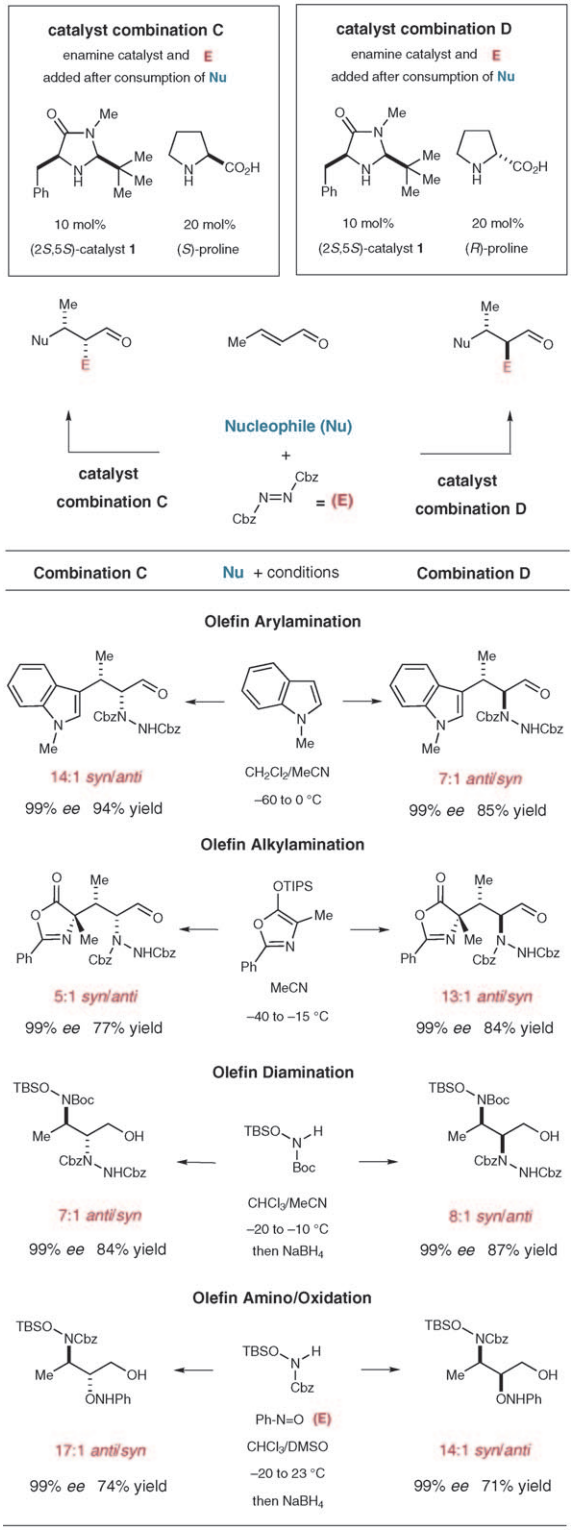
A central goal of our cascade-catalysis studies has been to develop reaction classes that are widely viewed as important yet elusive within the field of asymmetric catalysis. In this context, we directed our initial studies on cycle-specific catalysis towards the enantioselective olefin hydroamination,[10] olefin hydro-oxidation,[11] and reductive Mannich reaction.[12] To this end, our preliminary experiments were performed using β-methylcinnamaldehyde, Hantzsch ester, two separate combinations of proline (**2**) and imidazolidinone **3**, and one of three electrophiles that are known to be susceptible to bifunctional enamine activation. As revealed in Scheme 2, a hydrogenation–amination sequence using catalyst combination **A** along with the aza-Michael acceptor dibenzylazodicarboxylate[13] provided the olefin 1,2-hydroamination product with near-perfect enantiocontrol and excellent *anti* diastereoselectivity (99% *ee*, 6:1 *anti*/*syn*). In accord with our design plan, using the other enantiomer of the proline catalyst while retaining the imidazolidinone isomer (as performed with combination **B**) resulted in complete reversal of diastereocontrol to provide the *syn* hydroamination adduct without loss in reaction efficiency or enantioselectivity (82% yield, 99% *ee*, 8:1 *syn*/*anti*). We next examined the capacity of our cycle-specific cascade system to formally perform an olefin hydration by an enal β-reduction/α-formyl oxidation mechanism. In this case, use of nitrosobenzene[14] as the electrophilic partner with catalyst combination **A** provided the 1,2-hydro-oxidation adduct with excellent stereoselectivity (99% *ee*, 11:1 *anti*/*syn*). Once again, the isomeric catalyst blend **B** enforced an inversion in relative stereochemistry (10:1 *syn* selectivity) while achieving exquisite enantioinduction (62% yield, 99% *ee*). To round out this electrophile survey, we examined the use of Hantzsch ester with a glyoxylate imine in an attempt to perform a cascade reductive Mannich reaction.[15,16] As outlined in Scheme 2, this ideal was brought to fruition with catalyst combination **A** to afford the *syn–anti* Mannich triad while the *anti–anti* species was readily furnished with combination **B**.

