THE CATALYTIC ENANTIOSELECTIVE CLAISEN REARRANGEMENT

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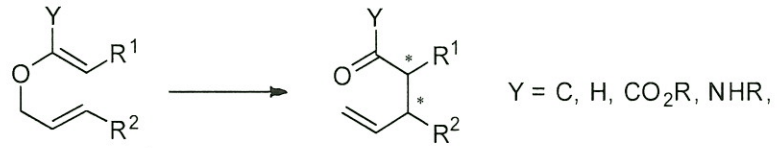
INTRODUCTION

In the family of [3,3] sigmatropic rearrangements, the Claisen rearrangement has long been one of the most utilized.[1] In its simplest form, the Claisen rearrangement produces γ,δ-unsaturated carbonyl compounds from allyl vinyl ethers (AVEs)(Scheme 1).[2] The reaction is highly exothermic and has a low barrier to activation. Furthermore, the rearrangement takes place through a chair-like transition state that results in predictable and high diastereoselectivity.[3] Due to these advantages, diastereoselective Claisen rearrangements have been used as key transformations in the total synthesis of steroids, alkaloids and other natural products.[4]

Scheme 1



In contrast, the enantioselective Claisen variant remains severely underdeveloped[1]. The generation of two, potentially quaternary, stereocenters as well as a geometrically defined olefin allows for the rapid buildup of complexity for synthetic purposes, thus making the enantioselective variant a highly desirable transformation. The facile nature of the rearrangement, as well as the relative inertness of the ethereal oxygen stymied efforts towards an effective chiral catalyst for most of the 20th century.[1,4]

CATALYSIS BY ORGANOMETALLIC SPECIES

Yamamoto et. al. was the first to demonstrate a feasible catalyst.[5] 2-Silyl-AVEs rearranged with good enantioselectivity in the presence of a BINOL-derived ligand-Al^{3+} complex. A ball-and-stick model revealed that the C_3-symmetric catalyst forms a groove around the aluminum, which preferentially accommodates one transition state. This work was extended to 6-subsituted-AVEs using a tris(2-naphtholyl)aluminum complex.[6] The increased Lewis basicity of the carbonyl oxygen with respect to the ether necessitated a superstoichiometric amount of catalyst in both cases. Hiersemann developed a Cu(II)-Pybox catalyst capable of multiple turnovers for the rearrangement of 2-carbomethoxy-AVEs.[7] The presence of a second coordinating group ameliorated product inhibition by lessening the difference in binding enthalpy between the product and substrate. The observed selectivity was attributed to a distorted square-planar complex around the copper that destabilizes one of the chair transition states.

Pd metal catalysts have also been used to facilitate the Claisen rearrangement by coordination to the olefins. Kozlowski used *t*BuPHOX in conjunction with Pd(II) to access allyl oxindoles from indole-2-methylesters.[8] Control experiments showed that the reaction did not proceed through π-allyl chemistry, which has been shown to be operative in other cases by Overman.[9] Ditriflamides were found to be effective ligands for Pd(II) in the rearrangement of cyclohexenyl allyl ethers into 2-allyl cyclohexanones, albeit with moderate stereoselectivity.[10] Surprisingly, the reaction was found to proceed through a boatlike transition state due to the coordination of Pd to both olefins.

CATALYSIS BY NONMETALLIC SPECIES

Recent developments include the use of non-metallic catalysts. Jacobsen developed a chiral guanidinium catalyst that facilitates the rearrangement of 2-carbomethoxy-AVEs.[11] Quaternary stereocenters could be formed with excellent diastereoselectivity and enantioselectivity. Rigidification of the AVE backbone by hydrogen-bonding from the guanidinium species forms a well-defined C2-symmetric complex that leads to the observed selectivity. Bode employed NHC catalysts to alkylate kojic acid derivatives into synthetically useful pyrans via a Claisen rearrangement.[12] Rate studies showed that a stereodetermining addition into an acyl azolium followed by rearrangement was responsible for the observed selectivity.

The catalytic asymmetric Claisen rearrangement offers a powerful method to introduce stereogenic centers into complicated molecules.[13] A well-ordered transition state allows for accurate predictions about product stereochemistry. Furthermore, the precursors are easy to synthesize from ketones and the allyl vinyl ether moiety is robust enough to survive other chemical transformations. A general, catalytic asymmetric Claisen rearrangement could present a major new avenue in the way chemists think about setting stereocenters.

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