Development of Coupling Strategies for *Peri*-Substituted Main Group Systems

Alice Martin | aem28@st-andrews.ac.uk | Kilian Research Group

University of St Andrews

Introduction

Synthetic chemistry is the discipline used to produce complex compounds. From relatively simple reagents, a series of stepwise reactions can be combined in order to produce a huge variety of molecules. This field is therefore hugely important across all areas of chemistry. The work of synthetic chemists reaches many parts of industry, from pharmaceuticals to green chemistry. The Kilian research group focuses on synthetic chemistry, specifically synthesis of main group ring systems.

These collection of molecules share a structure based off naphthalene; two connected benzene rings. The aromatic 'backbone' locks atoms into a specific geometry within a molecule, forcing atoms closer together than expected, in sub Van der Waals distances. The resulting molecule can therefore undergo coupling reactions to produce a new molecules, which can be stored with relative ease. One of the long-term goals of this research is its application towards green chemistry, as a catalyst. By using ring-system molecules as catalysts, finite toxic heavy-metal catalysts currently used can be discarded. This is a much safer and more environmentally friendly approach to large industrial processes with applications across many disciplines.

The reaction mechanism of the decoupling reaction shows the formation of a radical on one of the peri-positions in the first step, followed in the second step by the formation of new bond between the two *peri*-atoms. This forces one atom/substituent group to be removed from each atom at the peri-positions, which combine to form a new molecule, shown in the diagram below:

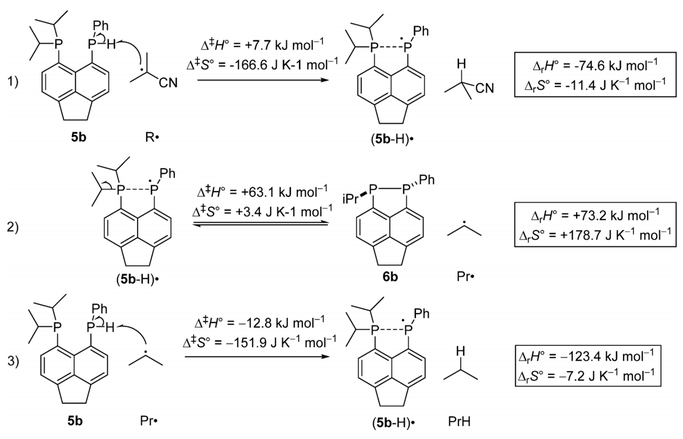


Figure 1: Proposed Radical Chain for Propane Elimination in the Presence of AIBN, with Computed Activation Parameters and Thermodynamic Driving Forces Shown.[1]

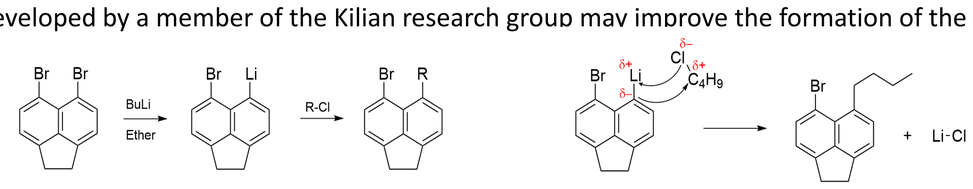
The focus of this project is researching the synthesis of *peri*-substituted main group systems, by applying the above mechanism to a collection of new ring system molecules, specifically group 14 elements at one of the *peri*-positions. The use of group 14, specifically carbon is of interest due to is natural abundance. Synthetic routes of interest that would produce the precursor molecules to the coupling reaction will be developed then tested and analysed in the lab.

Synthetic Routes

A variety of synthetic routes were proposed based on two principles; either adding a large carbon-based substituent group to the *peri*-position in one step, or by adding carbons in stepwise reactions to increase the length of the carbon chain at the *peri*-position.

1. Adding a large carbon-based substituent group:

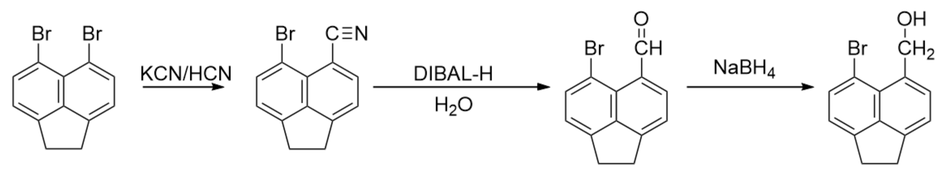
A variety of ideas were proposed for this method, with particular focus on the use of organolithium reagents. Organolithium reagents are carbon-based molecules that contain a lithium atom which dissociates from the carbon chain to react with a halogen in a variety of ways. One way is through the formation of organolithium intermediate, which can react with a haloalkane to add a carbon-based group to the correct *peri*-position. An alteration to a procedure developed by a member of the Kilian research group may improve the formation of the desired product, using a chloroalkane.