To probe the scope of the nucleophilic component in this cycle-specific sequence we employed crotonaldehyde as the enal substrate, in conjunction with dibenzylazodicarboxylate, two separate combinations of proline (**2**) and imidazolidinone **1** (combinations **C** and **D**), and a series of heteroatom and aryl nucleophiles that are known to be susceptible to iminium-activated substrates (Scheme 3). Application of 1-methylindole as the π nucleophile[17a] with catalyst combination **C** provided the 1,2-arylamination product with excellent yield and stereocontrol (94% yield, 99% *ee*, 14:1 *syn*/*anti*). As anticipated, access to the corresponding *anti* isomer is achieved by use of the diastereomeric dual-catalyst system **D** (99% *ee*, 7:1 *anti*/*syn*). Moreover, employing a silyloxyoxazole as the iminium nucleophile[18] resulted in the generation of an alkylamination adduct that contains three contiguous stereocenters; all of which can be formed with modular



Scheme 2. Cycle-specific organocatalysis: representative electrophiles. Cbz = benzyloxycarbonyl, PMP = *p*-methoxyphenyl.

stereocontrol by use of the appropriate catalyst combination. Given our agenda that organocascade catalysis should provide a new avenue for reaction invention, it is important to note that prior to this study there were no documented methods to perform either olefin arylamination or alkylamination in an enantioselective, diastereoselective, or racemic format. Two transformations that have received considerable attention from the catalysis community are olefin 1,2-diamination[19,20] and 1,2-amino-oxidation.[21,22] We have found that our cascade-catalysis strategy provides enantioselective and modular access to differentially protected 1,2-



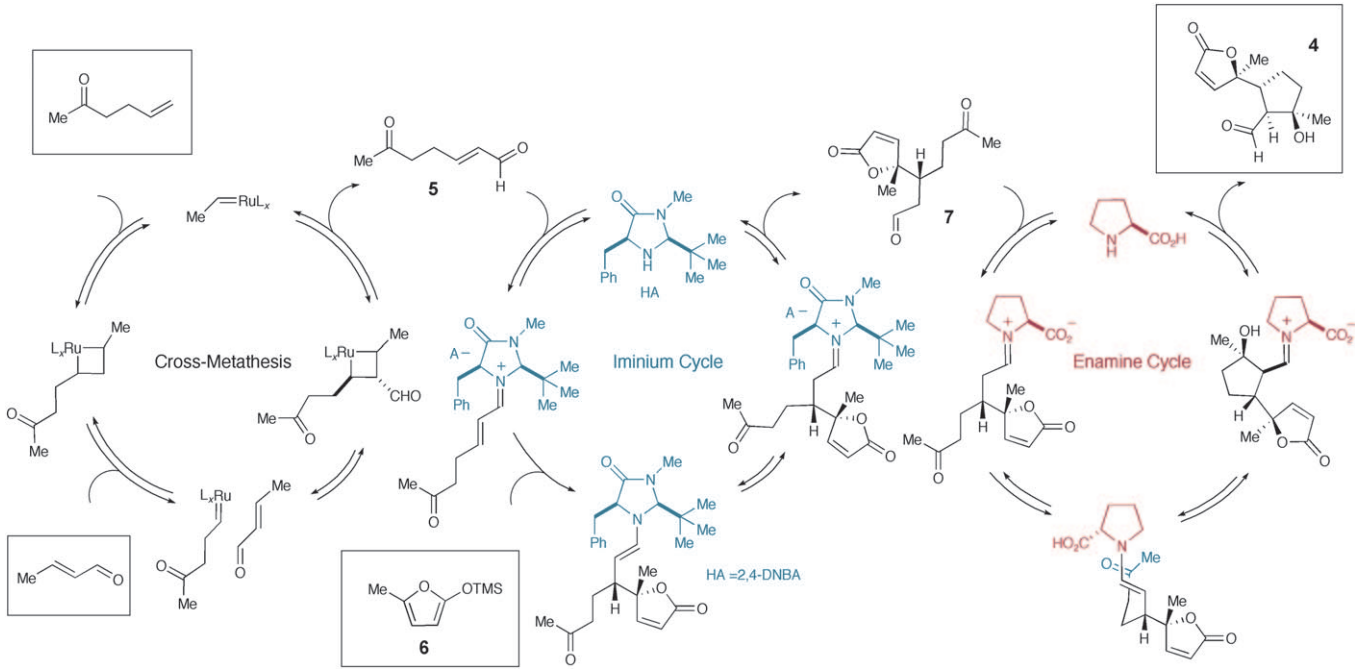
Scheme 3. Cycle-specific organocatalysis: representative nucleophiles. TIPS = triisopropylsilyl, TBS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl.

