STEREOABLATIVE ENANTIOCONVERGENT CATALYSIS

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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. 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.

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). 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. 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. Because of its significant synthetic utility, this transformation is often frequently employed in natural product synthesis.
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. Most recently, the scope of these transformations has been expanded to include the cross-coupling of olefins with secondary and tertiary alkyl halides.

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. Mechanistic studies suggest a stereoablative pathway by the formation of a carbocation, suggesting that an SN1-type reaction might be operative. Although this area is still in its infancy, these initial results are promising leads for future development.

References