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Asymmetric Claisen Rearrangements Enabled by Catalytic Asymmetric Di(allyl) Ether Synthesis

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Ester enolate (Ireland)-Claisen rearrangements are largely differentiated from related [3,3] sigmatropic rearrangements by their extensive applications in synthesis enterprises.[1] The general utility of Ireland-Claisen rearrangements can be attributed to the enhanced functional group compatibility, superior stereocontrol, and facilitated substrate preparation afforded by this activated Claisen variant (Figure 1). We recently introduced olefin isomerization-Claisen rearrangement (ICR) reactions as a means of imparting similarly advantageous features to "unactivated" aliphatic Claisen rearrangements.[2,3] With the goal of broadening the utility of the ICR methodology in asymmetric synthesis, we were interested in exploiting the ICR reaction design to devise an efficient and operationally simple strategy for affecting enantioselective Claisen rearrangements. This report describes the integration of a catalytic asymmetric synthesis of di(allyl) ether substrates into an expedient, two-step protocol for realizing asymmetric aliphatic Claisen rearrangements from readily available starting materials.

Rigorous substrate-to-product chirality translation is among the defining characteristics of [3,3] sigmatropic rearrangements.[4] Thermal Claisen rearrangements routinely proceed via chairlike transition states that orient substituents residing at the carbinol stereocenter (R_{eq}) in pseudoequatorial positions (Figure 1). This observation inspired a reaction design for asymmetric Claisen rearrangements predicated on merging catalytic asymmetric organometallic-aldehyde addition reactions with in situ O-allylation of the putative metal alkoxide reaction intermediate (step 1). The resulting enantioenriched di(allyl) ethers **1** constitute direct progenitors of asymmetric Claisen rearrangements by virtue of the ICR technology (step 2), thereby providing a simple two-step sequence to enantioenriched Claisen adducts **2** from easily obtained precursors.

With the goal of using catalytic asymmetric transformations to establish substrate chirality, amino alcohol-catalyzed dialkylzinc-aldehyde additions were selected as conduits to the requisite enantioenriched di(allyl) ether ICR substrates (eq 1). We envisioned that catalyzed diethylzinc additions to conjugated enals would afford enantioenriched allylic zinc alkoxides **3**. Ensuing O-allylation of the zinc alkoxide intermediate would deliver the desired ICR substrates.[5] Thus, (−)-MIB (**4**)-catalyzed addition of Et_2Zn to cinnamaldehyde (2 mol %, toluene, 0 °C) was used as a representative route to the enantioenriched zinc alkoxide **3** (93% ee).[6] Attempted Pd(0)-catalyzed O-allylation directly on **3** afforded minimal etherification. However, the zinc carboxylate **5**, obtained by selective protonation of the Et-Zn linkage with AcOH, proved considerably more reactive toward O-allylation. Thus, reacting alkoxide **3** directly with AcOH (1 equiv) followed by allyl acetate and a catalyst system composed of $Pd(OAc)_2$ (5 mol %) and PPh_3 (25 mol %) (THF, 60 °C, 6 h) delivered the di(allyl) ether ICR precursor **6a** in 79% yield (93% ee).[7] Subjecting ether **6a** to the ICR reaction conditions (1 mol % $Ir(PCy_3)_3^+$ then 3 mol % PPh_3, 40 °C)[2] delivered the 2,3-syn Claisen adduct **7a** with enantiomeric purity paralleling that of the di(allyl) ether precursor (92% ee).

