INTERMOLECULAR ENANTIOCONVERGENT CATALYSIS VIA CARBOCATION INTERMEDIATES

Reported by Shelby King March 9, 2021

INTRODUCTION

Carbocations have recently captivated the attention of chemists as highly useful intermediates for enantioconvergent catalysis. This sterically unencumbered, prochiral intermediate is primed for enantioselective functionalization and forms easily from racemic starting materials (Figure 1). Although carbocations mediate many well-established intermolecular reactions (e.g., S_N1 or Friedel-Crafts reactions), analogous enantioselective transformations are much less developed. Many examples are limited in scope and synthetic utility.[1] Intermolecular enantioconvergent reactions represent a unique challenge because carbocations with no nearby stereocenters have two enantiotopic, prochiral faces for nucleophilic attack. In addition, carbocations are highly prone to elimination to a more stable alkene and require a strategy for stabilizing the cation until it can be functionalized. Recent examples of enantioconvergent catalytic reactions proceeding through carbocation intermediates include substitutions, allylations, and Friedel-Crafts alkylations.

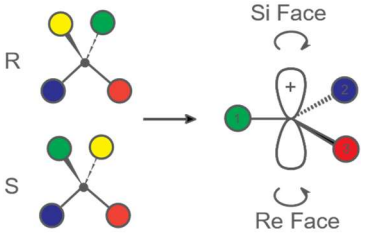
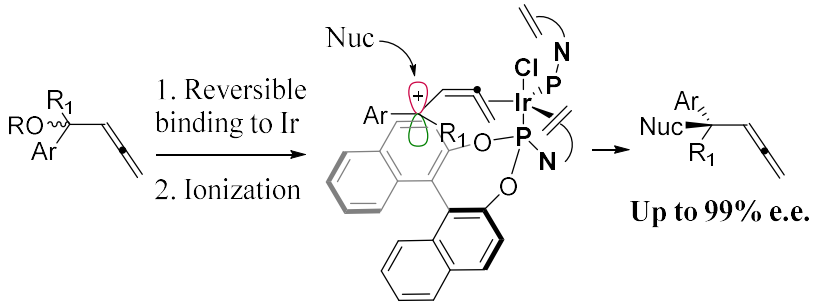


Figure 1. Prochiral carbocation.

ENANTIOCONVERGENT SUBSTITUTIONS

Carreira and co-workers recently reported two enantioconvergent substitution reactions which utilize a chiral iridium catalyst, shown in Scheme 1.[2,3] The carbocation is datively bound to the catalyst through an η^2-allene ligand. The enantiodetermining addition of the nucleophile is catalyst-controlled, as the sterically bulky ligand on the metal blocks one enantiotopic face from attack. Both protected and unprotected alcohols can be used as the leaving group in this reaction and the nucleophile scope includes alkyl Grignard reagents and hydride sources.

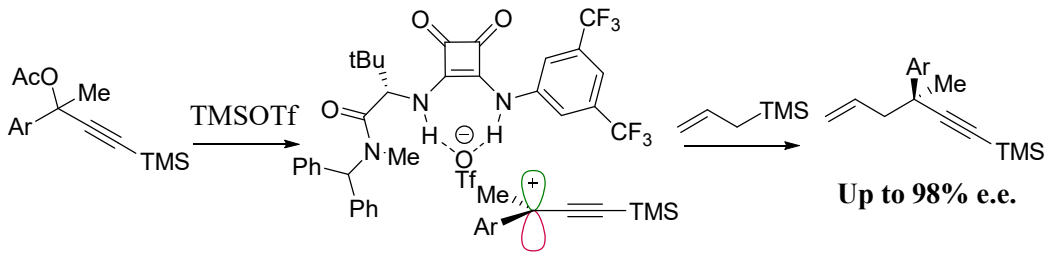
Scheme 1. **Enantioconvergent Substitutions. R1 = H, alkyl. Nuc = H, alkyl. OR = OBoc, OH.**



ENANTIOCONVERGENT ALLYLATIONS

Jacobsen and co-workers recently reported an enantioselective allylation reaction utilizing a chiral hydrogen bond donor (Scheme 2).[4] The hydrogen bond donor coordinates to the counteranion, resulting

Scheme 2. Chiral Hydrogen Bond Donor (HBD)-Catalyzed Allylation.

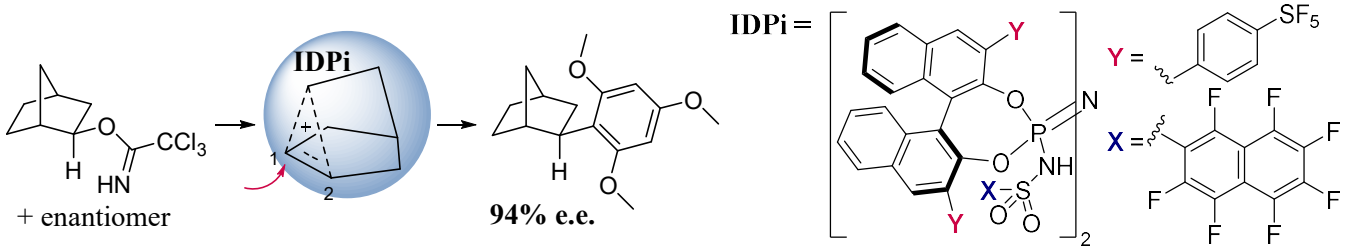


in a chiral, stabilized direct ion pair between the counteranion and the carbocation. In this chiral ion pair, the substrate is oriented to minimize unfavorable steric interactions with the catalyst and the allyl nucleophile then attacks the cation at the enantiotopic face opposite to where the catalyst is positioned.

ENANTIOCONVERGENT FRIEDEL-CRAFTS ALKYLATION

In a highly unique strategy, List and co-workers recently showed that their IDPi chiral phosphoric acid scaffold can be used in an enantioselective Friedel-Crafts alkylation with a carbonium ion intermediate (Scheme 3).[6] Using a variety of racemic or achiral starting materials, this group showed that they could stabilize and generate an asymmetric environment around the carbonium ion to result in

Scheme 3. IDPi-Catalyzed Friedel-Crafts Alkylation.



enantioselective functionalization. The mechanisms for formation of the carbonium ion range from simple protonation of an alkene to C-C and C-F bond activation (not shown in Scheme 3). This method differs from all previous examples due to the enantioselectivity arising from enantiotopic group selectivity rather than enantiotopic facial selectivity on the carbocation.

REFERENCES

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