New Developments in Enantioselective Allylation and Crotylation Reactions
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Stereocontrolled addition to carbonyl compounds is arguably the most important tactic employed in the synthesis of complex molecules. Among these, the allylation and crotylation reaction of aldehydes is a great way to introduce complexity to simple molecules. Crotylation reactions, for example, can introduce two new stereocenters in one step along with a new carbon-carbon bond. The homoallylic alcohols and related products of this reaction are important building blocks in many organic natural products. Novel methods promise greater stability of the allylating reagents along with new methods in catalysis that offer new environments for the allylation of natural products.

The allylation and crotylation reaction involves an allyl/crotyl donor, an electrophile, and, in some cases, a Lewis acid. The reaction was first shown by Mikhailov in 1972. Hoffman was the first to perform this reaction with a degree of enantioselectivity using a camphor derived chiral auxiliary. Two reagents seem to dominate in synthesis today–Roush’s diisopropyl tartrate derived borane and Brown’s pinene derived borane. The Brown reagent is very wide spread; however, it suffers from substrate controlled diastereoselectivity. The Roush reagent does give some reagent control, but the mismatched cases can have lower diastereoselectivity than is desired (<9:1). All of these boron reagents suffer from the lack of air stability and lack of storability. This forces the user to make these reagents before use, taking both time and effort.

Figure 1. Some early allylating reagents containing boron

Type I allylations use boron reagents and go through a six-membered ring transition state. This allows the crotylation product to be stereospecific with regard to the olefin geometry. Z-olefins give syn and E-olefins give anti relative stereochemistry. The chiral auxiliary influences the facial selectivity of the reaction relative to the aldehyde.

Scheme 1. Relative stereochemical model of a crotyl borane reagent.
Type II allylations use silicon or tin reagents instead of boron. Silicon and tin are generally not reactive enough to add to a carbonyl without the aid of a Lewis acid. These type II reactions are believed to proceed through an open transition state. Because of this open transition state, the reaction is stereoconvergent with respect to olefin geometry. Steric factors dictate whether the reaction is syn or anti diastereoselective.5

Recent developments in the allylation reaction are numerous, especially transition metal catalyzed allylations that give good stereoselectivity. These are beyond the scope of this discussion. Here, two developments will be described—the new organocatalytic allylations and air stable allylating reagents. Organocatalytic reagents open up different reaction conditions which often is important in the synthesis of natural products. Air stable reagents offer time saving techniques to chemists during synthesis.

The Antilla group from the University of South Florida reported in 2010 the chiral phosphoric acid catalyzed allylation with allyl borane pinicol ester and TRIP-PA which is a binol derived phosphoric acid. Here, Antilla reports yields for aliphatic, aromatic, and conjugated aldehydes of >90% with enantiomeric excesses usually above 90% as well. Presumably, the facial selectivity comes through a six-membered ring ion pair transition state.6

Another development in new catalysts is the use of Lewis bases. The Lewis base in the presence of allyl silyl chlorides catalyzes the allylation reaction. These reactions offer an alternative to the acidic reactions that generally accompany traditional allylations. The Lewis bases that have been used range from chiral sulfoxides to chiral dinitrones and pyridine oxides from the Scettri, Nakajima, and Malkov, respectively.7, 8, 9

Figure 2: Lewis bases to catalyze allylations
Reagents that are air stable and storable offer ease of use and faster reactions by not having to make the reagent before use. The stable species are especially intriguing to industry for large scale reactions without added safety hazards. Borate salts such as organotrifluoroborate salts and dioxazaborolidines have been shown by Batey and Rychnovsky to catalyze allylations. These reactions require a Lewis acid and the borate salt to react with aldehydes. (generally with greater than 95:5 diastereoselectivity)\textsuperscript{11, 12} Batey’s work with organotrifluoroborates can also be used with ketones. Some of the most interesting work is being done by Leighton at Columbia University. Leighton found that by using strained silacycles stereospecificity from the olefin is maintained. Interestingly, complete reagent control of diastereo and enantioselectivity can be seen when scandium triflate is used as a Lewis acid. The chiral aldehydes tested gave respectable yields and diastereoselectivity. (up to 86% yield and 99:1 dr)\textsuperscript{12} This overcomes the shortcomings of substrate control along with being shelf stable. Leighton has even made a mix of these reagents with the Lewis acid in the bottle which only requires addition of a stoichiometric amount of the crotyl mix along with the aldehyde and good yield is seen.

![Figure 2. Leighton group most recent chiral crotylating agent.](image)

Allylations and crotylations are powerful carbon-carbon bond forming reactions. New advances in the chemical catalyst open new avenues available to chemist for synthesis along with air stability offer exciting new opportunities to complete new total syntheses. Scalable reactions are also possible with new air and shelf stable reagents that may be useful to industry. While a simple allylation done with the Roush or Brown procedures may still be synthetically useful, the new silacycles by Leighton offer reagent controlled reactions for the more complex cases.