ASYMMETRIC COUNTER-ANION DIRECTED CATALYSIS

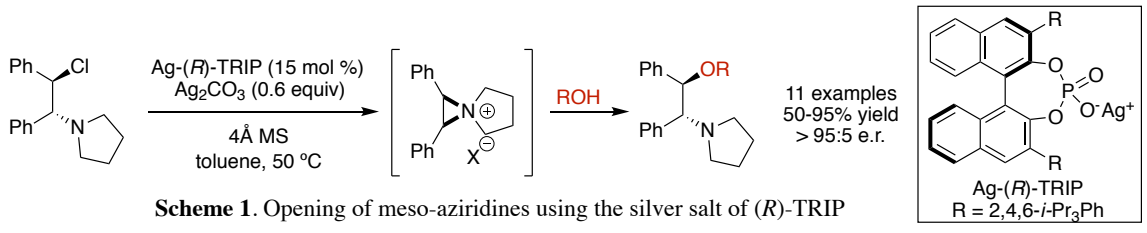
Reported by Travis Menard November 5th, 2019

INTRODUCTION

Asymmetric counter-anion directed catalysis (ACDC) can be viewed as any catalytic reaction which uses a chiral anion to control the stereochemical outcome of a transformation with a cationic reaction intermediate. The first successful applications of chiral anions outside of phase transfer catalysis were demonstrated in 2004 by Terada and Akiyama in their independent use of chiral phosphoric acids for asymmetric nucleophilic additions to iminium ions.[1,2] Chiral phosphates quickly became the most ubiquitous chiral anions used and comprise much of the field today. Modern ACDC can be grouped into three distinct subsets of transformations: chiral phosphate mediated, transition metal mediated, and anion binding mediated catalysis.[3]

CHIRAL PHOSPHATE MEDIATED

Chiral phosphate mediated transformations are the most abundant owing to their simplicity. A chiral phosphate ion will stabilize cationic reaction intermediates through direct electrostatic interaction. Nearly all early examples of this type are Brønsted acid catalyzed reactions of imines which result in highly reactive iminium ions whose steric environment is well controlled by the phosphate conjugate base. Toste was the first to demonstrate that hydrogen bonding interactions were not essential by controlling the asymmetric opening of cationic tetracoordinate aziridinium ions which have no capacity to hydrogen bond and are likely purely ionic (Scheme 1).[4] This demonstration expanded the field to a number of quaternary iminium ions and advanced the scope beyond simple Brønsted acid catalysis. Challenges in this area stem from a lack of mechanistic insight into the nature of the interaction between catalysts and substrates. It can be difficult to decipher subtle differences on the spectrum between covalent and ionic interactions. Most examples likely fall somewhere in between and do not truly constitute full ionic character of the counterion.

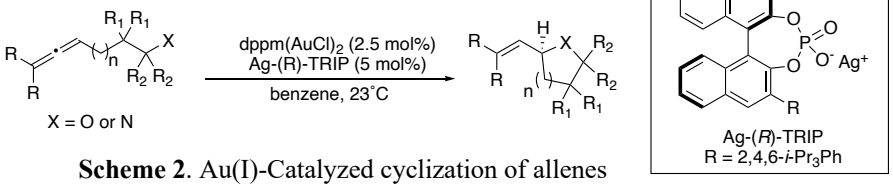


Scheme 1. Opening of meso-aziridines using the silver salt of (*R*)-TRIP

TRANSITION-METAL MEDIATED

Transition-metal mediated ACDC makes use of chiral anions as stereodifferentiating agents for the reactions of achiral cationic metal complexes. This approach can present advantages over the use of chiral ligands in that the optimization of the catalyst and the anion can be performed separately. An additional advantage of a chiral counterion is that it does not rely on direct proximity to the metal and

can influence stereochemical outcomes at more remote sites away from the reactive center. This concept has been especially advantageous with linear gold complexes in which the ligands on the metal are required to be approximately 180˚ from the substrate because of geometric constraints of gold complexes. This concept was demonstrated by Toste in the use of cationic Au(I) complexes for the asymmetric hydroxylation, hydroamination, and hydroalkoxylation of allenes to form substituted heterocycles (Scheme 2).[5] One of the greatest shortcomings in this area is the lack of mechanistic evidence for ionic interactions. In many cases it is unclear whether the chiral anion truly has electrostatic interaction only or if it is simply acting as a chiral ligand. In many cases the interactions are unclear and, in some instances, it may be misleading to term the interactions ionic.



Scheme 2. Au(I)-Catalyzed cyclization of allenes

ANION-BINDING MEDIATED

In anion-binding mediated catalysis an achiral anion, typically a halogen or simple conjugate base, is bound to a chiral coordinating group which can control the steric environment around the adduct. This form of catalysis generally makes use of hydrogen bonding donors which are well studied. Many methods suffer from challenges associated with oragnocatalysis such a high catalyst loadings and low reaction concentrations however, the reactions are usually highly selective. Although this area is the least well explored recent mechanistic insights from Jacobsen and coworkers have shed light on many key interactions and set the stage for promising advancement in this area (Figure 1).[6,7] A better mechanistic understanding of the non-covalent interactions involved in all types of anion-mediated catalysis will be crucial in expanding utilization and development of new reactions.

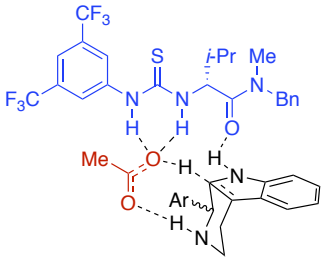


Figure 1. Key transition state for ion-binding catalysis in an asymmetric Pictet-Spenger reaction.

References

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