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Au(I)-Catalyzed Annulation of Enantioenriched Allenes in the Enantioselective Total Synthesis of (−)-Rhazinilam

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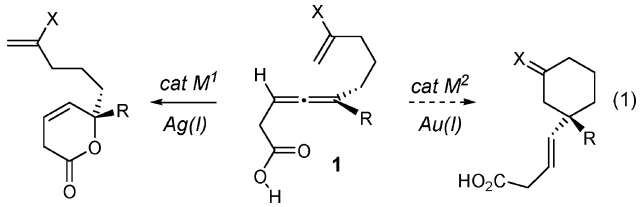
The utility of allenes in metal-catalyzed addition reactions has made these intermediates increasingly popular for an array of synthesis activities. In this context, allenes parallel closely alkynes in their reactivity toward metal-mediated nucleophilic additions.[1] However, unlike alkyne substrates, allenes offer the potential for relaying the associated axial chirality to ensuing bond constructions.[2] For example, allene chirality is faithfully translated to tertiary carbinol stereocenters during Ag(I)-catalyzed cyclization of enantioenriched allene acetic acid derivatives **1** (eq 1).[3]



On the basis of this precedent, a strategy for enantioselective annulative quaternary carbon construction would evolve from engaging latent carbon-based nucleophiles tethered at the allene terminus in similar metal-catalyzed allene additions. The enantioselective total synthesis of (−)-rhazinilam (**2**) reported herein demonstrates the success of this reaction design using Au(I)-catalyzed pyrrole−allene additions (Figure 1).

Scrutinizing (−)-rhazinilam's structure revealed the tetahydroindolizine ring system and the chiral quaternary carbon as the key architectural features of the natural product.[4] While atropisomerism about the $C_{12}-C_{13}$ biaryl bond warranted appropriate consideration, a synthesis strategy relying on late-stage lactamization after C_5 stereocenter installation would ensure the correct atropisomer about the biaryl axis.[4a] To implement this strategy, we envisioned tetrahydroindolizine construction proceeding with concurrent installation of the quaternary carbon stereocenter. Specifically, intramolecular pyrrole addition to a metal-activated allene **3** constituted an expedient entry to the tetrahydroindolizine unit **4** provided efficient translation of allene chirality to the incipient quaternary carbon was realized. S_N2' ring opening of optically active β-lactone **5** would provide an especially concise synthesis of the requisite enantioenriched pyrrole-substituted allene **6**.

Considering the pivotal nature of the putative pyrrole−allene cyclization in our synthesis design, preliminary investigations focused on validating this transformation as a conduit to rhazinilam. Toward this goal, β-lactone **5** (97% ee, 79%) was prepared by the Al(III)-catalyzed acyl halide−aldehyde cyclocondensation (AAC) of 2-pentynal (**6**) and acetyl bromide (5 mol % of **7**, ^{i}Pr$_2$NEt) (Scheme 1).[5] Copper(I)-catalyzed S_N2' ring opening of **5** with the pyrrole-substituted Grignard reagent **8**[6] provided the enantioenriched allene **9** (88%). Assaying the optical purity of **9** required conversion to unsaturated δ-lactone **10** (10 mol % of $AgNO_3$, ^{i}Pr$_2$NEt, then DBU) and confirmed only modest stereochemical erosion had accompanied β-lactone ring opening (91% ee, 83%). The proclivity of Pd(II) complexes for activating alkenes as electrophiles inspired our initial decision to explore Pd-based annulation catalysts. Thus, reacting allene **11** with $Cl_2Pd(CH_3CN)_2$ (20 mol %) promoted 6-endo-trig cyclization to directly afford the tetrahydroindolizine core

