

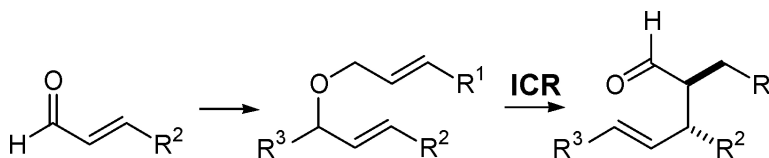
Communication

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Catalyzed Olefin Isomerization Leading to Highly Stereoselective Claisen Rearrangements of Aliphatic Allyl Vinyl Ethers

Scott G. Nelson,* Christopher J. Bungard, and Kan Wang

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received July 30, 2003; E-mail: sgnelson@pitt.edu

Claisen and related [3,3] sigmatropic rearrangements share the defining characteristic of rapidly introducing molecular complexity from simple, easily obtained starting materials.¹ Activated variants of the Claisen rearrangement have greatly extended the synthetic utility of the parent allyl vinyl ether rearrangement by allowing reactions to be performed under conditions that afford excellent stereocontrol and substrate compatibility while facilitating substrate preparation.² The parent Claisen rearrangements offer useful complements to the more extensively utilized enolate Claisen variants by affording direct access to aldehyde functionalities amenable to immediate elaboration using the wealth of transformations available for these functional groups.³ With the goal of broadly exploiting Claisen-derived α -chiral aldehydes in synthesis activities, we have developed highly stereoselective Claisen rearrangements from easily prepared di(allyl) ethers **1** (Figure 1). The Claisen rearrangements involve catalyzed olefin isomerization to generate the vinyl ether moiety followed by thermal [3,3] sigmatropic rearrangement to afford *syn*-2,3-dialkyl-4-pentalen derivatives **2** with high diastereoselectivity.

The strategic nature of Claisen rearrangements in synthesis activities has generated considerable interest in addressing the operational limitations associated with aliphatic allyl vinyl ether rearrangements.^{4,5} Among the strategies for simplifying vinyl ether rearrangements, several groups have recognized metal-catalyzed allyl ether isomerization as a convenient route to the enol ether component of Claisen substrates. Bis(allyl) or allyl homoallylic ethers are subject to metal-catalyzed isomerization to the corresponding vinyl ether Claisen substrates.⁶ Unfortunately, these olefin isomerization catalyst systems have not been integrated into generally applicable, highly diastereoselective Claisen rearrangements.

Considering the ready availability of bis(allyl) ethers **1** from nucleophilic addition to α,β -unsaturated aldehydes followed by O-allylation, we sought alkene isomerization catalysts that would render these substrates effective precursors to highly stereoselective Claisen rearrangements. These catalysts would necessarily achieve both chemo- and stereoselective isomerization of only one allyl residue and would not interfere with the ensuing thermal Claisen rearrangement nor accelerate epimerization of the emergent aldehyde reaction product. Successfully developing catalysts satisfying these criteria would allow thermolysis of bis(allyl) ethers in the presence of the catalyst complex to afford direct access to diastereomerically enriched 2,3-dialkyl 4-pentalen derivatives **2**.

Considering the success of iridium-based complexes as alkene isomerization catalysts, we initially examined Ir(I)-based catalyst systems for effecting chemo- and stereoselective allyl ether isomerization in bis(allyl) ether substrates.⁷ Preliminary investigations revealed efficiency of both alkene isomerization and the ensuing Claisen rearrangement to be critically dependent on catalyst composition. Typical Ir(I)-phosphine precatalysts were prepared by reacting $[(C_8H_{14})_2IrCl]_2$ **3**⁸ with varying amounts of phosphine ligand followed by halide abstraction to afford the reactive cationic

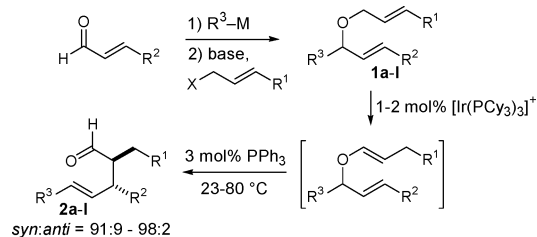
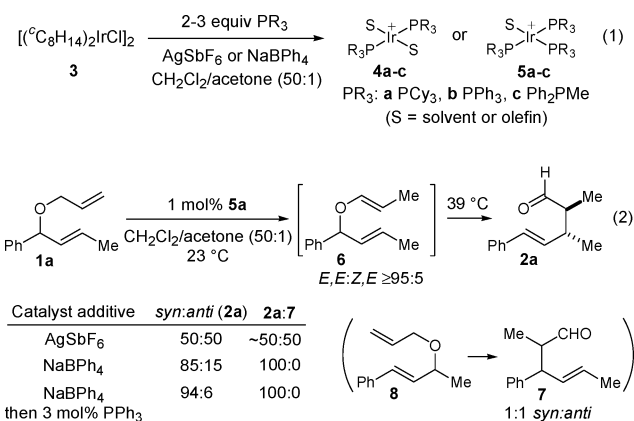


Figure 1. Isomerization-Claisen rearrangement (ICR) reactions.