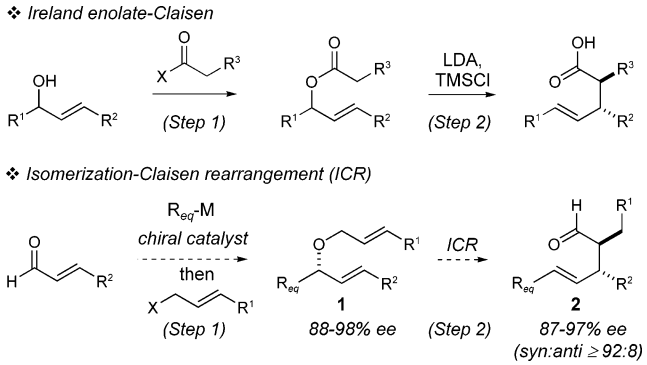
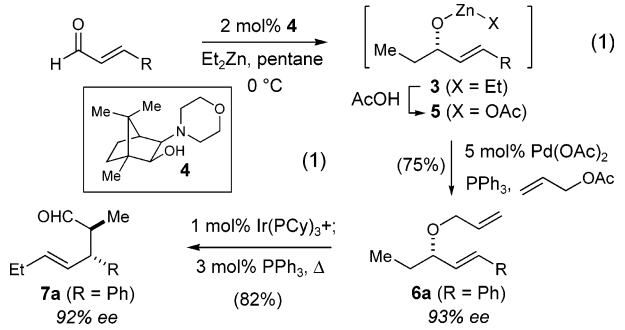


Figure 1. Two-step, enantioselective [3,3] sigmatropic rearrangements.



Merging the one-step enantioselective di(allyl) ether synthesis with subsequent ICR reactions provided access to a variety of enantioenriched Claisen adducts from readily obtained Et_2Zn and conjugated enal reaction partners (Table 1). The merged addition-allylation sequence affords di(allyl) ether ICR substrates **6a**−**f** incorporating C_3 aryl (entries a, b, and f), alkenyl (entry c), aliphatic alkyl (entry d), or oxygen-substituted alkyl substituents (entry e) in good yields and with consistently high enantioselectivies (88−98% ee). As anticipated, each of these di(allyl) ether substrates participated in subsequent ICR reactions with faithful translation of chirality, delivering the enantioenriched 2,3-syn-disubstituted pentenal derivatives **7a**−**f** with high absolute and relative stereocontrol (87−97% ee, 84−94% de). These di(allyl) ether syntheses are not limited to unsubstituted allyl acetate alkylating agents as 1-acetoxy-3-trimethylsilylpropene affords di(allyl) ether **8** (77% yield, 93% ee) (entry g). Subjecting **8** to the optimized ICR reaction conditions provided the enantioenriched heptenal **9** in 91% ee (50% yield).[8]

Enantioenriched di(allyl) ether ICR substrates can also be assembled from easily obtained terminal alkyne precursors (eq 2). For example, 1-heptyne and 3,3-dimethyl-1-butyne were transformed to the alkenyl zinc reagents **10a**/**b** by hydroboration and B → Zn transmetalation.[9] The alkenyl zinc reagents reacted with benzaldehyde in the presence of **4** (2 mol %) followed by Pd(0)-catalyzed O-allylation to generate di(allyl) ethers **11a** (87% ee) or

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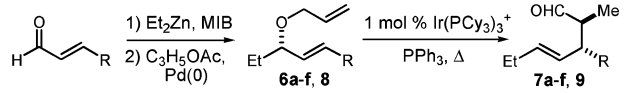
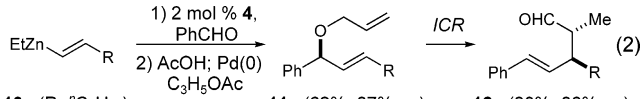
Table 1. Synthesis and ICR of Enantioenriched Di(allyl) Ethers **6**



entry	% yield **6** (% ee)[a]	% yield **7** (*syn*:*anti*)[b]	% ee **7**[c]
a	**6a** (R = Ph) 75 (93)	**7a** (R = Ph) 82 (95:5)	92
b	**6b** (R = 2-furyl) 79 (96)	**7b** (R = 2-furyl) 75 (95:5)	96
c	**6c** (R = *E*-CHCHPh) 87 (93)	**7c** (R = *E*-CHCHPh) 77 (95:5)	93
d	**6d** (R = ^{n}C$_5$H$_{11}$) 80 (88)	**7d** (R = ^{n}C$_5$H$_{11}$) 70 (97:3)	87
e	**6e** (R = CH$_2$OBn) 73 (93)	**7e** (R = CH$_2$OBn) 60 (96:4)	92
f[e]	**6f** 84 (98)	**7f** 81 (92:8)[d]	97
g	**8** 77 (93)	**9** 50 (95:5)	91

[a] Enantiomeric excess determined for allylic alcohol obtained by protonation of the zinc alkoxide prior to O-allylation. [b] Diastereomer ratios determined by ^{1}H NMR of crude product mixtures. [c] Enantiomer ratios determined by chiral HPLC or GC. [d] Claisen adduct **7f** was obtained as an 83:17 *E*:*Z* mixture of olefin isomers; enantiomer and diastereomer ratios are reported for the *E* isomer.