Scheme 1: Reaction route and mechanism for direct alkylation of 5,6-dibromoacenaphthene

2. Stepwise C-C bond forming reactions:

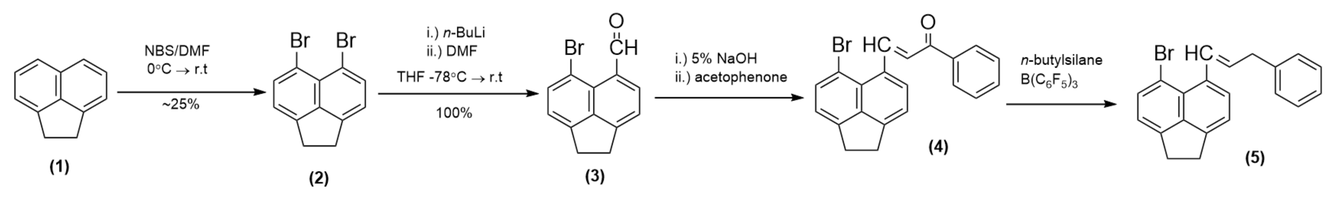
This method of synthesis was based off reactions found in literature, where C-C bond forming reactions involving similar reagents to those required had relatively high yields and purity. The first idea for addition of a single carbon atom onto position 5 of acenaphthene was through nucleophilic aromatic substitution using a nitrile group. After the substitution of the nitrile group, further reactions were conducted to reduce the nitrile group to an aldehyde, then to a primary alcohol, removing the nitrogen atom entirely. This method was different to ones previously pursued and showed some promise, however, had some drawbacks, specifically the use of a nitrile group. In order to introduce this into the reaction, the use of potassium cyanide and hydrogen cyanide would be required. These compounds are too toxic for use, so this specific route was deemed too dangerous and was not pursued further.



Scheme 2: Synthetic Route for the nucleophilic aromatic substitution

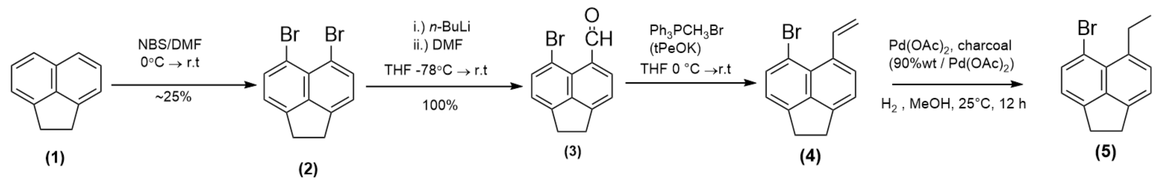
The second method was initially developed at the University of Cambridge by the Congrave research group,[2] placing an aldehyde at the desired position. The formation of an aldehyde at position 5 of acenaphthene with relatively safe reagents was of real interest in this research and as such, two synthetic routes were established using the aldehyde intermediate.

The first synthetic route was based off the Aldol Condensation. This method combined the aldehyde previously synthesised with a ketone in order to form a new carbon-carbon double bond, which through further reactions could be reduced to the C-C bond required. In order to limit side reactions, one of the reagents used needs to be un-enolisable, so the aldehyde previously formed, 5-bromo-6-acenaphthaldehyde can be used. By combining this with the use of a less electrophilic ketone, side reactions may be limited. The proposed synthetic route is shown below.



Scheme 3: Synthetic Route for the preparation of 5-Bromo-6-(3-Phenylpropyl)-1,2-dihydroacenapthene

The second synthetic route took advantage of the Wittig Reaction. This reaction converted the aldehyde group sitting at position 5 to an alkene through a phosphorus ylid intermediate.[3] Further reactions could then be applied to the alkene in order to convert it to an alkene, or other functional groups. This reaction had a few advantages over the Aldol Condensation shown above because there would be no possible side reactions, and the final product can be altered significantly based on the reagents used. This allowed for flexibility in the reactions, which could be altered with relative ease based on computational studies for the feasibility of different substituents at the required position.



Scheme 4 : Synthetic Route for the preparation of 5-bromo-6-ethyl-acenaphthene

Computational Results

The flexibility in the both the Wittig Reaction and Aldol Condensation reactions allows for a variety of reagents to be used to form different molecules. A large variety of substituents were modelled in order to determine which would be successful in the coupling reaction itself, and as such which molecules to focus on synthesising.

The calculations run focused on the energy associated with each of the transition states of the mechanism, particularly focusing on the first step of the reaction which has been determined as rate determining. For the first step to be feasible, the Gibbs Free Energy of the transition state, $\Delta G^{\ddagger}$, is required to be below 120 $\mathrm{kJmol^{-1}}$ which has previously been determined as the limit of feasibility.

The results showed that $\Delta G^{\ddagger}$ was much higher than desired. This issue seemed to arise because one or two of the groups attached to the carbon at position 5 were hydrogens. This means that in the reaction mechanism, hydrogen is removed preferentially to any carbon group. In computational models for other systems, mainly when using group 15 atoms, this process didn't occur. This may be due to added stability that comes with increasing the length of the carbon chain.

Despite this, the synthetic routes determined were tested, in order to determine whether the coupling reaction takes place. The computational results were based of the reaction mechanism used for group 15 coupling reactions. There is no reason to suggest that a coupling reaction between a group 14 and 15 elements should proceed via a different mechanism but testing of the coupling reaction would confirm the mechanistic route for the reaction.

Conclusion

A series of synthetic routes were developed to produce molecules with a carbon-based functional group at one *peri*-position. Calculations were run to establish whether the coupling mechanism was feasible with the molecules developed. The calculations suggested that the mechanism is not energetically feasible if a hydrogen atom is attached to the carbon at the *peri*-position. However, the results suggest further research into forming a carbon-based functional group with no hydrogen bonded on the *peri*-position should be undertaken as this may lead to successful coupling.

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