Ir(I)-bis(phosphine) or Ir(I)-tris(phosphine) complexes **4** and **5**, respectively (eq 1).⁹ Catalysts incorporating σ -basic phosphines having large cone angles provided very efficient alkene isomerization catalysts. Thus, the di- and triphosphine complexes obtained using PCy_3 mediated highly *E*-selective isomerization exclusively at the less substituted allyl ether in **1a** to afford the corresponding vinyl ether **6** (eq 2). Iridium complexes derived from aryl (less basic) phosphines provide catalysts exhibiting attenuated reactivity toward allyl ether isomerization. More importantly, attempted isomerization of bis(allyl) ether **1a** using the aryl phosphine-derived catalysts **4b/c** or **5b/c** was complicated by competing allyl ether migration, affording variable amounts of Claisen adduct **7** derived from the isomeric bis(allyl) ether **8**.



The method used for halide abstraction in preparing the reactive cationic Ir(I) catalysts also proved critical in defining the efficiency of the isomerization-Claisen rearrangement reactions. Cationic Ir(I) complexes obtained using AgSbF₆ achieved highly selective allyl ether isomerizations; however, these reactions produced equimolar mixtures of the expected Claisen adduct **2a** and pentalen **7** derived from competing allyl ether migration, each as a stereorandom mixture (eq 2). In general, Lewis acidic contaminants present during the thermal Claisen rearrangements, whether they are derived from Lewis acidic Ir(I)-phosphine species or Ag(I) salt byproducts, lead to poor diastereoselection in the putative Claisen adducts.

These investigations identified the complex obtained by reacting $[(C_8H_{14})_2IrCl]_2$ with PCy_3 (3 equiv/Ir) and NaBPh₄ as the halide abstractor in 50:1 CH_2Cl_2 /acetone (or 1,2-DCE/acetone) as the

Table 1. ICR Reactions of Substituted Bis(allyl) Ethers **1** (Figure 1)

| entry | bis(allyl) ether 1 ^a | syn:anti ^b | % yield ^c |
|-------|---|-----------------------|----------------------|
| a | R ¹ = H, R ² = CH ₃ , R ³ = Ph (1a) | 94:6 | 80 |
| b | R ¹ = H, R ² = R ³ = Ph (1b) | 98:2 | 92 |
| c | R ¹ = H, R ² = ⁱ Pr, R ³ = Ph (1c) | 95:5 | 93 |
| d | R ¹ = H, R ² = ⁿ Bu, R ³ = Ph (1d) | 97:3 | 70 |
| e | R ¹ = CH ₃ , R ² = R ³ = Ph (1e) | 95:5 | 84 |
| f | R ¹ = H, R ² = CH ₃ , R ³ = CH ₂ SiMe ₃ (1f) | 93:7 | 84 |
| g | R ¹ = H, R ² = Ph, R ³ = CH ₂ SiMe ₃ (1g) | 96:4 | 93 |
| h | R ¹ = H, R ² = CH ₃ , R ³ = ^t Bu (1h) | 92:8 | 86 |
| i | R ¹ = R ² = CH ₃ , R ³ = ^t Bu (1i) | 93:7 | 62 |
| j | R ¹ = H, R ² = CH ₃ , R ³ = ⁿ Bu (1j) | 86:8 ^d | 85 |
| k | R ¹ = H, R ² = Ph, R ³ = ⁿ Bu (1k) | 96:4 | 62 |
| l | R ¹ = H, R ² = Ph, R ³ = CH ₂ CH ₃ (1l) | 95:5 | 93 |

^a Claisen rearrangement conducted at 23 °C (entries b,e), 39 °C (entries a,c,d,f,g), or 80 °C (entries h–l). ^b Diastereomer ratios determined by ¹H NMR of crude product mixtures (entry i determined by GC). ^c Isolated yields are reported for the primary alcohols derived from ^tBu₂AlH reduction of the initial aldehyde products **2a–l**. ^d Reaction afforded 6% of the 2,3-*syn*, 4*Z* diastereomer.