diamination products by the use of a silyloxycarbamate[17b] in conjunction with dibenzylazodicarboxylate (combination **C** = 99% *ee*, 7:1 *anti*/*syn*; combination **D** = 99% *ee*, 8:1 *syn*/*anti*). Moreover, a similar amine nucleophile can be employed in a cascade-catalysis sequence with nitrosobenzene to rapidly generate optically pure 1,2-amino-oxidation adducts (≥99% *ee*, ≥71% yield). Once again, the flexibility of this strategy allows ready access to either 1,2-amino-oxidation diastereomer (catalysts **C**, 17:1 *anti*/*syn*; catalysts **D**, 14:1 *syn*/*anti*). It is important to note that catalyst combinations **A** and **B** can be used as a blend from the outset of the reaction, whereas the transformations performed shown in Scheme 3 (combinations **C** and **D**), required the addition of the enamine catalyst after the iminium cycle step is complete.

A fundamental goal of our cascade-catalysis studies has been to demonstrate that cycle-specific sequences can be readily applied to the production of architectural complexity in the form of natural products or medicinal agents. In this context, we envisioned an expedient synthesis of (−)-aromadendranediol (Scheme 4), a widely distributed sesquiterpene that has been isolated from the marine coral *Sinularia mayi*[23] as well as from the leaves of the Amazonian tree *Xylopia brasiliensis*.[24] While the biological activity of the aromadendranediol family has not been extensively studied, these isolates are known to be constituents of extracts used in Brazilian[24] and Chinese[25] folk medicine as sedatives and analgesics, and to treat lung inflammation. Aromadendranediol presents a variety of architectural challenges for chemical synthesis, most notably a tricyclic framework that contains six stereocenters (five of which are contiguous), two tertiary hydroxy groups, and a 1,1-dimethylated cyclopropane ring. While no total synthesis of this natural isolate has been reported to date, Djerassi and co-workers have documented a semisynthesis founded upon the related sesquiterpene (+)-spathulenol.[23]

In brief, we hypothesized that the bicyclic butenolide **4**, which contains four of the six stereocenters (all contiguous) and 12 of the 15 carbons found in aromadendranediol, might be generated in a single operation from commercial materials using a triple-cascade-catalysis sequence (Scheme 4). We proposed that treatment of crotonaldehyde with 5-hexene-2-one in the presence of a suitable Grubbs ruthenium alkylidene catalyst would initiate a cross-metathesis to generate the keto-enal **5**. At this stage, the introduction of silyloxyfuran **6** with amine catalyst **1** should enable a Mukaiyama–Michael iminium cycle[17c] with enal **5**, thereby forging two of the required contiguous chiral centers with absolute and relative stereocontrol. We presumed the resulting keto-aldehyde **7** would then enter a third catalytic cycle with proline to undergo a diastereoselective intramolecular aldol reaction to produce butenolide **4**, a step that would build the requisite *trans*-substituted cyclopentyl ring, the third and fourth contiguous stereocenters, and the remaining tertiary alcohol found in aromadendranediol.

In the event, sequential addition of Grubbs II catalyst, imidazolidinone **1**, and proline (catalyst combination **E**) along with the respective addition of crotonaldehyde, 5-hexene-2-one, and trimethylsilyloxyfuran **6** in wet dichloromethane/ethyl acetate resulted in formation of the desired cascade adduct in 64% yield and 95% *ee*, and with a 5:1 preference for the desired diastereomer (Scheme 5).[26] The structural and stereochemical orientation of butenolide **4** was confirmed by single-crystal X-ray analysis.[27]



Scheme 4. Proposed mechanism of the triple-cascade catalysis to generate the stereochemical core of aromadendranediol. 2,4-DNBA = 2,4-dinitrobenzoic acid.