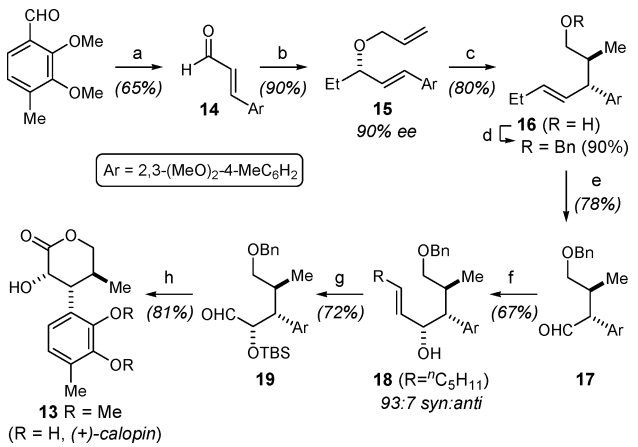
11b (92% ee);[10] the ensuing ICR sequence provided the 2,3-syn-disubstituted pentenals **12a** and **12b** in 86 and 93% ee, respectively (**12a**: 80%; **12b**: 80% yield).



10a (R=^{n}C$_5$H$_{11}$) **11a** (62%, 87% ee) **12a** (80%, 86% ee)
10b (R=CMe$_3$) **11b** (63%, 92% ee) **12b** (80%, 93% ee)

An enantioselective synthesis of the (+)-calopin dimethyl ether (**13**) highlights the potential utility of the ICR technology in asymmetric synthesis activities (Scheme 1).[11] Thus, reacting 2,3-dimethoxy-4-methylbenzaldehyde[12] with Meyers' lithio enaminophosphonate reagent provided enal **14**.[13] Enal **14** was then converted to the enantioenriched di(allyl) ether **15** using the optimized reaction conditions described herein (90% yield, 90% ee). ICR reorganization of **15** with in situ reduction of the intervening aldehyde function generated the 2,3-syn-disubstituted 4-pentenol **16** (90% ee, syn/anti = 94:6). Alcohol protection was followed by oxidative olefin cleavage to provide aldehyde **17** (70% for two steps). Aldehyde **17** participated in highly Felkin-selective alkenyl zinc addition with the reagent obtained from 1-heptyne hydrozirconation and Zr → Zn transmetalation to give allylic alcohol **18** (67%, 93:7 syn/anti).[14] The allylic alcohol was protected prior to oxidative alkene cleavage to afford aldehyde **19** (72%). Aldehyde oxidation to the corresponding carboxylic acid preceded benzyl ether hydrogenolysis and direct oxidation of the intervening lactol. Silyl ether deprotection then completed the synthesis of the calopin dimethyl ether **13** (81% for three steps).

Scheme 1 [a]



[a] (a) ^{t}BuN=CHCH$_2$PO(OEt)$_2$, LDA; H$^+$. (b) See text. (c) 1 mol % Ir(PCy$_3$)$_3^+$; 3 mol % PPh$_3$, 80 °C; NaBH$_4$. (d) NaH, BnBr. (e) 1.5 mol % OsO$_4$, NMO; NaIO$_4$. (f) ^{n}C$_5$H$_{11}$CHCHZrClCp$_2$, ZnEt$_2$. (g) i. TBSCl, imid; ii. O$_3$; NaClO$_2$, NaH$_2$PO$_4$. (h) i. H$_2$, Pd/C then 5 mol % TPAP, NMO; ii. TASF, DMF.

The asymmetric di(allyl) ether synthesis-ICR reaction sequence provides convenient access to enantioselective aliphatic Claisen rearrangements from easily obtained starting materials. The potential of this reaction technology to simplify the execution of enantioselective Claisen rearrangements should allow these reactions to be readily integrated into asymmetric synthesis activities.

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

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