Part 1 – Synthesis of piperidines via aziridinium ylides

Nitrogen-containing motifs are large structural patterns in approved drugs. Recent reviews report that 59% of FDA-approved drugs contain nitrogen heterocycle. The Schomaker group has been focused on harnessing allene and alkene aziridination as a platform to efficiently access a variety of densely functionalized, nitrogen-containing molecules. Previous studies in the Schomaker group demonstrated that treatment of methylene aziridines with strong electrophiles, such as rhodium-bonded carbones, led to endocyclic methylene azetidines in excellent yields and dr. Experimental and computational studies suggested formation of an aziridinium ylide that undergoes Stevens-type rearrangement to yield methylene azetidine.

Using the same hypothesis, I proposed that treatment of trans- and cis-aziridines with vinyl electrophilic rhodium-bound carbones could react to form aziridinium ylides. The resulting aziridinium ylides could then undergo [2,3]-sigmatropic rearrangement to afford highly substituted piperidines. Following this hypothesis, treatment of cis-aziridines with 3 mol% Rh₂OAc and vinyl diazo reaction partners resulted in the synthesis of highly substituted piperidines in excellent yields and dr. The use of rhodium was found to be uniquely successful, in comparison to other carbene catalysts such as copper. The reaction tolerated various functional groups (Scheme 1). However, trans-aziridines afforded no reaction. To probe the mechanism, enantioenriched cis-aziridine was subjected under the reaction conditions, yielding enantioenriched piperidine with no enantioerosion, which indicates full transfer of stereochemical information.

Future works in this area would be centered on aziridine ring-expansion to access various nitrogen-containing heterocycles. Triazoles are common carbene precursors that can decompose to form reactive diazo imines. Treatment of 16, electrophilic rhodium catalyst and 18 should proceed via an aziridinium ylide to yield piperazines 20 (Scheme 2).

Part 2 – Development of a highly regioselective hydroformylation of 1,1',3-trisubstituted allenes, 1,1,2-trisubstituted allenes and 1,1'-disubstituted allenes

Hydroformylation is an excellent atom-economical, catalytic, one-carbon homologation reaction, in which a rhodium or cobalt catalyst is used in the presence of syngas (1:1 CO/H₂) to make aldehydes. Hydroformylation is the largest industrial process for the synthesis of commodity chemicals. Hydroformylation of monosubstituted and 1,2-disubstituted allenes is known and works very well. However, hydroformylation of 1,1'-disubstituted and 1,1,2-trisubstituted allenes are scarce. This is mainly due to preferential formation of the undesired linear aldehyde (Keulman’s rule), as well as hydrogenation of the alkene to an alkane (Scheme 3). Selective branched hydroformylation of 1,1'-disubstituted and 1,1,2-trisubstituted alkenes would result in the formation of tetrasubstituted aldehydes, useful synths in the production of pharmaceuticals and fine chemicals. Related chiral tetrasubstituted sterogenic centers are prevalent in numerous drug candidates and bioactive natural products, such as sofosbuvir. This has inspired me to target the synthesis of octa-substituted aldehydes.

To overcome formation of linear aldehyde, I hypothesized that introduction of inductive electron-withdrawing groups should favor formation of tertiary alkyl-Rh intermediate. Furthermore, I hypothesized that introduction of a gas mixtures enriched in CO should disfavor formation of hydrogenated byproducts. Overcome all, I hypothesized that the interplay of stericas, electronics, and ring strain can be harnessed to provide the valuable desired products. Initial studies using 21 and various commercially available ligands revealed that the Landis catalyst, rhodium-bisdiazaphos, was superior, yielding highly regio- and enantioselective octa-tetrasubstituted aldehydes. As hypothesized, several electron-withdrawing groups, in particular acrylates and acetates, facilitated fast rates (up to 50 turnovers/h) and selectivities (up to 95% ee and > 50:1 branched selectivity) under mild reaction conditions (150 psi CO/H₂, 60 °C, 1 mol% of catalyst). Furthermore, various electronically activated strained allenes yielded tetrasubstituted aldehydes in excellent yields and selectivities (> 50: 1αβ, >19:1 dr), and fast rates (up to 50 turnovers/h) under mild conditions.