The synthesis of aromadendranediol was then completed as outlined in Scheme 5 by the global reduction of cascade adduct **4** to afford a tetraol which upon persilylation with triethylsilyl triflate and chemoselective oxidation of the primary alcohols, furnished the respective dialdehyde **8**. Wittig olefination prior to ring-closing metathesis furnished smoothly the [5.7.0] bicyclic system **9** in excellent yield for the five-step sequence (46% yield). The *gem*-dimethyl cyclopropane moiety was then installed in a diastereoselective fashion by a two-step sequence involving dibromocarbene followed by treatment with lithium dimethylcuprate and methyl iodide[28] to afford triethylsilyl-protected (−)-aromadendranediol as a single isomer. Removal of the protecting groups using standard procedures furnished synthetic (−)-aromadendranediol, which was identical in all respects to the natural isolate. It is important to note that this synthetic pathway incorporates the first examples of 1) a dual-cascade organometallic–organocatalytic sequence, 2) a triple-catalysis-cycle-specific mechanism, and 3) an organocascade catalytic approach towards the construction of a natural product.[29]

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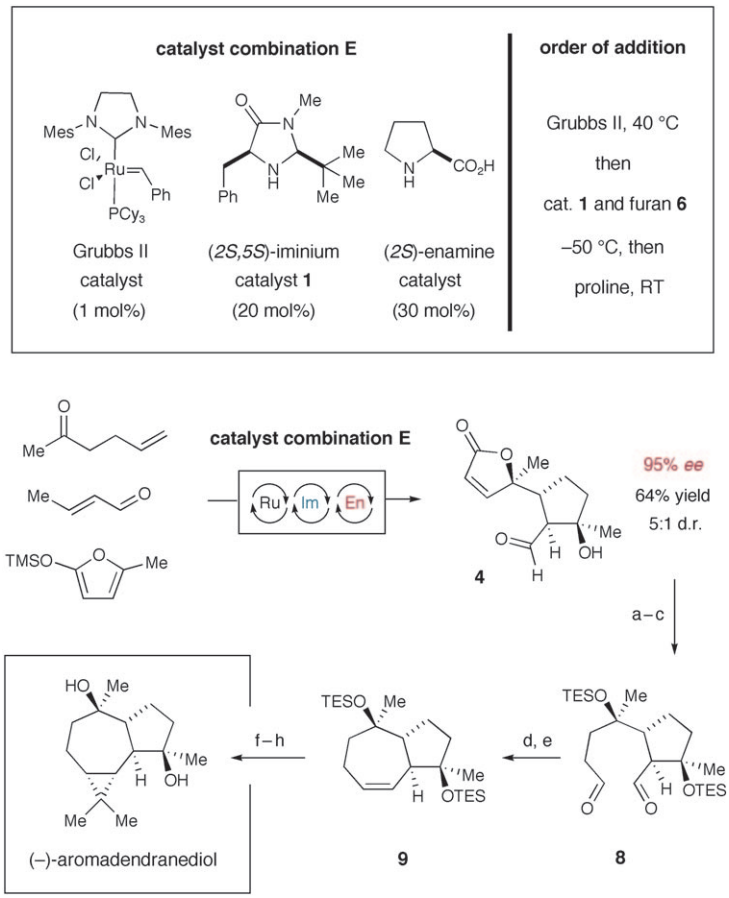

Scheme 5. Total synthesis of (−)-aromadendranediol: a) Pd/C, 1 atm H_2, EtOH, 23 °C; $LiAlH_4$, THF, 0 °C, 85%; b) TESOTf, pyridine, CH_2Cl_2, 0 °C, 95%; c) and d) DMSO, $(CO)_2Cl_2$, Et_3N, −78 to −40 °C, then $MePPh_3Br$, *n*BuLi, THF, 0 °C to RT, 72% (over two steps); e) Grubbs II, CH_2ClCH_2Cl, 70 °C, 78%; f) KO*t*Bu, $CHBr_3$, hexane, 0 °C, 96% single diastereomer; g) Me_2CuLi, MeI, Et_2O, −20 to 0 °C, 99%; h) HF, MeCN, RT, 93%. TES = triethylsilyl.

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