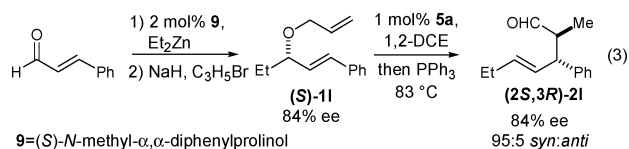
optimum catalyst for merging allyl ether isomerization with ensuing [3,3] sigmatropic rearrangement.¹⁰ In the standard test reaction, di(allyl) ether **1a** was reacted with 1 mol % **5a** (30 min, 23 °C) to afford the Claisen substrate **6** (>95:5 *E,E:Z,E*); directly warming **6** to 39 °C for 12 h afforded 4-pentenal derivative **2a** (80%) as a 85:15 (*syn:anti*) mixture of diastereomers. Claisen diastereoselection was substantially higher for reactions employing the putative Ir(I)-tris(phosphine) complex **5a** relative to the analogous bis(phosphine) complex **4a**.¹¹ Presumably, utilizing 3 equiv of ligand attenuates the Lewis acidity of the derived Ir(I) complex, thereby limiting the potential for Lewis acid-accelerated aldehyde epimerization during the Claisen rearrangement. Catalyst preparations employing NaBPh₄ also eliminate AgCl contaminants that mediate competing ether migration and function to attenuate Claisen diastereoselection.

On the basis of the preceding analysis, we reasoned that Claisen diastereoselection could be further improved by rigorously ensuring that the Ir(I)-phosphine complex could not participate in epimerization of the α -chiral aldehyde Claisen products. With the goal of passivating any residual Lewis acidic character in the Ir catalyst, additional phosphine ligand was added to saturate the metal's coordination sphere prior to thermolysis. Thus, ether **6** was reacted with 1 mol % **5a** prior to adding PPh₃ (3 mol %) and warming the resulting reaction mixture to 39 °C (12 h). Under these conditions, pentenal **2a** was obtained with excellent *syn* diastereoselection (*syn:anti* = 94:6) in 80% yield from the bis(allyl) ether **1a**.¹²

Under the optimized isomerization-Claisen rearrangement (ICR) reaction conditions, a variety of structurally diverse bis(allyl) ethers **1a–l** participate in highly diastereoselective Claisen rearrangements. Ether substrates incorporating various linear or branched alkyl substituents at the allylic (R²) or carbinol carbon (R³) positions exhibit uniformly high *syn* diastereoselection (*syn:anti* = 91:9 to 98:2) (Table 1). Internal allyl ether substrates prepared as *E,Z*-olefin mixtures are also effective ICR substrates due to the high *E*-selectivity that characterizes Ir(I)-catalyzed allyl ether isomerization (entries e, i). Substrates incorporating R³ substituents capable of labilizing the adjacent C–O σ -bond (cf., Ph, CH₂SiMe₃)¹³ require temperatures only as high as 39 °C to achieve useful Claisen reaction rates (entries a–g). While most substrates exhibited equally high selectivity for delivering the (*E*)-pentenal products, ether **1j** combining small alkyl groups at both R² and R³ delivered a measurable amount of the (*Z*)-2,3-*syn* diastereomer (6%) (entry j).¹⁴ This stereochemical leakage may result from the higher reaction temperatures (80 °C) required for substrates possessing simple alkyl R³ substituents.

The success of the ICR reactions suggested an operationally simple strategy for realizing asymmetric reaction variants (eq 3).

Enantioenriched (*S*)-*E*-1-phenyl-1-penten-3-ol was prepared by the *N*-methyl- α,α -diphenylprolinol (**9**)-catalyzed addition of Et₂Zn to cinnamaldehyde (84% ee).^{15,16} Following O-allylation, subjecting the resulting (*S*)-bis(allyl) ether (*S*)-**11** to the optimized ICR conditions delivered pentenal (2*S*,3*R*)-**21** in 84% ee with excellent diastereoselection (*syn:anti* = 95:5).



The ICR reaction technology provides convenient access to highly diastereoselective aliphatic Claisen rearrangements from easily prepared starting materials. This reaction methodology also offers an efficient entry to enantioenriched *syn*-2,3-dialkyl 4-pentenal derivatives by merging asymmetric dialkyl zinc additions with the ensuing ICR transformations.

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Supporting Information Available: Experimental procedures and representative ¹H and ¹³C spectra (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (10) Acetone was added to solubilize the NaBPh₄. Miyaura has also found acetone to accelerate related catalyzed isomerizations; see ref 7.
- (11) Complex **5a** is formulated as the tris(phosphine) complex on the basis of reaction stoichiometry and is not necessarily intended to represent the reactive catalyst complex that may be accessed by reversible phosphine dissociation.
- (12) Isolated yields are reported for the primary alcohols derived from ^tBu₂AlH reduction of the initial Claisen products due to epimerization of the α -chiral aldehydes during attempted chromatographic purification. See Supporting Information for full procedural details.
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