The presence of hydrogenated byproducts suggests that there is a slow CO migratory insertion, step due to the desired formation of sterically congested tertiary alkyl-Rh intermediates. Formation of tertiary alkyl-Rh intermediate III.5 leads to competitive trapping of the Rh-alkyl intermediate with H₂ to give III.6 before migratory insertion can occur to ultimately furnish the desired III.8 through the intermediacy of III.7. I hypothesized that the alkyl intermediate III.5 may accumulate in high enough concentrations to be detectable by ³H NMR spectroscopy in the absence of H₂. This hypothesis was tested by direct NMR observation of the reaction of pre-formed catalyst and 10 equivalents of 1, as monitored by ³¹P(¹H) NMR in the absence of H₂ at 0 °C and under 1 atm CO (Scheme 3). These studies establish a rare example of the interception of a trialkyl metal complex intermediate in a catalytic reaction and establish

Scheme 1. Synthesis of piperidines via aziridinium ylide

Previous uses of aziridinium ylides in synthesis:

Scheme 2. Synthesis of piperazines via aziridinium ylide.
Josephine Eshon – University of Wisconsin-Madison, Clark Landis Group and Jennifer Schomaker Group

that, compared with secondary and primary alkyl-Rh intermediates, CO insertion into the tertiary alkyl-Rh bond is substantially slower. These studies also suggest that more detailed kinetic and mechanistic analyses of hydroformylation processes to produce tetrasubstituted aldehydes are feasible.

The hydroformylation of allenes is notably more challenging than hydroformylation of alkenes, due to undesired side reactions. For example, hydroformylation can occur at either two of the double bonds of the allenes to yield four different aldehydes. In addition, competing alkene hydrogenation, secondary hydroformylation, and isomerization of β,γ-unsaturated aldehydes can occur. However, hydroformylation of allenes that are 1,1’,3-trisubstituted is synthetically useful because it provides functional group handles for a diverse range of chemical transformations. Therefore, such a process would present a rapid, atom-economical route to value-added compounds.

Furthermore, hydroformylation of 1,1’,3-trisubstituted allenes would yield chiral β,γ-unsaturated aldehydes that have been employed as building blocks for several natural products such as premonensin and palmerolide C.

To overcome regioselectivity issues, I hypothesized that insertion of Rh-H to the center carbon of the allene should be favored. Next, I hypothesized that introduction of inductive electron withdrawing groups (R²-Scheme 4) should favor addition of acyl group. Initial studies using 33 and various commercially available ligands revealed that the Landis catalyst, rhodium- bisdiazaphos, was superior, yielding highly regioselective chiral β,γ-unsaturated aldehydes.

Remarkably, various trisubstituted aryl allenes, heterocyclic allenes, homoallylic esters, and allenoals underwent hydroformylation with high conversions and regioselectivities, using catalyst loading as low as 0.1 mol % (Scheme 4). For substrates containing inductivity electron-withdrawing groups, the data indicates a preference for the addition of hydrogen to the central carbon of the allene. In addition, the reaction substrate scope was expanded to include a variety of functional groups, making this an ideal process for a variety of synthetic transformations. High regioselectivity of chiral β,γ-unsaturated aldehydes is due to the identity of the bisdiazaphos ligand. Lastly, turnover rates of 10^5-10^6 h⁻¹ were observed, notably marking hydroformylation of 1,1’,3-trisubstituted allenes as the second fastest class of substrates in hydroformylation.

In conclusion, our studies on hydroformylation of trisubstituted allenes, trisubstituted allenes and disubstituted allenes have transformed the field of hydroformylation. Greater understandings of the mechanism and variables that control regioselectivity and enantioselectivity have been gained. The reaction substrates scopes have been expanded. The knowledge gained from these studies will improve the future of hydroformylation.