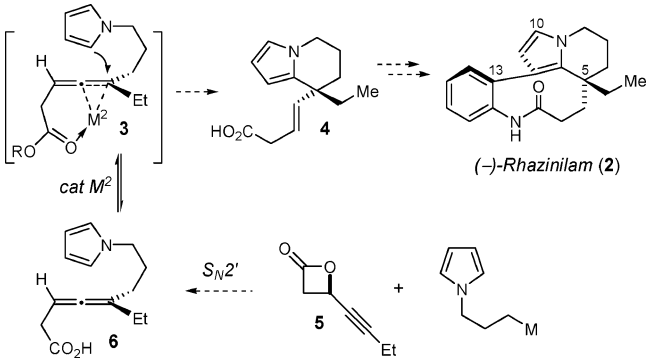
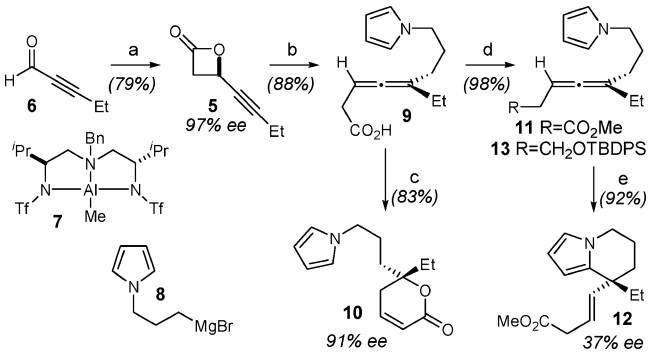


Figure 1. Allene templates for asymmetric annulation reactions.

Scheme 1 [a]



[a] Conditions: (a) 5 mol % of **7**, ^{i}Pr$_2$NEt, −78 °C; (b) **8**, 10 mol % of CuCN, −78 °C; (c) (i) 10 mol % of $AgNO_3$, ^{i}Pr$_2$NEt; (ii) DBU; (d) $TMSCHN_2$, C_6H_6/MeOH; (e) 20 mol % of $(MeCN)_2PdCl_2$, CH_2Cl_2.

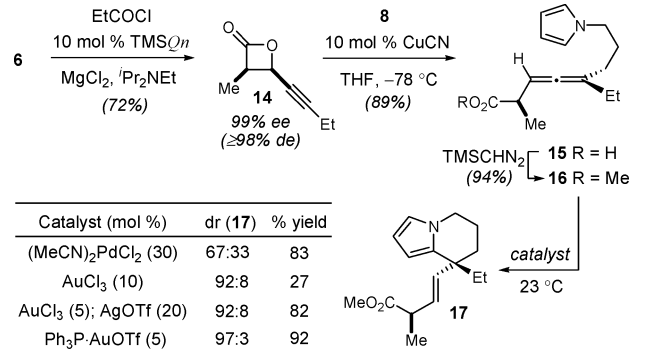
12 of rhazinilam (37% ee, 92%). However, in addition to the high catalyst loadings, this reaction pathway was compromised by the poor enantioselectivity accompanying Pd(II) catalysis.

On the basis of these observations, elucidating catalyst systems that would effectively translate allene chirality to the annulation process was essential for realizing our synthesis strategy. Substrate-directed catalyst association to the allene π-orbital *syn* to the pendant carboxylate ester was envisioned as a mechanism for ensuring efficient chirality transfer by forcing nucleophilic attack opposite the activating metal (**3**, Figure 1). Poor enantioselection achieved under Pd(II) catalysis was ascribed to the limited Lewis acidity of $PdCl_2$ and the resulting lability of the directing Lewis acid−base contact. The further erosion of enantioselectivity observed for the Pd(II)-catalyzed cyclization of allene **13** (16% ee) lacking a Lewis basic directing group provided confirmatory evidence for this hypothesis. This analysis suggested that the most successful catalysts would express both hard and soft Lewis acid characteristics required for simultaneous association with both the ester carbonyl and allene π-system, respectively.

To expedite ensuing investigations, the 3,4-*cis*-disubstituted β-lactone **14** was selected as the allene precursor in preference to **5**, thereby eliminating the need for repetitive allene → lactone conversion to assay S_N2' stereoselection (Scheme 2). Thus, β-lac-

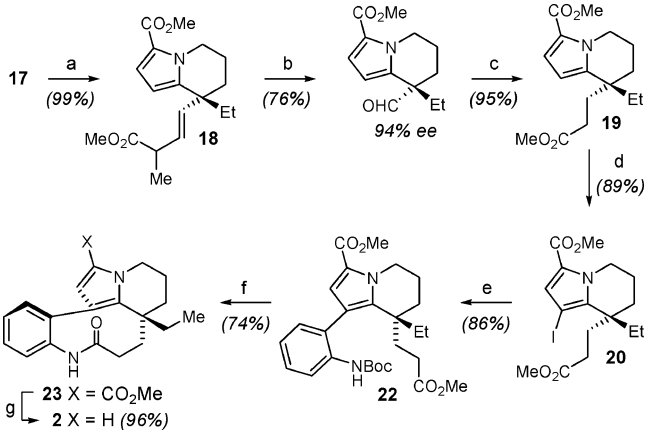
10.1021/ja0629110 CCC: $33.50

Scheme 2



Catalyst (mol %)	dr (**17**)	% yield
$(MeCN)_2PdCl_2$ (30)	67:33	83
$AuCl_3$ (10)	92:8	27
$AuCl_3$ (5); AgOTf (20)	92:8	82
$Ph_3P{\cdot}AuOTf$ (5)	97:3	92

