STEREOABLATIVE ENANTIOCONVERGENT CATALYSIS

Reported by Matthew Bock October 8, 2019

INTRODUCTION

Synthetic chemists are continuously searching for new methods pertaining to the enantioselective construction of chiral molecules. To solve this problem, enantioconvergent catalysis, the complete conversion of a racemic substrate into a single, enantiomerically enriched compound, has arisen as an important strategy.[1] This area of catalysis has primarily been dominated by two approaches: dynamic kinetic resolution (DKR) and dynamic kinetic asymmetric transformation (DYKAT); while a third plausible tactic, stereoablative enantioconvergent catalysis, has considerably received less attention.

Operating under similar kinetic principles as DYKAT, stereoablative reactions do exactly as the name implies — a stereogenic center is irreversibly removed from the substrate, generating a prochiral compound, **B** (Figure 1). Notably, unlike DYKAT, there is no equilibration between the *R* and *S* enantiomers of the racemic substrate and the prochiral compound. Upon interaction with the chiral catalyst, diastereomeric complexes are generated. Thereafter, a variety of processes can occur (e.g. nucleophilic or electrophilic attack, reductive elimination); however, in all cases, the rate of product formation will be faster for one of the diastereomeric complexes compared to the other.

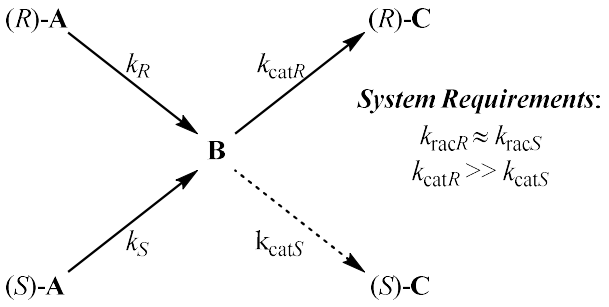
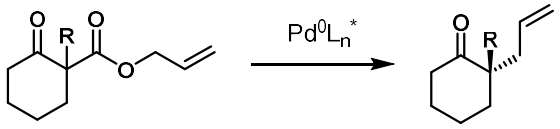


Figure 1. Stereoablative enantioconvergent catalysis.

ENOLATE-MEDIATED STEREOABLATION

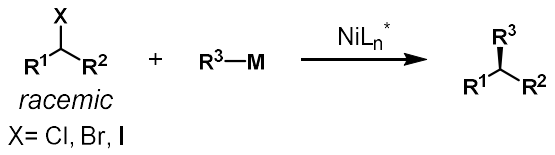
Enolates are an ideal intermediate in stereoablative catalysis because generation of these species is well established. Arriving at this species in a creative manner, Stoltz and coworkers reported an enantioselective decarboxylative allylic alkylation in 2005 (Scheme 1).[2] Using a β-keto-ester as the allyl source, this palladium-catalyzed transformation builds quaternary centers in high enantioselectivity. The reaction is versatile and has been extended to over 15 unique substrate classes.[1] In contrast to the Tsuji-Trost reaction, which often proceeds through external attack of the Pd-π-allyl species by a nucleophile, computational and experimental evidence has suggested that this transformation proceeds through an inner-sphere mechanism.[3] Because of its significant synthetic utility, this transformation is often frequently employed in natural product synthesis.[4]



Scheme 1. Stoltz's enantioselective decarboxylative allylic alkylation (L_n* = chiral ligand).

RADICAL-MEDIATED STEREOABLATION

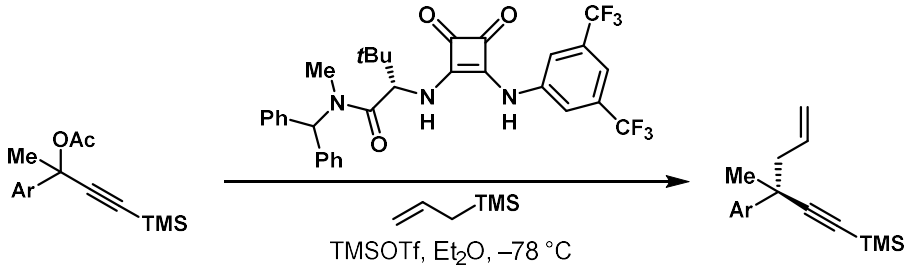
A variety of enantioselective nickel-catalyzed, cross-coupling methods have been developed by Fu and coworkers that enable the direct, enantioselective synthesis of C_{sp3}-C_{sp3} bonds (Scheme 2). For these nickel-catalyzed couplings, mechanistic studies suggest that alkyl halide abstraction results in the formation of a radical that is captured by a chiral catalyst.[5-6] Most recently, the scope of these transformations has been expanded to include the cross-coupling of olefins with secondary and tertiary alkyl halides.[7]



Scheme 2. Generalized system for Fu's enantioselective cross-couplings (L_n* = chiral ligand).

CARBOCATION-MEDIATED STEREOABLATION:

When paired with an appropriate catalyst, carbocations can be exploited in stereoablative catalysis. In a key finding, Jacobsen and coworkers demonstrated that a chiral squaramide catalyst could build quaternary centers by an enantioconvergent allylation.[8] Mechanistic studies suggest a stereoablative pathway by the formation of a carbocation, suggesting that an S_N1-type reaction might be operative. Although this area is still in its infancy, these initial results are promising leads for future development.



Scheme 3: Jacobsen's S_N1-type allylation

References

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