SYNTHESIS OF AXIALLY CHIRAL ALLENES VIA ASYMMETRIC CATALYSIS

Reported by Justin D. Wright April 18, 2013

INTRODUCTION

Allenes have long fascinated chemists with their unusual cumulated double bonds and the orthogonal orientation of their substituents. Allenes with different substituents at both termini (Figure 1, $R^1 \neq R^2$ and $R^3 \neq R^4$) possess axial chirality. Axially chiral allenes are found in biologically active molecules such as the carotinoids fucoxanthin and peridinin, antibiotics such as marasin, and synthetic pharmaceuticals such as the PGE2 inhibitor enprostil.[1] Introduction of axially chiral allenes into advanced materials has been proposed as a method to synthesize polymers that emit circularly polarized light, or develop materials with chiral switching and sensing capabilities.[2] Axially chiral allenes are most commonly prepared by the reaction of esters of chiral propargylates with organocuprates, or are obtained from racemic allenes by kinetic resolution. Several groups have recently reported the discovery of catalytic methods to synthesize axially chiral allenes from achiral or racemic precursors. These methods allow the preparation of chiral allenes with two, three, or four substituents.

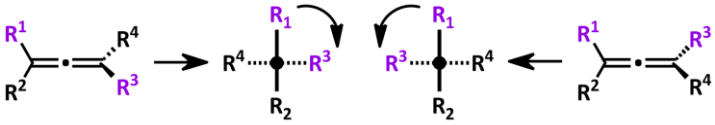


Figure 1. Axially chiral allenes, with $R^1 \neq R^2$ and $R^3 \neq R^4$. R^1 and R^3 have higher priority than R^2 and R^4, respectively.

TRANSITION METAL-CATALYZED METHODS

Several catalytic asymmetric reactions have been developed that feature C–C or C–N bond formation along with the introduction of axial chirality. The most extensively studied reactions in this class are the Pd-catalyzed S_N2' or S_N2'' reactions of 2-bromo-1,3-dienes.[3] The mechanism of these reactions has been studied, and has been shown to involve the formation of diastereomeric alkylidene-π-allylpalladium species, and an equilibration between them facilitated by dibenzalacetone. In addition, Pd-catalyzed aminations exploiting dynamic kinetic resolution (DKR) have been reported that can be used to prepare enantioenriched allenyl amines from racemic allenyl carbamates[4] and acetates.[5]

A Rh-catalyzed 1,6-addition of a variety of aryltitanate reagents to cyclic 1,3-enynones has been reported which yields tetrasubstituted allenes with high enantioselectivity.[6] A Rh-catalyzed 1,6-addition of arylboronic acids to 1,3-enynamides has also been reported.[7] A variety of aryl groups were tolerated and enantioselectivity was very high. Interestingly, the reaction is applicable to Weinreb amides, which allows access to a variety of other functional groups such as aldehydes and ketones.

PHASE TRANSFER, ACID, AND BASE-CATALYZED METHODS

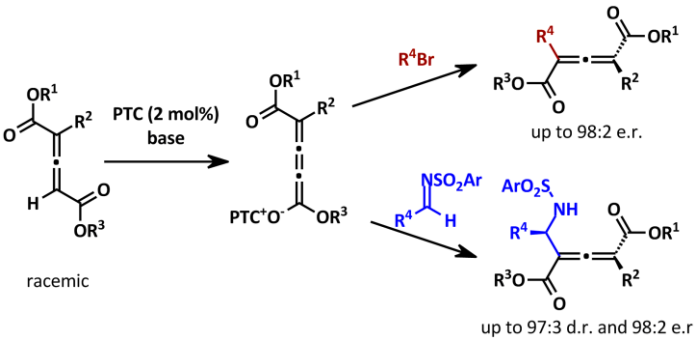
In the first reported isolation of a chiral allene, an allylic alcohol was dehydrated with camphorsulfonic acid to yield an enantioenriched tetrasubstituted allene.[8] More recently, the

isomerization of alkynes to allenes has been explored using chiral phase transfer catalysts (PTCs)[9] and chiral guanidine bases.[10] The mechanism of the guanidine-catalyzed reaction has been examined computationally.[11] In one report, racemic α-substituted propargylic esters were converted to enantioenriched trisubstituted allenes through a DKR process with a chiral guanidine catalyst containing an intramolecular base.[12]

In 2012, alkylation of racemic trisubstituted allenoates was reported using a chiral PTC to achieve excellent enantioselectivity (Scheme 1).[13] The reaction was extended to an alleno-Mannich reaction with non-enolizeable *N*-sulfonylimines to give tetrasubstituted allenes with high diastereo- and enantioselectivity. Both reactions occur through an intermediate cumulenolate.

SUMMARY

A variety of catalytic asymmetric methods have been developed for the synthesis of chiral allenes. Recent advances have enabled access to more substituted and more complex products with ever increasing enantioselectivity. Future advances may open up substrate scope considerably, allowing synthetic chemists to approach the synthesis of axially chiral allenes from a wider variety of starting materials, and to more frequently utilize these asymmetric catalytic methods over older stoichiometric reactions.



Scheme 1. Preparation of chiral tetrasubstituted allenes by PTC.

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