Scheme 3 [a]



[a] Conditions: (a) Cl_3COCl; NaOMe; (b) (i) 10 mol % of OsO_4, NMO then $NaIO_4$; (c) (i) $Ph_3P{=}CHCO_2Me_3$; (ii) 10% Pd/C, H_2, MeOH; (d) I_2, $AgCO_2CF_3$; (e) 2-C_6H_4(Bpin)NHBoc (**21**), 2.5 mol % of $Pd_2(dba)_3$, 10 mol % of SPhos, K_3PO_4, aq THF; (f) (i) $Ba(OH)_2$; (ii) TFA; (iii) HATU, $^iPr_2NEt$; (g) (i) 50% NaOH; (ii) aq HCl.

tone **14** was obtained in 99% ee (≥98% de) from the alkaloid-catalyzed propionyl chloride-2-pentynal AAC reaction (10 mol % of *O*-trimethylsilylquinine (TMS*Qn*), $MgCl_2$, $^iPr_2NEt$).[7] β-Lactone ring opening with **8** provided allene **15** that was readily determined to be a single diastereomer by ^1H NMR (89%). To ensure that the methyl-bearing stereocenter had no affect on annulation stereoselection, methyl ester **16** was subjected to Pd(II)-catalyzed cyclization that, in accord with previous results, provided **17** as a 2:1 mixture of diastereomers (83%).

Our success using Ag(I) catalysts to affect intramolecular carboxylic acid−allene additions led us to concentrate subsequent catalyst screening on group 11 metal complexes.[3] While Ag(I) complexes proved completely ineffective as catalysts, reacting **16** with $AuCl_3$ (10 mol %) afforded bicyclic pyrrole **17** in 84% de, albeit in a modest 27% yield.[8] The putative cationic Au(III) complex obtained using AgOTf as a co-catalyst with $AuCl_3$ elicited a dramatic improvement in annulation efficiency, affording **17** in 82% yield (84% de).[9,10] Evaluating reaction efficiency as a function of Au/Ag structure and stoichiometry revealed $Ph_3P{\cdot}AuOTf$ (5 mol %)[11] as the optimal annulation catalyst, providing tetrahydroindolizine **17** with nearly complete translation of allene chirality (94% de, 92%).[12]

Having addressed both tetrahydroindolizine construction and quaternary carbon installation in preparing **17**, introducing the C_{12} aniline moiety represented the only significant obstacle to completing the total synthesis. To circumvent difficulties associated with heterocycle oxidation, pyrrole basicity was effectively attenuated by regioselective carboxylation to provide **18** (99%).[13] Oxidative olefin cleavage (72%), Horner−Wittig homologation, and catalyzed dihydrogenation (95% over two steps) afforded ester **19** with the C_5 tether correctly formatted for eventual lactamization. Biaryl bond construction proceeded by regioselective pyrrole iodination (89%)[4c] and ensuing Suzuki−Miyaura cross-coupling of iodide **20** with *N*-Boc aniline boronic ester **21** using Buchwald's SPhos ligand (2.5 mol % of $Pd_2(dba)_3$, 10 mol % of SPhos, K_3PO_4, aq THF) to afford the 3-aryl pyrrole **22** (86%).[14] Chemoselective ester saponification and aniline N-deprotection (93% for two steps) preceded HATU-mediated lactamization of the resulting amino acid to deliver 10-(carbomethoxy)rhazinilam **23** (74% over three steps). Pyrrole decarboxylation (NaOH; HCl, 50 °C) then provided synthetic (−)-rhazinilam (**2**) in 96% yield (94% ee).

Asymmetric Au(I)-catalyzed pyrrole additions to enantioenriched allenes afford a unique entry to optically active heterocycles. Trisubstituted allenes provide convenient templates for heterocycle annulation with concomitant asymmetric quaternary carbon construction. An enantioselective total synthesis of (−)-rhazinilam highlights the potential utility of this reaction technology in target-oriented synthesis.

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Supporting Information Available: Experimental procedures and representative ^1H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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